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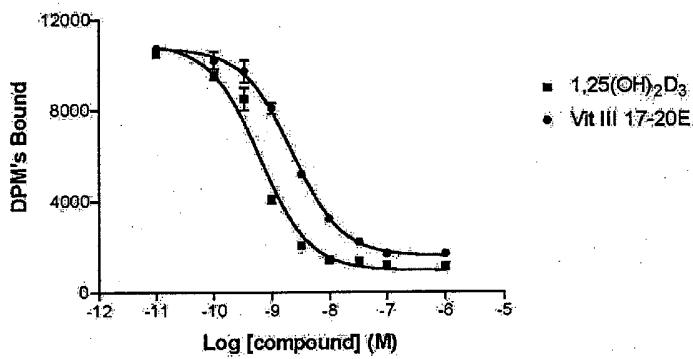
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[Continued on next page]

## (54) Title: 17,20(E)-DEHYDRO VITAMIN D ANALOGS AND THEIR USES

## Competitive VDR Binding



$K_D$ :  $1,25(\text{OH})_2\text{D}_3 = 1.1 \times 10^{-10} \text{ M}$   
 $\text{Vit III 17-20E} = 3.8 \times 10^{-10} \text{ M}$

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(57) Abstract: This invention discloses 17,20(E)-dehydro vitamin D analogs, and specifically 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> and pharmaceutical uses therefor. This compound exhibits pronounced activity in arresting the proliferation of undifferentiated cells and inducing their differentiation to the monocyte thus evidencing use as an anti-cancer agent and for the treatment of skin diseases such as psoriasis as well as skin conditions such as wrinkles, slack skin, dry skin and insufficient sebum secretion. This compound also has little, if any, calcemic activity and therefore may be used to treat autoimmune disorders and inflammatory diseases in humans as well as renal osteodystrophy and obesity.



RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

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## 17,20(E)-DEHYDRO VITAMIN D ANALOGS AND THEIR USES

## BACKGROUND OF THE INVENTION

5 This invention relates to vitamin D compounds, and more particularly to 17,20(E)-dehydro vitamin D analogs and their pharmaceutical uses, and especially 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D<sub>3</sub>, its biological activities, and its pharmaceutical uses.

10 The natural hormone, 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> and its analog in the ergosterol series, i.e. 1 $\alpha$ ,25-dihydroxyvitamin D<sub>2</sub> are known to be highly potent regulators of calcium homeostasis in animals and humans, and their activity in cellular differentiation has also been established, Ostrem et al., Proc. Natl. Acad. Sci. USA, 84, 2610 (1987). Many structural analogs of these metabolites have been prepared and tested, including 1 $\alpha$ -hydroxyvitamin D<sub>3</sub>, 1 $\alpha$ -hydroxyvitamin D<sub>2</sub>, various side chain 15 homologated vitamins and fluorinated analogs. Some of these compounds exhibit an interesting separation of activities in cell differentiation and calcium regulation. This difference in activity may be useful in the treatment of a variety of diseases such as renal osteodystrophy, vitamin D-resistant rickets, osteoporosis, psoriasis, and certain malignancies.

20 Another class of vitamin D analogs, i.e. the so called 19-nor-vitamin D compounds, is characterized by the replacement of the A-ring exocyclic methylene group (carbon 19), typical of the vitamin D system, by two hydrogen atoms. Biological testing of such 19-nor-analogs (e.g., 1 $\alpha$ ,25-dihydroxy-19-nor-vitamin D<sub>3</sub>) revealed a selective activity profile with high potency in inducing cellular

differentiation, and very low calcium mobilizing activity. Thus, these compounds are potentially useful as therapeutic agents for the treatment of malignancies, or the treatment of various skin disorders. Two different methods of synthesis of such 19-nor-vitamin D analogs have been described (Perlman et al., Tetrahedron Lett. 31, 1823 5 (1990); Perlman et al., Tetrahedron Lett. 32, 7663 (1991), and DeLuca et al., U.S. Pat. No. 5,086,191).

In U.S. Pat. No. 4,666,634, 2 $\beta$ -hydroxy and alkoxy (e.g., ED-71) analogs of 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> have been described and examined by Chugai group as potential drugs for osteoporosis and as antitumor agents. See also Okano et al., Biochem. 10 Biophys. Res. Commun. 163, 1444 (1989). Other 2-substituted (with hydroxyalkyl, e.g., ED-120, and fluoroalkyl groups) A-ring analogs of 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> have also been prepared and tested (Miyamoto et al., Chem. Pharm. Bull. 41, 1111 (1993); Nishii et al., Osteoporosis Int. Suppl. 1, 190 (1993); Posner et al., J. Org. Chem. 59, 7855 (1994), and J. Org. Chem. 60, 4617 (1995)).

15 2-substituted analogs of 1 $\alpha$ ,25-dihydroxy-19-nor-vitamin D<sub>3</sub> have also been synthesized, i.e. compounds substituted at 2-position with hydroxy or alkoxy groups (DeLuca et al., U.S. Pat. No. 5,536,713), with 2-alkyl groups (DeLuca et al. U.S. Patent No. 5,945,410), and with 2-alkylidene groups (DeLuca et al. U.S. Patent No. 5,843,928), which exhibit interesting and selective activity profiles. All these studies indicate that 20 binding sites in vitamin D receptors can accommodate different substituents at C-2 in the synthesized vitamin D analogs.

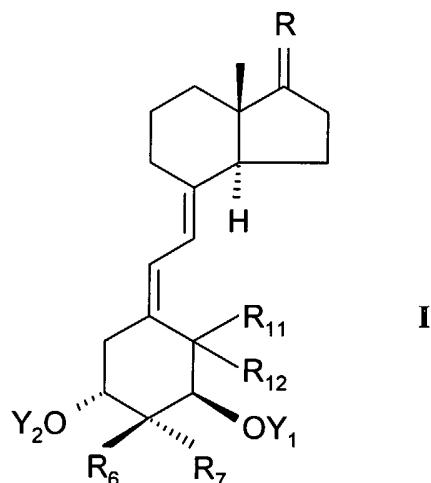
In a continuing effort to explore the 19-nor class of pharmacologically important vitamin D compounds, analogs which are characterized by the presence of a methylene substituent at carbon 2 (C-2), a hydroxyl group at carbon 1 (C-1), and a shortened side 25 chain attached to carbon 20 (C-20) have also been synthesized and tested. 1 $\alpha$ -hydroxy-2-methylene-19-nor-pregnacalciferol is described in U.S. Patent 6,566,352 while 1 $\alpha$ -hydroxy-2-methylene-19-nor-homopregnacalciferol is described in U.S. Patent 6,579,861

and 1 $\alpha$ -hydroxy-2-methylene-19-nor-bishomopregnacalciferol is described in U.S. Patent 6,627,622. All three of these compounds have relatively high binding activity to vitamin D receptors and relatively high cell differentiation activity, but little if any calcemic activity as compared to 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>. Their biological activities make 5 these compounds excellent candidates for a variety of pharmaceutical uses, as set forth in the '352, '861 and '622 patents.

### SUMMARY OF THE INVENTION

The present invention is directed toward 17,20(E)-dehydro vitamin D analogs, 10 and their pharmaceutical uses, and more specifically toward 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D<sub>3</sub>, their biological activity, and various pharmaceutical uses for these compounds.

Structurally these 17,20(E)-dehydro-vitamin D analogs are characterized by the general formula I shown below:

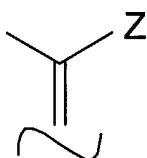


15 where Y<sub>1</sub> and Y<sub>2</sub>, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where R<sub>11</sub> and R<sub>12</sub> are each hydrogen or taken together are a methylene group, where R<sub>6</sub> and R<sub>7</sub>, which may be the same or different, are each selected from the group consisting of hydrogen,

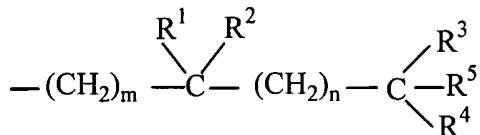
alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or R<sub>6</sub> and R<sub>7</sub> when taken together may represent the group -(CH<sub>2</sub>)<sub>x</sub>- where x is an integer from 2 to 5, or R<sub>6</sub> and R<sub>7</sub> when taken together may represent the group =CR<sub>8</sub>R<sub>9</sub> where R<sub>8</sub> and R<sub>9</sub>, which may be the same or different, are each selected from the group consisting of hydrogen,

5 alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together R<sub>8</sub> and R<sub>9</sub> may represent the group -(CH<sub>2</sub>)<sub>x</sub>- where x is an integer from 2 to 5, and where the group R represents any of the typical side chains known for vitamin D type compounds.

More specifically R can represent a saturated or unsaturated hydrocarbon radical of 1 to 35 carbons, that may be straight-chain, branched or cyclic and that may contain one or more additional substituents, such as hydroxy- or protected-hydroxy groups, fluoro, carbonyl, ester, epoxy, amino or other heteroatomic groups. Preferred side chains of this type are represented by the structure below



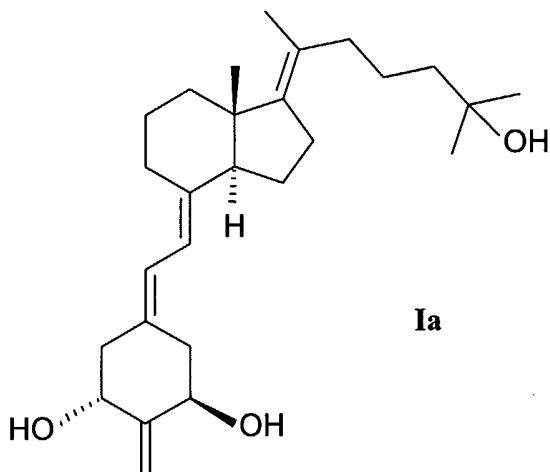
15 where the side chain and 17-ene double bond is in the E configuration and where Z is selected from Y, -OY, -CH<sub>2</sub>OY, -C≡CY and -CH=CHY, where the double bond in the side chain may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, -COR<sup>5</sup> and a radical of the structure:



20 where m and n, independently, represent the integers from 0 to 5, where R<sup>1</sup> is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C<sub>1-5</sub>-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or

protected-hydroxy substituent, and where each of R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup>, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C<sub>1-5</sub> alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R<sup>1</sup> and R<sup>2</sup>, taken together, represent an oxo group, or an alkylidene group having a general formula C<sub>k</sub>H<sub>2k</sub>– where k is an integer, the group =CR<sup>2</sup>R<sup>3</sup>, or the group –(CH<sub>2</sub>)<sub>p</sub>–, where p is an integer from 2 to 5, and where R<sup>3</sup> and R<sup>4</sup>, taken together, represent an oxo group, or the group –(CH<sub>2</sub>)<sub>q</sub>–, where q is an integer from 2 to 5, and where R<sup>5</sup> represents hydrogen, hydroxy, protected hydroxy, or C<sub>1-5</sub> alkyl and wherein any of the CH–groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups –CH(CH<sub>3</sub>)–, –(CH<sub>2</sub>)<sub>m</sub>–, –CR<sub>1</sub>R<sub>2</sub>– or –(CH<sub>2</sub>)<sub>n</sub>– at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

The preferred analog is 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D<sub>3</sub> which has the following formula **Ia**:



15

The above compounds of formula I, especially formula **Ia**, exhibit a desired, and highly advantageous, pattern of biological activity. These compounds are characterized by relatively high binding to vitamin D receptors, but very low intestinal calcium transport activity, as compared to that of 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>, and have very low ability to mobilize calcium from bone, as compared to 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>.

Hence, these compounds can be characterized as having little, if any, calcemic activity. It is undesirable to raise serum calcium to supraphysiologic levels when suppressing the preproparathyroid hormone gene (Darwish & DeLuca, Arch. Biochem. Biophys. 365, 123-130, 1999) and parathyroid gland proliferation. These analogs having little or no calcemic activity while being very active on cell differentiation are also expected to be useful as a therapy for suppression of secondary hyperparathyroidism of renal osteodystrophy.

The compounds I, and particularly Ia, of the invention have also been discovered to be especially suited for treatment and prophylaxis of human disorders which are characterized by an imbalance in the immune system, e.g. in autoimmune diseases, including multiple sclerosis, lupus, diabetes mellitus, host versus graft rejection, and rejection of organ transplants; and additionally for the treatment of inflammatory diseases, such as rheumatoid arthritis, asthma, and inflammatory bowel diseases such as celiac disease, ulcerative colitis and Crohn's disease. Acne, alopecia and hypertension are other conditions which may be treated with the compounds of the invention.

The above compounds I, and particularly Ia, are also characterized by relatively high cell differentiation activity. Thus, these compounds also provide therapeutic agents for the treatment of psoriasis, or as an anti-cancer agent, especially against leukemia, colon cancer, breast cancer, skin cancer and prostate cancer. In addition, due to their relatively high cell differentiation activity, these compounds provide therapeutic agents for the treatment of various skin conditions including wrinkles, lack of adequate dermal hydration, i.e. dry skin, lack of adequate skin firmness, i.e. slack skin, and insufficient sebum secretion. Use of these compounds thus not only results in moisturizing of skin but also improves the barrier function of skin.

The compounds of the invention of formula I, and particularly formula Ia, are also useful in preventing or treating obesity, inhibiting adipocyte differentiations, inhibiting SCD-1 gene transcription, and/or reducing body fat in animal subjects.

Therefore, in some embodiments, a method of preventing or treating obesity, inhibiting adipocyte differentiations, inhibiting SCD-1 gene transcription, and/or reducing body fat in an animal subject includes administering to the animal subject, an effective amount of one or more of the compounds or a pharmaceutical composition that includes one or more 5 of the compounds of formula I, and in particular the compound of formula Ia.

Administration of one or more of the compounds or the pharmaceutical compositions to the subject inhibits adipocyte differentiation, inhibits gene transcription, and/or reduces body fat in the animal subject.

One or more of the compounds may be present in a composition to treat or 10 prevent the above-noted diseases and disorders in an amount from about 0.01 $\mu$ g/gm to about 1000  $\mu$ g/gm of the composition, preferably from about 0.1 $\mu$ g/gm to about 500 $\mu$ g/gm of the composition, and may be administered topically, transdermally, orally, rectally, nasally, sublingually, or parenterally in dosages of from about 0.01 $\mu$ g/day to about 1000 $\mu$ g/day, preferably from about 0.1 $\mu$ g/day to about 500  $\mu$ g/day.

15

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1-5 illustrate various biological activities of 17(E)-1 $\alpha$ ,25-dihydroxy- 20 17(20)-dehydro-2-methylene-19-norvitamin D<sub>3</sub>, hereinafter referred to as "VIT-III," as compared to the native hormone 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>, hereinafter "1,25(OH)<sub>2</sub>D<sub>3</sub>."

Figure 1 is a graph illustrating the relative activity of VIT-III and 1,25(OH)<sub>2</sub>D<sub>3</sub> to compete for binding with [<sup>3</sup>H]-1,25-(OH)<sub>2</sub>-D<sub>3</sub> to the full-length recombinant rat vitamin D receptor;

Figure 2 is a graph illustrating the percent HL-60 cell differentiation as a function of the concentration of VIT-III and 1,25(OH)<sub>2</sub>D<sub>3</sub>;

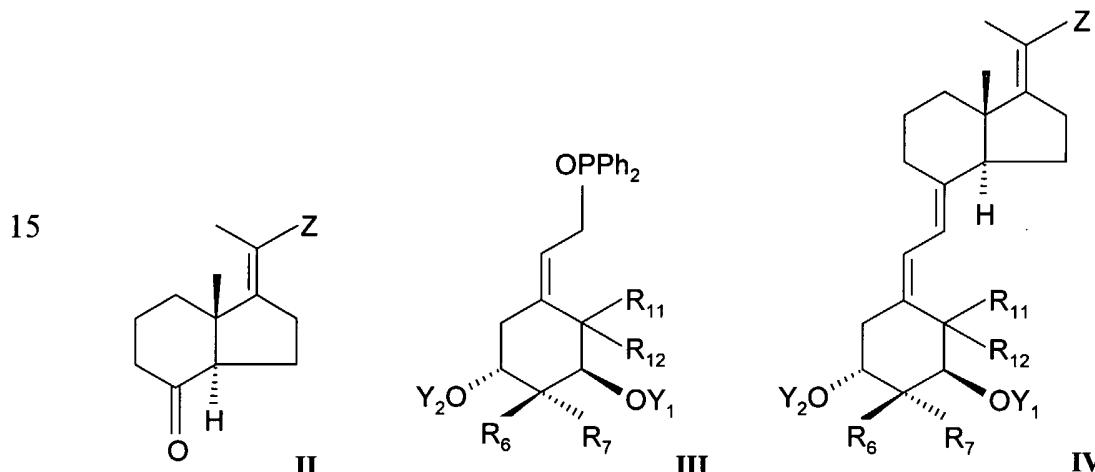
25 Figure 3 is a graph illustrating the in vitro transcription activity of 1,25(OH)<sub>2</sub>D<sub>3</sub> as compared to VIT-III;

Figure 4 is a bar graph illustrating the bone calcium mobilization activity of  $1,25(\text{OH})_2\text{D}_3$  as compared to VIT-III; and

Figure 5 is a bar graph illustrating the intestinal calcium transport activity of  $1,25(\text{OH})_2\text{D}_3$  as compared to VIT-III.

## DETAILED DESCRIPTION OF THE INVENTION

The preparation of 17,20(E)-dehydro vitamin D analogs having the structure I can be accomplished by a common general method, i.e. the condensation of a bicyclic Windaus-Grundmann type ketone II with the allylic phosphine oxide III to the corresponding 17,20(E)-dehydro vitamin D analog IV followed by deprotection at C-1 and C-3 to provide I:



20 In the structures III and IV, groups  $Y_1$  and  $Y_2$  are hydroxy-protecting groups, preferably t-butyldimethylsilyl, it being also understood that any functionalities that might be sensitive, or that interfere with the condensation reaction, be suitably protected as is well-known in the art. The process shown above represents an application of the convergent synthesis concept, which has been applied effectively for the preparation of vitamin D compounds [e.g. Lythgoe et al., J. Chem. Soc. Perkin Trans. I, 590 (1978); Lythgoe, Chem. Soc. Rev. 9, 449 (1983); Toh et al., J. Org. Chem. 48, 1414 (1983); Baggolini et al., J. Org. Chem. 51, 3098 (1986); Sardina et al., J. Org. Chem. 51, 1264 (1986); J. Org.

Chem. 51, 1269 (1986); DeLuca et al., U.S. Pat. No. 5,086,191; DeLuca et al., U.S. Pat. No. 5,536,713].

The hydrindanones of the general structure II are not known. They can be prepared by the method shown in the Schemes herein (see the preparation of compound 5 VIT-III).

For the preparation of the required phosphine oxides of general structure III, a synthetic route has been developed starting from a methyl quinate derivative which is easily obtained from commercial (IR,3R,4S,5R)-(-)-quinic acid as described by Perlman et al., Tetrahedron Lett. 32, 7663 (1991) and DeLuca et al., U.S. Pat. No. 5,086,191.

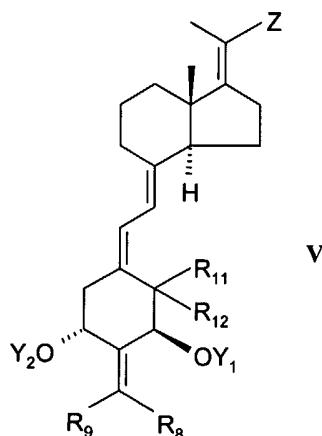
10 The overall process of the synthesis of compounds I and Ia is illustrated and described more completely in U.S. Patent No. 5,843,928 entitled "2-Alkylidene-19-Nor-Vitamin D Compounds" the specification of which is specifically incorporated herein by reference.

15 Particularly preferred 17,20(E)-dehydro vitamin D analogs are those encompassed by general formula I wherein carbon-2 on the A-ring is substituted with an alkylidene group or an alkyl group, or are hydrolyzable slow release compounds (whether substituted at carbon-2 or not substituted at carbon-2).

### 2-Alkylidene Compounds

20 Structurally these 2-alkylidene analogs are characterized by the general formula V shown below:

25



where  $Y_1$ ,  $Y_2$ ,  $R_{11}$ ,  $R_{12}$  and  $Z$  are as previously defined herein, and  $R_8$  and  $R_9$ , which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl and fluoroalkyl, or, when taken together represent the group

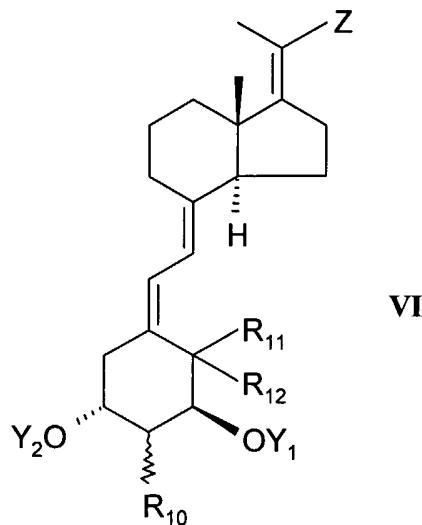
5  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5.

### 2-Alkyl Compounds

Structurally these 2-alkyl analogs are characterized by the general formula VI shown below:

10

15



where  $Y_1$ ,  $Y_2$ ,  $R_{11}$ ,  $R_{12}$  and  $Z$  are as previously defined herein, and  $R_{10}$  is selected from

20 the group consisting of alkyl, hydroxyalkyl and fluoroalkyl.

### Slow Release Compounds

Modified vitamin D compounds that exhibit a desirable and highly advantageous pattern of biological activity in vivo, namely, the more gradual onset and more prolonged duration of activity, may also be used herein.

Structurally, the key feature of the modified vitamin D compounds having these desirable biological attributes is that they are derivatives of 17,20(E)-dehydro-vitamin D analogs, in which a hydrolyzable group is attached to the hydroxy group at carbon 25 and,

optionally, to any other of the hydroxy groups present in the molecule. Depending on various structural factors -- e.g. the type, size, structural complexity -- of the attached group, these derivatives hydrolyze to the active 17,20(E)-dehydro-vitamin D analog, at different rates *in vivo*, thus providing for the “slow release” of the biologically active 5 vitamin D compound in the body.

The “slow release” *in vivo* activity profiles of such compounds can, of course, be further modulated by the use of mixtures of derivatives or the use of mixtures consisting of one or more vitamin D derivative together with underivatized vitamin D compounds.

It is important to stress that the critical structural feature of the vitamin 10 derivatives identified above is the presence of a hydrolyzable group attached to the hydroxy group at carbon 25 of the molecule. The presence of a hydrolyzable group at that position imparts on the resulting derivatives the desirable “slow-release” biological activity profile mentioned above. Other hydroxy functions occurring in the molecule (e.g. hydroxy functions at carbons 1 or 3) may be present as free hydroxy groups, or one 15 or more of them may also be derivatived with a hydrolyzable group.

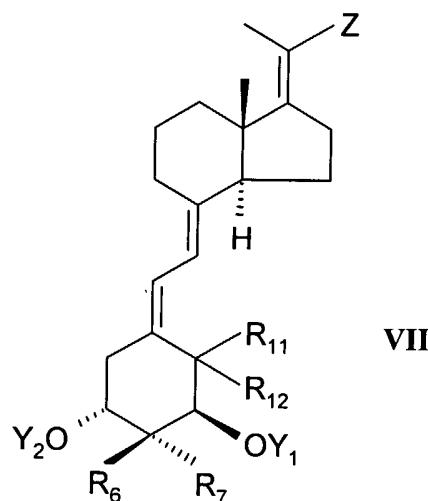
The “hydrolyzable group” present in the above-mentioned derivatives is preferably an acyl group, i.e. a group of the type  $Q^1CO-$ , where  $Q^1$  represents hydrogen or a hydrocarbon radical of from 1 to 18 carbons that may be straight chain, cyclic, branched, saturated or unsaturated. Thus, for example, the hydrocarbon radical may be a 20 straight chain or branched alkyl group, or a straight chain or branched alkenyl group with one or more double bonds, or it may be an optionally substituted cycloalkyl or cycloalkenyl group, or an aromatic group, such as substituted or unsubstituted phenyl, benzyl or naphthyl. Especially preferred acyl groups are alkanoyl or alkenoyl groups, of which some typical examples are formyl, acetyl, propanoyl, hexanoyl, isobutyryl, 2- 25 butenoyl, palmitoyl or oleoyl. Another suitable type of hydrolyzable group is the hydrocarbyloxycarbonyl group, i.e. a group of the type  $Q^2-O-CO-$ , where  $Q^2$  is a  $C_1$  to  $C_{18}$  hydrocarbon radical as defined above. Exemplary of such hydrocarbon radicals are methyl, ethyl, propyl, and higher straight chain or branched alkyl and alkenyl radicals, as well as aromatic hydrocarbon radicals such as phenyl or benzoyl.

These modified vitamin D compounds are hydrolyzable in vivo to the active analog over a period of time following administration, and as a consequence regulate the in vivo availability of the active analog, thereby also modulating their activity profile in vivo. The term "activity profile" refers to the biological response over time of vitamin D compounds. Individual modified compounds, or mixtures of such compounds, can be administered to "fine tune" a desired time course of response.

As used herein the term "modified vitamin D compound" encompasses any vitamin D compound in which one or more of the hydroxy functions present in such a compound are modified by derivatization with a hydrolyzable group. A "hydrolyzable group" is a hydroxy-modifying group that can be hydrolyzed in vivo, so as to regenerate the free hydroxy functions.

In the context of this disclosure, the term hydrolyzable group preferably includes acyl and hydrocarbyloxycarbonyl groups, i.e. groups of the type  $Q^1CO-$  and  $Q^2-O-CO$ , respectively, where  $Q^1$  and  $Q^2$  have the meaning defining earlier.

Structurally, the modified vitamin D compounds encompassed may be represented by the formula **VII** shown below:



where  $Y_1$ ,  $Y_2$ ,  $R_{11}$ ,  $R_{12}$ ,  $R_6$ ,  $R_7$  and  $Z$  are as previously defined herein with respect to formula **I** with the exception that  $R^5$  in the side chain is  $-OY_3$  and  $Y_3$  is an acyl group or a hydrocarbyloxycarbonyl group, as previously defined herein.

Some specific examples of such modified vitamin D compounds include 2-substituted derivatives such as:

1,3,25-Triacetates where  $Y_1=Y_2=Y_3$  and is  $CH_3CO$ ;

1,3,25-Trihexanoates where  $Y_1=Y_2=Y_3$  and is  $CH_3(CH_2)_4CO$ ;

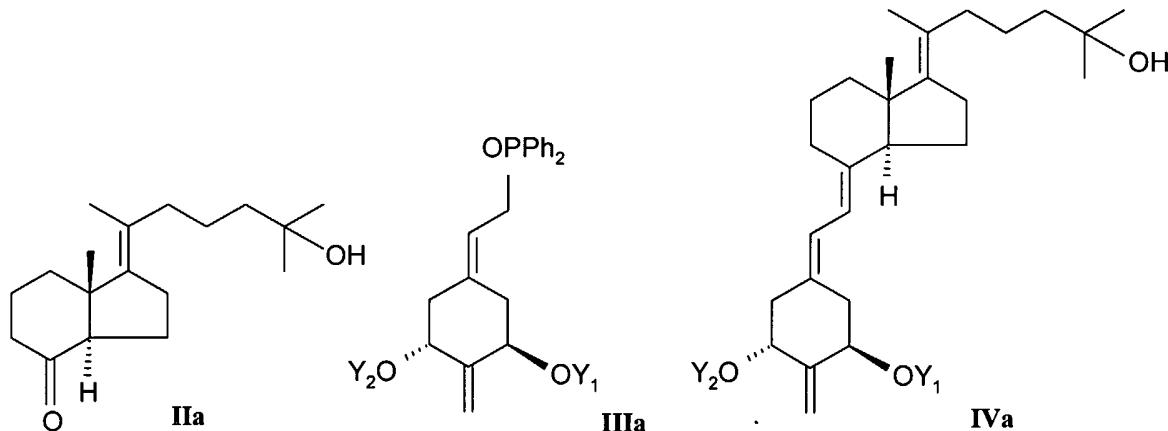
5 1,3,25-Trinonanoates where  $Y_1=Y_2=Y_3$  and is  $CH_3(CH_2)_7CO$ ; and

25-Acetates where  $Y_1=Y_2$  and is H and  $Y_3$  is  $CH_3CO$ .

These compounds can be prepared by known methods. See for example WO97/11053 published March 27, 1999, and the previous description herein.

10 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> (referred to herein as VIT-III) was synthesized and tested. Structurally, this 19-nor analog is characterized by the general formula **Ia** previously illustrated herein.

15 The preparation of 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> having the structure **Ia** can be accomplished by the condensation of a bicyclic Windaus-Grundmann type ketone **IIa** with the allylic phosphine oxide **IIIa** to the corresponding 17(20)-dehydro-vitamin D analog **IVa** followed by deprotection at C-1 and C-3 to provide **Ia**:



20 In the structures **IIIa** and **IVa**, groups  $Y_1$  and  $Y_2$  are hydroxy-protecting groups, preferably t-butyldimethylsilyl, it being also understood that any functionalities that might be sensitive, or that interfere with the condensation reaction, be suitably protected as is well-known in the art. The process shown above represents a specific application of

the convergent synthesis concept, which was referred to previously herein and has been applied effectively for the preparation of vitamin D compounds

The hydrindanone of the general structure **IIa** is not known. It can be prepared by the method shown in the Schemes herein (see the preparation of compound VIT-III).

5 As used in the description and in the claims, the term "hydroxy-protecting group" signifies any group commonly used for the temporary protection of hydroxy functions, such as for example, alkoxycarbonyl, acyl, alkylsilyl or alkylarylsilyl groups (hereinafter referred to simply as "silyl" groups), and alkoxyalkyl groups. Alkoxycarbonyl protecting groups are alkyl-O-CO- groupings such as methoxycarbonyl, ethoxycarbonyl, 10 propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl or allyloxycarbonyl. The term "acyl" signifies an alkanoyl group of 1 to 6 carbons, in all of its isomeric forms, or a carboxyalkanoyl group of 1 to 6 carbons, such as an oxanyl, malonyl, succinyl, glutaryl group, or an aromatic acyl group such as benzoyl, or a halo, nitro or alkyl substituted benzoyl group. The word 15 "alkyl" as used in the description or the claims, denotes a straight-chain or branched alkyl radical of 1 to 10 carbons, in all its isomeric forms. "Alkoxy" refers to any alkyl radical which is attached by oxygen, i.e. an alkyl-o-group. Alkoxyalkyl protecting groups are groupings such as methoxymethyl, ethoxymethyl, methoxyethoxymethyl, or tetrahydrofuryl and tetrahydropyranyl. Preferred silyl-protecting groups are 20 trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, dibutylmethylsilyl, diphenylmethylsilyl, phenyldimethylsilyl, diphenyl-t-butylsilyl and analogous alkylated silyl radicals. The term "aryl" specifies a phenyl-, or an alkyl-, nitro- or halo-substituted phenyl group.

A "protected hydroxy" group is a hydroxy group derivatised or protected by any of the above groups commonly used for the temporary or permanent protection of 25 hydroxy functions, e.g. the silyl, alkoxyalkyl, acyl or alkoxycarbonyl groups, as previously defined. The terms "hydroxyalkyl", "deuteroalkyl" and "fluoroalkyl" refer to an alkyl radical substituted by one or more hydroxy, deuterium or fluoro groups respectively. An "alkylidene" refers to a radical having the general formula  $C_kH_{2k}$ -where k is an integer.

More specifically, reference should be made to the following description as well as to the Schemes herein for a detailed illustration of the preparation of compound VIT-III.

5

## SYNTHESIS

**Des-A,B-23,24-dinorcholan-8 $\beta$ ,22-diol (2).** A flame dried 1000 mL two necked flask was charged with ergocalciferol **1** (5 g, 12.6 mmol), pyridine (5 mL), and anhydrous MeOH (400 mL). The solution was cooled to -78 °C in an argon atmosphere. O<sub>3</sub> was bubbled through the solution until a deep blue color developed and persisted (about 10 h). The solution was treated with O<sub>2</sub> until the blue color faded (15 min). Then NaBH<sub>4</sub> (1.5 g, 39.7 mmol) was added. After 15 min. second portion of NaBH<sub>4</sub> (1.5 g, 39.7 mmol) was added and the reaction was allowed to warm to rt. Then the third portion of NaBH<sub>4</sub> (1.5 g, 39.7 mmol) was added and reaction stirred for over night. The reaction was quenched by adding water (50 mL). Methanol was evaporated in vacuo and residue was dissolved in ethyl acetate. The organic phase was washed with 1N aqueous solution of HCl (100 mL), saturated NaHCO<sub>3</sub> solution (100 mL) and brine (100 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. Purification by silica gel chromatography (25% ethyl acetate/hexane) afforded 2.18 g (10.3 mmol, 81%) of diol **2** as a white solid. Mp 110-111 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 0.96 (3H, s), 1.03 (3H, d, *J* = 6.6 Hz), 3.38 (1H, dd, *J* = 10.5, 6.7 Hz), 3.64 (1H, dd, *J* = 10.5, 3.2 Hz), 4.09 (1H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 69.2, 67.8, 52.9, 52.4, 41.8, 40.2, 38.2, 33.6, 26.6, 22.6, 17.4, 16.6, 13.6; MS *m/z* (relative intensity): 212 (M<sup>+</sup>, 2), 194 (M<sup>+</sup>-H<sub>2</sub>O, 15), 179 (M<sup>+</sup>-H<sub>2</sub>O-CH<sub>3</sub>, 18), 125 (43), 111 (100); exact mass calculated for C<sub>13</sub>H<sub>22</sub>O [M - H<sub>2</sub>O]<sup>+</sup> is 194.1671, measured is 194.1665.

25

**Des-A,B-22-(*p*-toluenesulfonyloxy)-23,24-dinorcholan-8 $\beta$ -ol (3).** A solution of diol **2** (1 g, 4.71 mmol) in anhydrous pyridine (12 mL) was cooled to -25 °C and a precooled solution of tosyl chloride (1.08 g, 5.66 mmol) in anhydrous pyridine (2mL) was added dropwise. The reaction mixture was stirred at that temperature for 4 h and

allowed to warm to 0 °C and stirred at that temperature for additional 20 h. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and washed with saturated CuSO<sub>4</sub> solution (30 mL), 1N HCl (30 mL), and water (50 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. Purification by silica gel chromatography (25% ethyl

5 acetate/hexane) yielded 1.7 g (4.64 mmol, 98%) of hydroxyl tosylate **3**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 0.89 (3H, s), 0.96 (3H, d, *J* = 6.6Hz), 2.45 (3H, s), 3.8 (1H, dd, *J* = 9.2, 6.2 Hz), 3.95 (1H, dd, *J* = 9.2, 3.0 Hz), 4.06 (1H, m), 7.35 (2H, d, *J* = 8.2 Hz), 7.78 (2H, d, *J* = 8.2 Hz); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>) δ: 144.7, 133.0, 129.8, 127.9, 75.6, 69.0, 60.4, 52.2, 41.9, 40.1, 35.7, 33.5, 26.4, 22.4, 21.6, 17.3, 16.7, 13.4; MS *m/z* 10 (relative integration): 366 (M<sup>+</sup>, 6), 194(14), 179(16), 125(30), 111(100); exact mass calculated for C<sub>20</sub>H<sub>30</sub>SO<sub>4</sub>Na (M + Na<sup>+</sup>) is 389.1763, measured is 389.1768.

**Des-A,B-8β-[(*tert*-butyldimethylsilyl)oxy]-22-(*p*-toluenesulfonyloxy)-23,24-dinorcholane (**4**).** To a 0 °C cooled solution of hydroxyl tosylate **3** (1.5 g, 4.09 mmol)

15 in anhydrous DMF (20 mL) was added 2,6-lutidine (0.580 mL, 0.52 g, 4.92 mmol) followed by TBSOTf (1.13 mL, 1.30g, 4.92 mmol). The solution was stirred at 0 °C for 15 min and water (10 mL) was added. The mixture was extracted with ethyl acetate (3 x 40 mL), and combined organic phases were washed with 1N aqueous solution of NaOH (40 mL) dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was 20 purified by silica gel column chromatography (5% ethyl acetate/hexane) to give 1.94g (4.04 mmol, 99%) of **4**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 0.01 (6H, s), 0.88 (12H, s), 0.96 (3H, d, *J* = 6.8Hz), 2.45 (3H, s), 3.81 (1H, dd, *J* = 9.2, 6.4Hz), 3.97 (1H, dd, *J* = 9.7, 3.0Hz), 3.99 (1H, m), 7.34 (2H, d, *J* = 8.08Hz), 7.79 (2H, d, *J* = 8.2Hz). <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>) δ: 114.5, 133.4, 129.8, 127.9, 74.8, 69.3, 52.3, 52.6, 42.2, 40.5, 25 35.8, 34.4, 26.6, 25.9, 23.0, 21.6, 18.0, 17.6, 16.8, 13.7, -4.8, -5.1.

**Des-A,B-8β-[(*tert*-butyldimethylsilyl)oxy]-23,24-dinorcholan-22-al (**5**).** A solution of **4** (1.9 g, 3.96 mmol) in DMSO (5 mL) was added to a suspension of NaHCO<sub>3</sub> (1.5 g, 17.9 mmol) in DMSO (20 mL) at rt. The mixture was heated to 150 °C under argon

for 15 min and cooled to rt. Water (50 mL) followed by ethyl acetate (50 mL) were added and aqueous phase was extracted with ethyl acetate (3 x 30 mL). The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. The residue was purified by column chromatography (2% ethyl acetate/hexane) to afford 0.93g (2.87 mmol, 76%) of aldehyde **5**.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.01 (6H, 2s), 0.89 (9H, s), 0.97 (3H, s), 1.09 (3H, d,  $J$  = 6.8Hz), 2.35 (1H, m), 4.03 (1H, m), 9.58 (1H, d,  $J$  = 3.2Hz).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ )  $\delta$ : 205.2, 69.1, 52.4, 51.8, 49.1, 42.7, 40.5, 30.8, 34.3, 26.2, 25.8, 23.3, 17.6, 14.1, 13.3, -4.7, -5.1.

10 **Des-A,B-8 $\beta$ -[(*tert*-butyldimethylsilyl)oxy]-pregnan-20-one (6).** A flame dried flask was charged with *t*-BuOK (1.55 g, 13.9 mmol) and anhydrous *t*-BuOH (30 mL) at room temperature.  $\text{O}_2$  was bubbled through the solution for 15 min. A solution of aldehyde **5** (0.9 g, 2.78 mmol) in anhydrous *t*-BuOH (15 mL) was added to the reaction mixture and  $\text{O}_2$  was bubbled through the solution for additional 10 min. The 15 reaction was quenched with water (15 mL) and extracted with ether (3 x 30 mL). The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. The residue was purified by silica gel column chromatography (3% ethyl acetate/hexane) to give 0.61 g (1.97 mmol, 71%) of the ketone **6**.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.01 (6H, s), 0.84 (3H, s), 0.87 (9H, s), 2.08 (3H, s), 2.46 (1H, t,  $J$  = 9.1Hz), 4.03 (1H, m).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ )  $\delta$ : 209.5, 69.0, 64.5, 53.2, 43.7, 39.8, 34.2, 31.6, 25.8, 23.2, 21.8, 17.6, 15.5, -4.8, -5.2.

25 **5-Bromo-2-methyl-2-pentanol (8).** To a -20 °C cooled solution of ethyl-4-bromobutyrate **7** (5g, 25.6 mmol) in anhydrous diethyl ether (50 mL) was added 3M solution of methylmagnesium bromide in diethyl ether (17.1 mL, 6.11 g, 51.3 mmol) under argon atmosphere over a period of 30min. The reaction mixture was stirred at room temperature for overnight. Saturated ammonium chloride solution was added to hydrolyse the reaction mixture followed by 1N HCl solution to dissolve the inorganic salts formed. The aqueous phase was extracted with ether (3 x 50mL). The combined

extracts were washed with water (100 mL), saturated NaCl solution (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was purified by silica gel column chromatography (20/80 ethyl acetate/hexane) to afford 3.1g (17.1 mmol, 67%) of tertiary alcohol. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 1.27 (6H, s), 1.64 (2H, m), 1.96 (2H, m), 3.44 (2H, t, J = 6.68 Hz).

5 **5-Bromo-2methyl-2[(*tert*-butyldimethylsilyl)oxy]-pentane (9).** To a -50 °C cooled solution of alcohol **8** (3 g, 16.6 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added 2,6-lutidine (2.32 mL, 2.13 g, 19.89 mmol) followed by TBSOTf (4.57 mL, 5.26 g, 19.9 mmol). The solution was stirred at 0 °C for 15 min and water (10 mL) was added. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 40 mL), and combined organic phases were washed with 1N aqueous solution of NaOH (40 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was purified by silica gel column chromatography (1% ethyl acetate/hexane) to give 3.9 g (13.2 mmol, 80%) of **9**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 0.07 (6H, s), 0.85 (9H, s), 1.21 (6H, s), 1.55 (2H, m), 1.95 (2H, m), 3.41 (2H, t, J = 6.8Hz)

**Des-A,B-cholest-17(20)-dehydro-8β,25-diols (15a and 15b):**

20 A solution of 5-bromo-2methyl-2[(*tert*-butyldimethylsilyl)oxy] pentane **9** (2.84g, 9.68 mmol) in anhydrous ether (20 mL, containing catalytic amount of iodine) was added dropwise to a stirred suspension of magnesium powder (0.23 g, 9.68 mmol) in anhydrous diethyl ether (5 mL) at room temperature with occasional warming it up to 35 °C under argon atmosphere. After generation of the Grignard reagent was complete the mixture was stirred for 1hr at room temperature and for 1hr at 40 °C. Then it was 25 cooled to 0 °C and a solution of ketone **6** (0.6 g, 1.94 mmol) in anhydrous diethyl ether (10 mL) was added dropwise over a period of 30 min. After stirring the reaction mixture at room temperature for 3h it was hydrolysed with aqueous solution of NH<sub>4</sub>Cl (20 mL). The organic layer was separated and aqueous phase was extracted with ethyl acetate (3 x 30 mL). The combined organic phases were washed with water (40 mL),

dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. Silica gel column chromatography of the residue gave 0.95 g (94%) of mixture of alcohols **10**. Phosphorous oxychloride (3 mL) was added dropwise to a solution of mixture of alcohols **10** (0.95 g, 1.8 mmol) in anhydrous pyridine (20 mL) under argon atmosphere. The reaction was stirred at room 5 temperature overnight and poured into ice-water and extracted with ether (3 x 20 mL). The organic layer was washed with saturated  $\text{CuSO}_4$  solution (30 mL), 1N HCl (30 mL), water (50 mL). The organic phase was dried ( $\text{NaSO}_4$ ), filtered and concentrated. Column Chromatography of crude mixture furnished 0.72 g (78%) of mixture of 10 olefins **11a**, **11b**, **12a**, **12b**, **13**. The olefin mixture without further purification was dissolved in methanol (20 mL) and *p*-Toluenesulfonic acid monohydrate (*p*-TSA) (0.100g) was added at 0  $^{\circ}\text{C}$ . The reaction mixture was stirred at room temperature for 3 days [Additional amounts of *p*-TSA were successively added (100 mg, 24h; 75 mg, 15 36h; 50 mg, 48h)]. Methanol was evaporated and residue was diluted with ethyl acetate (30 mL). The organic phase was washed with saturated aqueous  $\text{NaHCO}_3$  solution (20 mL) water (20 mL), dried ( $\text{Na}_2\text{CO}_3$ ) and evaporated. The residue was purified on column chromatography to yield 0.284 g (79%) of a mixture of olefin 15 alcohols **14a**, **14b**, **15a**, **15b**, **16**. The olefin alcohols were separated on HPLC.

**17(E)-Des-A,B-cholestan-17(20)-dehydro-8 $\beta$ ,25-diol (15a).** The olefin alcohols 20 were separated on HPLC (9.4 mm x 25 cm zorbax-sil column, 4ml/min) using IPA/hexane (4/96) solvent system. Pure diol 17-20E **15a** 70 mg (250  $\mu\text{mol}$ , 25%) was eluted at  $\text{R}_v$  = 50 mL.  $[\alpha]^{25}_{\text{D}} -16.5^0$  (c 1.02,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.09 (3H, s), 1.20 (6H, s), 1.67 (3H, t,  $J$  = 1.84Hz), 4.14 (1H, m).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ )  $\delta$ : 143.2, 123.7, 71.0, 69.8, 52.4, 43.9, 43.7, 38.3, 36.8, 33.4, 29.2, 28.5, 23.5, 25 22.2, 19.1, 17.9, 17.2. MS  $m/z$  (relative intensity): 280 ( $\text{M}^+$ , 16), 262 ( $\text{M}-\text{H}_2\text{O}^+$ , 7), 229 ( $\text{M}-2x\text{H}_2\text{O}-\text{CH}_3^+$ , 16) 179(54), 161(100); Exact mass calculated for  $\text{C}_{18}\text{H}_{32}\text{O}_2$   $[\text{M}+\text{Na}]^+$  is 303.2300, found 303.2297.

**17(E)-25-(Triethylsilyloxy)-des-A,B-cholestan-17(20)-dehydro-8-one (17a).** To a solution of alcohol **15a** (20 mg, 71  $\mu$ mol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (5 mL) was added PDC (40 mg, 107  $\mu$ mol) at rt. After stirring the reaction for 3 h under argon atmosphere the solution was passed through a pad of celite with ethyl acetate. The 5 filtrate was concentrated and applied on a Sep-Pak cartridge and eluted with ethyl acetate/hexane (20/80) to give 17 mg, (61.1  $\mu$ mol, 86%) of ketone as colorless oil. To a -50  $^{\circ}\text{C}$  cooled solution of ketone (17 mg, 61.1  $\mu$ mol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (5 mL) was added 2,6-lutidine (9  $\mu$ L, 7.86 mg, 73.3  $\mu$ mol) followed by TESOTf (17  $\mu$ L, 19.4 mg, 73.3  $\mu$ mol). The solution was stirred at 0  $^{\circ}\text{C}$  for 15 min and water (5 mL) was 10 added. The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 5 mL), and combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. The ketone was purified on HPLC (9.4-mm x 25-cm Zorbax-Sil column, 4ml/min) using 10% ethyl acetate/hexane solvent system. Pure ketone **17a** 14.4 mg (36.7  $\mu$ mol, 60%) was eluted at  $R_v$  = 20 mL as colorless oil.  $[\alpha]^{25}_{\text{D}} -14.4$  ( $c$  0.73,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz, 15  $\text{CDCl}_3$ )  $\delta$ : 0.56 (6H, q,  $J$  = 7.7Hz), 0.84 (3H, s), 0.94 (9H, t,  $J$  = 4.76Hz), 1.18 (6H, s), 1.71 (3H, t,  $J$  = 1.84Hz), 2.57 (1H, dd,  $J$  = 12, 6.2 Hz).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ )  $\delta$ : 212.2, 141.2, 126.1, 73.3, 61.8, 50.5, 44.7, 40.6, 36.9, 36.7, 29.9, 29.8, 28.7, 23.9, 22.1, 20.2, 17.8, 17.6, 7.1, 6.8. MS  $m/z$  (relative intensity): No  $\text{M}^+$ , 377( $[\text{M}-\text{CH}_3]^+$ , 3) 363( $[\text{M}-\text{C}_2\text{H}_5]^+$ , 9), 204(100), 189((18), 161(45). Exact mass calculated for 20  $\text{C}_{24}\text{H}_{44}\text{O}_2\text{Si} [\text{M}+\text{Na}]^+$  is 415.3008, found 415.3016.

**17(E)-1 $\alpha$ ,25 Dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D<sub>3</sub> (20a).** To a solution of phosphine oxide **18** (0.051 g, 87.6  $\mu$ mol) in anhydrous THF (500  $\mu$ L) at -25  $^{\circ}\text{C}$  was slowly added PhLi 1.2M in cyclohexane/ether (70/30) (80  $\mu$ L, 8.1 mg, 96.4  $\mu$ mol) under argon with stirring. The solution turned deep orange. The mixture was 25 stirred at that temperature for 20 min and cooled to -78  $^{\circ}\text{C}$ . A precooled (-78  $^{\circ}\text{C}$ ) solution of ketone **17a** (14 mg, 35.7  $\mu$ mol) in anhydrous THF (100  $\mu$ L) was added slowly. The mixture was stirred under argon atmosphere at -78  $^{\circ}\text{C}$  for 3h and at 0  $^{\circ}\text{C}$  for 18h. Ethyl acetate was added and organic phase was washed with brine, dried

(Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was applied on a Sep-Pak cartridge, and eluted with 1% ethyl acetate/hexane to give 19-nor protected vitamin derivative **19a** (8 mg of unreacted ketone **17a** was recovered). The protected vitamin was further purified by HPLC (9.4-mm x 25-cm Zorbax-Sil column, 4ml/min) using hexane/IPA (99.95/0.05) solvent system. Pure compound **19a**, 7.7mg (10.2  $\mu$ mol, 29%) was eluted at  $R_v = 20$  mL as colorless oil. UV (in hexane)  $\lambda_{max}$  243.1, 252, 262.2 nm; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 0.03, 0.05, 0.07, 0.08 (each 3H, each s), 0.56 (6H, q, J = 7.8 Hz), 0.74 (3H, s), 0.87 and 0.91 (each 9H, each s), 0.96 (9H, t, J = 7.8 Hz), 1.19 (6H, s), 1.68(3H, t, J = 1.86 Hz), 2.18 (1H, dd, J = 12.6, 8.3 Hz), 2.33 (1H, m) 2.46 (1H, dd, 12.6, 4.6 Hz), 2.53 (1H, dd, 13.3, 5.88 Hz), 2.80 (1H, m), 4.43 (2H, m), 4.93 and 4.97 (1H and 1H, each s), 5.88 and 6.21 (1H and 1H, each d, J = 11.2 Hz); MS *m/z* (relative intensity): No M<sup>+</sup>, 624(59), 366(32), 91(100); Exact mass calculated for C<sub>45</sub>H<sub>84</sub>O<sub>3</sub>Si<sub>3</sub> [M+Na]<sup>+</sup> is 779.5626, found 779.5648.

The protected vitamin **19a** (7.7 mg, 10.2  $\mu$ mol) was dissolved in anhydrous THF (500  $\mu$ L) and treated with TBAF (0.102 mL, 26.7 mg, 102  $\mu$ mol) and stirred at rt in dark for overnight. The solvent was removed in vaccuo and residue was applied on Sep-Pak cartridge, and eluted with 30% ethyl acetate/hexane to get the deprotected vitamin **20a**. The vitamin was further purified by HPLC (9.4-mm x 25-cm Zorbax-Sil column, 3 mL/min) using hexane/IPA (90/10) as solvent system. Pure vitamin **20a**, 2.9 mg (7  $\mu$ mol, 69%) was collected at  $R_v = 42$  mL as white solid: UV (in EtOH)  $\lambda_{max}$  242.9, 251, 261.2 nm; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 0.74 (3H, s), 1.22 (6H, s), 1.69 (3H, t, J = 1.94 Hz,), 2.29 (1H, dd, J = 13.0, 8.39 Hz), 2.32 (1H, dd, J = 13.9, 7.0 Hz), 2.57 (1H, dd, J = 13.4, 3.49 Hz), 2.79 (1H, br d) 2.87(1H, dd, J = 13.0, 4.59 Hz), 4.49 (2H, m), 5.09 and 5.11 (1H and 1H, each s), 5.92 and 6.35 (1H and 1H, each d, J = 11.29 Hz); MS *m/z* (relative intensity): 414 (M<sup>+</sup>, 36), 396([M-H<sub>2</sub>O]<sup>+</sup>, 6), 381([M-H<sub>2</sub>O-CH<sub>3</sub>]<sup>+</sup>, 8) 285(70), 149(61), 69(100).

**17(Z)-Des-A,B-cholest-17(20)-dehydro-8 $\beta$ ,25-diol (15b).** The olefin alcohols were separated on HPLC (9.4 mm x 25 cm zorbax-sil column, 4ml/min) using IPA/hexane

(5/95) solvent system. Diol 17-20Z **15b** and Diol 20-21 **16** eluted out together at  $R_v$  = 45 mL. The alcohols were oxidized together.

**17(Z)-25-(Triethylsilyloxy)-des-A,B-cholest-17(20)-dehydro-8-one (17b).** To a solution of mixture of alcohols **15b** and **16** (34 mg, 121  $\mu$ mol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (5 mL) was added PDC (55 mg, 145.7  $\mu$ mol) at rt. After stirring the reaction for 3h under argon atmosphere the solution was passed through a pad of celite with ethyl acetate. The filtrate was concentrated and applied on a Sep-Pak cartridge and eluted with ethyl acetate/hexane (20/80) to give a mixture of ketones **17b** and **16b** 30.2 mg (108.6  $\mu$ mol, 89%) as colorless oil. To a -50  $^{\circ}\text{C}$  cooled solution of ketones 30.2 mg (30.2 mg, 108.6  $\mu$ mol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (10 mL) was added 2,6-lutidine (16  $\mu$ L, 13.9 mg, 130.3  $\mu$ mol) followed by TESOTf (30  $\mu$ L, 34.5 mg, 130.3  $\mu$ mol). The solution was stirred at 0  $^{\circ}\text{C}$  for 15min and water (10 mL) was added. The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 5 mL), and combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. The residue was purified by HPLC (9.4-mm x 25-cm Zorbax-Sil column, 4 ml/min) using ethyl acetate/hexane (5/95) solvent system. Pure ketone **17b** 7.7 mg (19.6  $\mu$ mol, 18%) was eluted at  $R_v$  = 34mL as colorless oil.  $^1\text{H}$  NMR (400.13 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.56 (6H, q,  $J$  = 7.78 Hz), 0.83 (3H, s), 0.94 (9H, t,  $J$  = 7.9 Hz), 1.2 (6H, s), 1.57 (3H, br s), 2.57 (1H, dd,  $J$  = 11.8, 6.3 Hz);  $^{13}\text{C}$ NMR (100MHz,  $\text{CDCl}_3$ )  $\delta$ : 212.18, 141.1, 126.8, 73.2, 62.0, 50.5, 45.3, 40.7, 37.1, 34.5, 29.9, 29.8, 24.0, 23.8, 20.2, 20.1, 18.7, 7.1, 6.8. MS  $m/z$  (relative intensity): No  $\text{M}^+$ , 363 ( $[\text{M} - \text{C}_2\text{H}_5]^+$ , 10), 334 ( $[\text{M} - 2\text{xC}_2\text{H}_5]^+$ , 1), 204 (100).

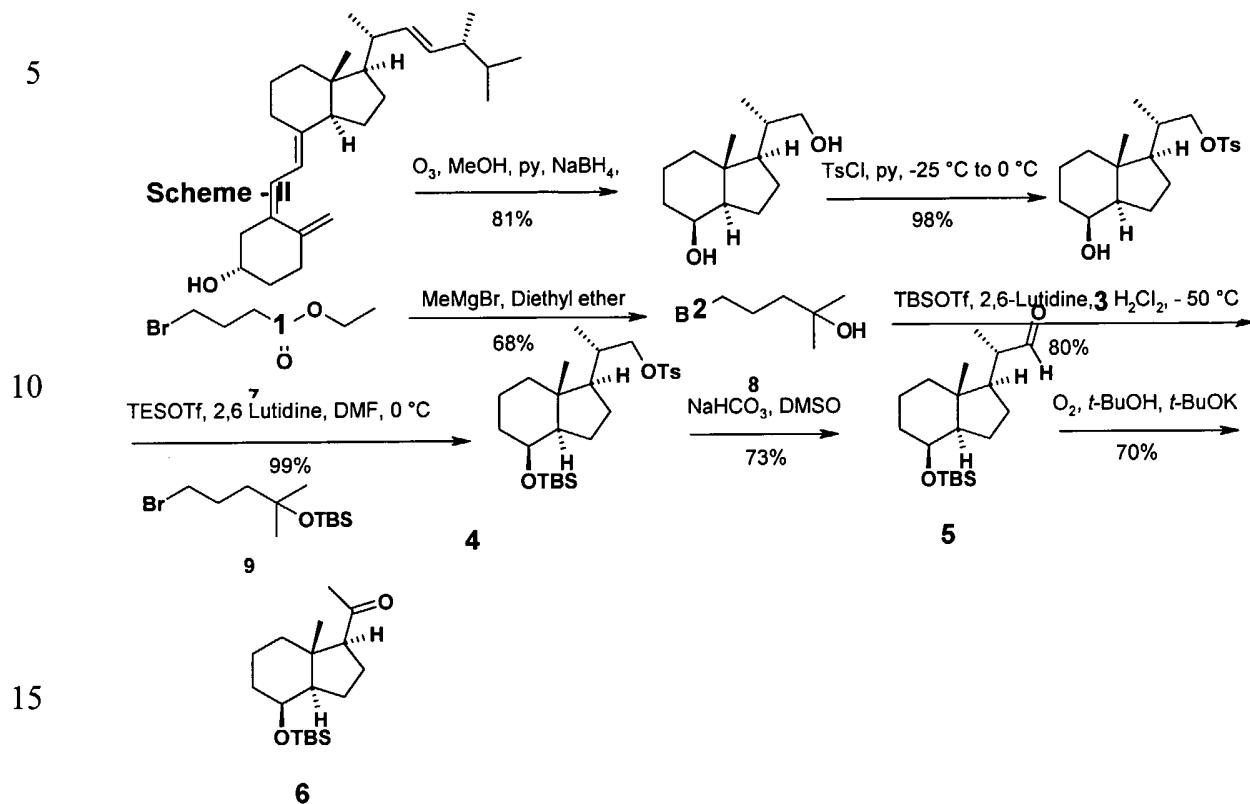
**17(Z)-1 $\alpha$ ,25 Dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D<sub>3</sub> (20b).** To a solution of phosphine oxide **10** (62 mg, 106.5  $\mu$ mol) in anhydrous THF (750  $\mu$ L) at -25  $^{\circ}\text{C}$  was slowly added PhLi 1.8 M in Di-n-butyl ether (59  $\mu$ L, 8.9mg, 106.5  $\mu$ mol) under argon with stirring. The solution turned deep orange. The mixture was stirred at that temperature for 20 min and cooled to -78  $^{\circ}\text{C}$ . A precooled (-78  $^{\circ}\text{C}$ ) solution of ketone **17b** (7.7 mg, 19.6  $\mu$ mol) in anhydrous THF (100  $\mu$ L) was added slowly. The mixture was stirred under argon atmosphere at -78  $^{\circ}\text{C}$  for 3h and at 0  $^{\circ}\text{C}$  for 18h.

Ethyl acetate was added and organic phase was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. The residue was applied on a Sep-Pak cartridge, and eluted with 1% ethyl acetate/hexane to give the 19-nor protected vitamin derivative. The vitamin was further purified by HPLC (9.4-mm x 25-cm Zorbax-Sil column, 4ml/min) using hexane/IPA (99.95:0.05) solvent system. Pure compound **19b**, 12.8 mg (16.9  $\mu\text{mol}$ , 86%) was eluted at  $R_v = 19$  mL as colorless oil.  $[\alpha]^{25}_D -9.35$  ( $c$  0.64,  $\text{CHCl}_3$ ); UV (in hexane):  $\lambda_{\text{max}}$  244.4, 253.2, 263.2 nm;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.026, 0.050, 0.067, 0.082 (each 3H, each s), 0.56 (6H, q,  $J = 7.84$  Hz), 0.74 (3H, s), 0.86, 0.89 (each 9H, each s), 0.94 (9H, t,  $J = 7.96$  Hz), 1.19 (6H, s), 1.56 (3H, br s), 2.14 (1H, dd,  $J = 12.5, 4.8$  Hz), 2.33 (1H, dd,  $J = 13.1, 2.8$  Hz), 2.46 (1H, dd,  $J = 12.7, 4.4$  Hz), 2.53 (1H, dd,  $J = 13.3, 6.0$  Hz), 2.80 (1H, br d,  $J = 13.5$  Hz), 4.43 (2H, m), 4.92 and 4.97 (each 1H, each s), 5.88 and 6.21 (each 1H, each d,  $J = 11.1$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 152.9, 142.2, 140.8, 132.8, 125.9, 122.3, 116.3, 106.2, 73.3, 72.5, 71.6, 56.7, 47.6, 46.8, 45.4, 30.1, 29.8, 28.5, 25.8, 25.7, 23.9, 23.6, 23.0, 19.9, 18.2, 18.1, 17.8, 7.1, 6.8, -4.8, -5.0; MS  $m/z$  (relative intensity): No  $\text{M}^+$ , 366(2), 263(100); Exact mass calculated for  $\text{C}_{45}\text{H}_{84}\text{O}_3\text{Si}_3[\text{M}+\text{Na}]^+$  is 779.5626, found 779.5647.

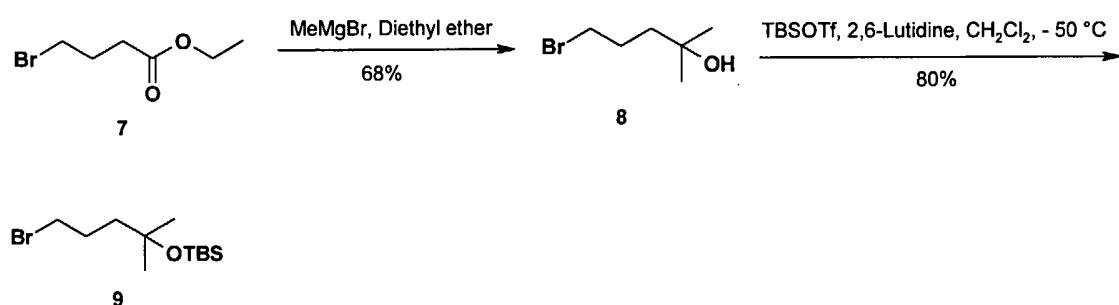
The protected vitamin **19b** (12.8 mg, 16.9 mmol) was dissolved in anhydrous THF (500  $\mu\text{L}$ ) and treated with TBAF (170  $\mu\text{L}$ , 44.2 mg, 169  $\mu\text{mol}$ ) and stirred at rt in dark for overnight. The solvent was removed in vaccuo and residue was applied on Sep-Pak cartridge, and eluted with 30% ethyl acetate/hexane to get the deprotected vitamin. The vitamin was further purified by HPLC (9.4-mm x 25-cm Zorbax-Sil column, 4ml/min) using hexane/IPA (85/15) as solvent system. Pure vitamin **20b**, 4.3mg (10.3  $\mu\text{mol}$ , 62%) was eluted at  $R_v = 33$  mL. UV (in ethanol):  $\lambda_{\text{max}}$  244.1, 252.5, 262.1nm;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.74 (3H, s), 1.21 (6H, s), 1.57 (3H, br s), 2.30 (2H, m), 2.57 (1H, dd,  $J = 13.3, 3.6$  Hz), 2.79 (1H, dd,  $J = 11.6, 2.52$  Hz), 2.85 (1H, dd,  $J = 13.1, 4.44$  Hz), 4.48 (2H, m), 5.09 and 5.11 (1H and 1H, each s), 5.92 and 6.35 (1H and 1H, each d,  $J = 11.3$  Hz); MS  $m/z$  (relative intensity): 414 ( $\text{M}^+$ , 90), 399 ( $\text{M}-\text{CH}_3^+$ , 17), 381 [ $\text{M}-\text{CH}_3-\text{H}_2\text{O}]^+$ , 18), 363 ( $[\text{M}-\text{CH}_3-2 \times \text{H}_2\text{O}]^+$ , 7), 285 (86), 243 (35), 91 (100); exact mass calculated for  $\text{C}_{27}\text{H}_{42}\text{O}_3$  ( $[\text{M}+\text{Na}]^+$ ) is 437.3032, measured is 437.3026.

## SCHEMES

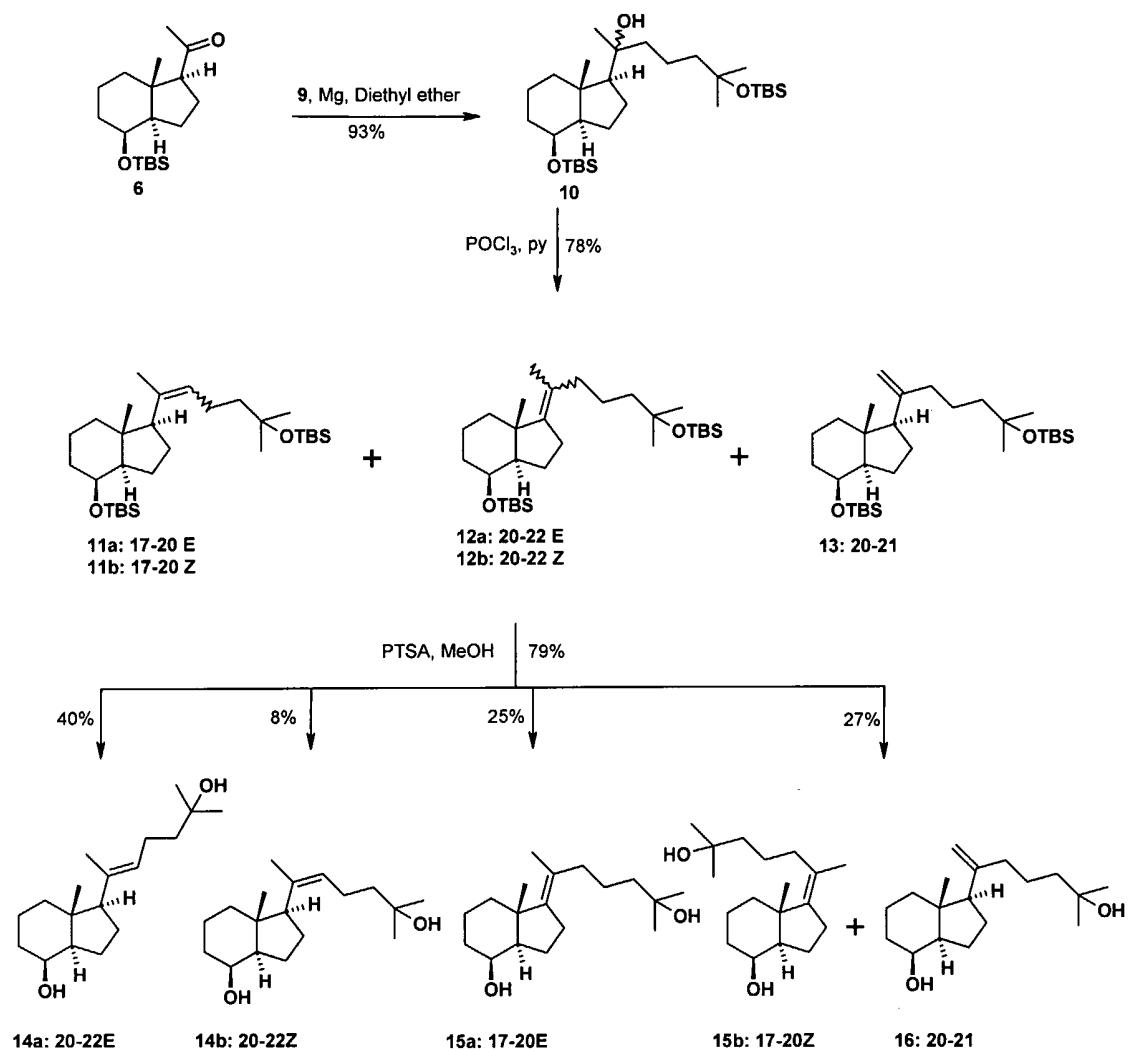
Scheme - I



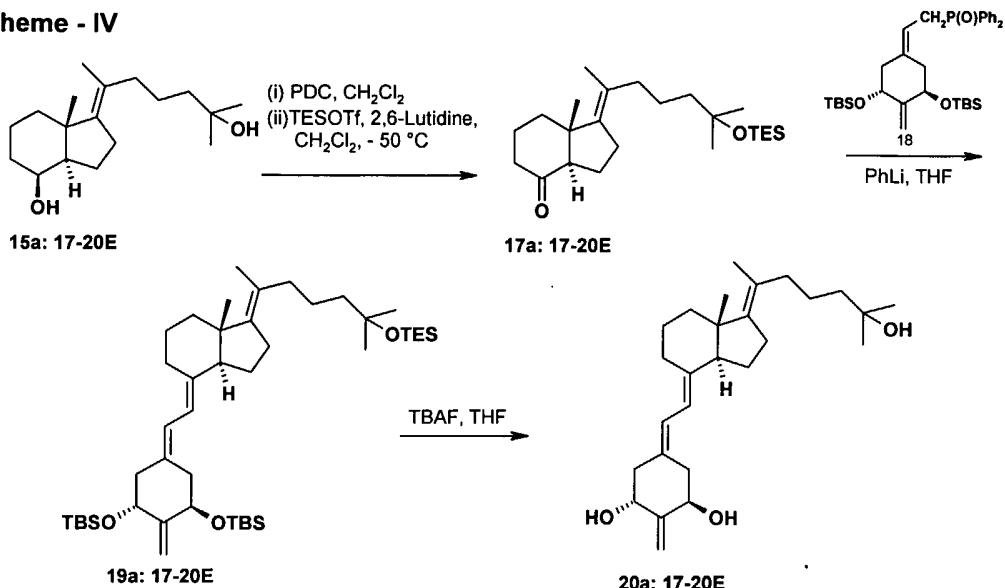
Scheme - II



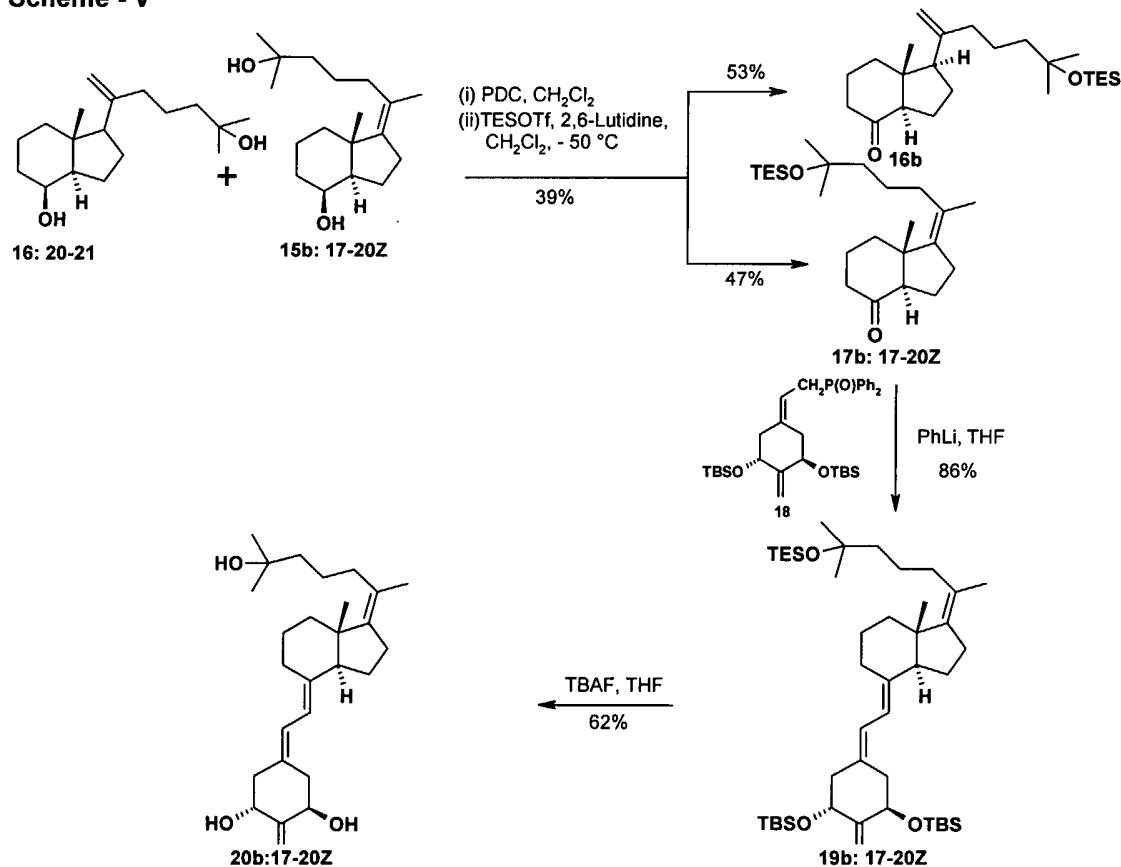
Scheme - III



Scheme - IV



Scheme - V



BIOLOGICAL ACTIVITY OF 17(E)-1 $\alpha$ ,25-DIHYDROXY-17(20)-  
DEHYDRO-2-METHYLENE-19-NORVITAMIN D<sub>3</sub>

The introduction of a methylene group to the 2-position, the introduction of a double bond between the 17 and 20 positions, and orientating the side chain of 1 $\alpha$ ,25-dihydroxy-19-nor-vitamin D<sub>3</sub> in its E configuration had little or no effect on binding to the full length recombinant rat vitamin D receptor, as compared to 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>. The compound VIT-III bound equally well to the receptor as compared to the standard 1,25-(OH)<sub>2</sub>D<sub>3</sub> (Figure 1). It might be expected from these results that compound VIT-III would have equivalent biological activity. Surprisingly, 10 however, compound VIT-III is a highly selective analog with unique biological activity.

Figure 5 shows that VIT-III has little activity as compared to that of 1,25-dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>), the natural hormone, in stimulating intestinal calcium transport.

Figure 4 demonstrates that VIT-III has very little bone calcium mobilization 15 activity, as compared to 1,25(OH)<sub>2</sub>D<sub>3</sub>.

Figures 4-5 thus illustrate that VIT-III may be characterized as having little, if any, calcemic activity.

Figure 2 illustrates that VIT-III is as potent as 1,25(OH)<sub>2</sub>D<sub>3</sub> on HL-60 cell differentiation, making it an excellent candidate for the treatment of psoriasis and cancer, 20 especially against leukemia, colon cancer, breast cancer, skin cancer and prostate cancer. In addition, due to its relatively high cell differentiation activity, this compound provides a therapeutic agent for the treatment of various skin conditions including wrinkles, lack of adequate dermal hydration, i.e. dry skin, lack of adequate skin firmness, i.e. slack skin, and insufficient sebum secretion. Use of this compound thus not only results in 25 moisturizing of skin but also improves the barrier function of skin.

Figure 3 illustrates that the compound VIT-III has about the same transcriptional activity as 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> in bone cells. This result, together with the cell differentiation activity of Figure 2, suggests that VIT-III will be very effective in psoriasis

because it has direct cellular activity in causing cell differentiation and in suppressing cell growth. These data also indicate that VIT-III may have significant activity as an anti-cancer agent, especially against leukemia, colon cancer, breast cancer, skin cancer and prostate cancer.

5 The strong activity of VIT-III on HL-60 differentiation suggests it will be active in suppressing growth of parathyroid glands and in the suppression of the preproparathyroid gene.

## EXPERIMENTAL METHODS

10 The compounds of the invention were prepared and studied using the following methods.

### Vitamin D Receptor Binding

#### Test Material

15 Protein Source

Full-length recombinant rat receptor was expressed in E. coli BL21 (DE3) Codon Plus RIL cells and purified to homogeneity using two different column chromatography systems. The first system was a nickel affinity resin that utilizes the 20 C-terminal histidine tag on this protein. The protein that was eluted from this resin was further purified using ion exchange chromatography (S-Sepharose Fast Flow). Aliquots of the purified protein were quick frozen in liquid nitrogen and stored at -80°C until use. For use in binding assays, the protein was diluted in TEDK<sub>50</sub> (50 mM Tris, 1.5 mM EDTA, pH7.4, 5 mM DTT, 150 mM KCl) with 25 0.1% Chaps detergent. The receptor protein and ligand concentration was optimized such that no more than 20% of the added radiolabeled ligand was bound to the receptor.

### Study Drugs

Unlabeled ligands were dissolved in ethanol and the concentrations determined using UV spectrophotometry (1,25(OH)<sub>2</sub>D<sub>3</sub>: molar extinction coefficient = 18,200 and  $\lambda_{max}$  = 265 nm). Radiolabeled ligand (<sup>3</sup>H-1,25(OH)<sub>2</sub>D<sub>3</sub>, ~159 Ci/mmole) was 5 added in ethanol at a final concentration of 1 nM.

### Assay Conditions

Radiolabeled and unlabeled ligands were added to 100  $\mu$ l of the diluted protein at a final ethanol concentration of  $\leq$ 10%, mixed and incubated overnight on 10 ice to reach binding equilibrium. The following day, 100  $\mu$ l of hydroxylapatite slurry (50%) was added to each tube and mixed at 10-minute intervals for 30 minutes. The hydroxylapatite was collected by centrifugation and then washed three times with Tris-EDTA buffer (50 mM Tris, 1.5 mM EDTA, pH 7.4) containing 0.5% Titron X-100. After the final wash, the pellets were transferred to scintillation 15 vials containing 4 ml of Biosafe II scintillation cocktail, mixed and placed in a scintillation counter. Total binding was determined from the tubes containing only radiolabeled ligand.

## HL-60 Differentiation

### Test Material

20

### Study Drugs

The study drugs were dissolved in ethanol and the concentrations determined using UV spectrophotometry. Serial dilutions were prepared so that a range of drug concentrations could be tested without changing the final concentration of ethanol ( $\leq$  25 0.2%) present in the cell cultures.

**Cells**

Human promyelocytic leukemia (HL60) cells were grown in RPMI-1640 medium containing 10% fetal bovine serum. The cells were incubated at 37°C in the presence of 5% CO<sub>2</sub>.

5

**Assay Conditions**

HL60 cells were plated at 1.2 x 10<sup>5</sup> cells/ml. Eighteen hours after plating, cells in duplicate were treated with drug. Four days later, the cells were harvested and a nitro blue tetrazolium reduction assay was performed (Collins et al., 1979; J. Exp.

10 Med. 149:969-974). The percentage of differentiated cells was determined by counting a total of 200 cells and recording the number that contained intracellular black-blue formazan deposits. Verification of differentiation to monocytic cells was determined by measuring phagocytic activity (data not shown).

15

**In vitro Transcription Assay**

Transcription activity was measured in ROS 17/2.8 (bone) cells that were stably transfected with a 24-hydroxylase (24Ohase) gene promoter upstream of a luciferase reporter gene (Arbour et al., 1998). Cells were given a range of doses. Sixteen hours after dosing the cells were harvested and luciferase activities were measured using a 20 luminometer. RLU = relative luciferase units.

Antagonism was tested by adding a combination of 1,25(OH)<sub>2</sub>D<sub>3</sub> and the compound in the same well keeping the final ethanol concentration the same.

**Intestinal Calcium Transport and Bone Calcium Mobilization**

25 Male, weanling Sprague-Dawley rats were placed on Diet 11 (Suda et al, J. Nutr. 100:1049, 1970) (0.47% Ca) + vitamins AEK for one week followed by Diet 11 (0.02% Ca) + vitamins AEK for 3 weeks. The rats were then switched to the same diet containing 0.47% Ca for one week followed by two weeks on the same diet containing 0.02% Ca. Dose administration began during the last week on 0.02% calcium diet. Four consecutive

ip doses were given approximately 24 hours apart. Twenty-four hours after the last dose, blood was collected from the severed neck and the concentration of serum calcium determined by atomic absorption spectrometry as a measure of bone calcium mobilization. The first 10 cm of the intestine was also collected for intestinal calcium 5 transport analysis using the everted gut sac method.

Antagonism was tested by administering a combination of 1,25(OH)<sub>2</sub>D<sub>3</sub> and the compound to the animal simultaneously.

#### INTERPRETATION OF DATA

10 VDR binding, HL60 cell differentiation, and transcription activity. VIT-III ( $K_i=3.8\times10^{-10}M$ ) is equivalent to the natural hormone 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> ( $K_i=1.1\times10^{-10}M$ ) in its ability to compete with [<sup>3</sup>H]-1,25(OH)<sub>2</sub>D<sub>3</sub> for binding to the full-length recombinant rat vitamin D receptor (Figure 1). There is also little difference between VIT-III ( $EC_{50}=1.7\times10^{-8}M$ ) in its ability (efficacy or potency) to promote HL60 15 differentiation as compared to 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> ( $EC_{50}=2.8\times10^{-8}M$ ) (See Figure 2). Also, compound VIT-III ( $EC_{50}=3.1\times10^{-11}M$ ) has about the same transcriptional activity in bone cells as 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> ( $EC_{50}=2.3\times10^{-10}M$ ) (See Figure 3). These results suggest that VIT-III will be very effective in psoriasis because it has direct 20 cellular activity in causing cell differentiation and in suppressing cell growth. These data also indicate that VIT-III will have significant activity as an anti-cancer agent, especially against leukemia, colon cancer, breast cancer, skin cancer and prostate cancer, as well as against skin conditions such as dry skin (lack of dermal hydration), undue skin slackness (insufficient skin firmness), insufficient sebum secretion and wrinkles. It would also be expected to be very active in suppressing secondary hyperparathyroidism.

25 Calcium mobilization from bone and intestinal calcium absorption in vitamin D-deficient animals. Using vitamin D-deficient rats on a low calcium diet (0.02%), the activities of VIT-III and 1,25(OH)<sub>2</sub>D<sub>3</sub> in intestine and bone were tested. As expected, the

native hormone (1,25(OH)<sub>2</sub>D<sub>3</sub>) increased serum calcium levels at all dosages (Fig. 4). Figure 4 shows that VIT-III has little, if any, activity in mobilizing calcium from bone. Administration of VIT-III at 260 pmol/day for 4 consecutive days did not result in mobilization of bone calcium, and increasing the amount of VIT-III to 2340 pmol/day and 5 then to 7020 pmol/day was also without any substantial effect.

Intestinal calcium transport was evaluated in the same groups of animals using the everted gut sac method (Figure 5). These results show that the compound VIT-III1 does not promote intestinal calcium transport when administered at 260 pmol/day, and has slight activity at 2340 pmol/day and does show some activity at 7020 pmol/day, whereas 10 1,25(OH)<sub>2</sub>D<sub>3</sub> promotes a significant increase at the 260 pmol/day dose. Thus, it may be concluded that VIT-III is essentially devoid of intestinal calcium transport activity at the tested doses.

These results illustrate that VIT-III is an excellent candidate for numerous human therapies as described herein, and that it may be particularly useful in a number of 15 circumstances such as suppression of secondary hyperparathyroidism of renal osteodystrophy, autoimmune diseases, cancer, and psoriasis. VIT-III is an excellent candidate for treating psoriasis because: (1) it has significant VDR binding, transcription activity and cellular differentiation activity; (2) it is devoid of hypercalcemic liability unlike 1,25(OH)<sub>2</sub>D<sub>3</sub>; and (3) it is easily synthesized. Since VIT-III has significant 20 binding activity to the vitamin D receptor, but has little ability to raise blood serum calcium, it may also be particularly useful for the treatment of secondary hyperparathyroidism of renal osteodystrophy.

These data also indicate that the compound VIT-III of the invention may be especially suited for treatment and prophylaxis of human disorders which are 25 characterized by an imbalance in the immune system, e.g. in autoimmune diseases, including multiple sclerosis, lupus, diabetes mellitus, host versus graft rejection, and rejection of organ transplants; and additionally for the treatment of inflammatory

diseases, such as rheumatoid arthritis, asthma, and inflammatory bowel diseases such as celiac disease, ulcerative colitis and Crohn's disease. Acne, alopecia and hypertension are other conditions which may be treated with the compound VIT-III of the invention.

The compounds of the invention of formula **I**, and particularly formula **Ia**, are also useful in preventing or treating obesity, inhibiting adipocyte differentiations, inhibiting SCD-1 gene transcription, and/or reducing body fat in animal subjects. Therefore, in some embodiments, a method of preventing or treating obesity, inhibiting adipocyte differentiations, inhibiting SCD-1 gene transcription, and/or reducing body fat in an animal subject includes administering to the animal subject, an effective amount of one or more of the compounds or a pharmaceutical composition that includes one or more of the compounds of formula **I**. Administration of one or more of the compounds or the pharmaceutical compositions to the subject inhibits adipocyte differentiation, inhibits gene transcription, and/or reduces body fat in the animal subject. The animal may be a human, a domestic animal such as a dog or a cat, or an agricultural animal, especially those that provide meat for human consumption, such as fowl like chickens, turkeys, pheasant or quail, as well as bovine, ovine, caprine, or porcine animals.

For prevention and/or treatment purposes, the compounds of this invention defined by formula **I** and **Ia** may be formulated for pharmaceutical applications as a solution in innocuous solvents, or as an emulsion, suspension or dispersion in suitable solvents or carriers, or as pills, tablets or capsules, together with solid carriers, according to conventional methods known in the art. Any such formulations may also contain other pharmaceutically-acceptable and non-toxic excipients such as stabilizers, anti-oxidants, binders, coloring agents or emulsifying or taste-modifying agents.

The compounds of formula **I** and particularly VIT-III of formula **Ia**, may be administered orally, topically, parenterally, rectally, nasally, sublingually, or transdermally. The compound is advantageously administered by injection or by intravenous infusion or suitable sterile solutions, or in the form of liquid or solid doses via

the alimentary canal, or in the form of creams, ointments, patches, or similar vehicles suitable for transdermal applications. A dose of from 0.01 $\mu$ g to 1000 $\mu$ g per day of the compounds I, particularly VIT-III, preferably from about 0.1 $\mu$ g to about 500  $\mu$ g per day, is appropriate for prevention and/or treatment purposes, such dose being adjusted  
5 according to the disease to be treated, its severity and the response of the subject as is well understood in the art. Since the compound exhibits specificity of action, each may be suitably administered alone, or together with graded doses of another active vitamin D compound -- e.g. 1 $\alpha$ -hydroxyvitamin D<sub>2</sub> or D<sub>3</sub>, or 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> -- in situations where different degrees of bone mineral mobilization and calcium transport  
10 stimulation is found to be advantageous.

Compositions for use in the above-mentioned treatments comprise an effective amount of the compounds I, particularly VIT-III, as defined by the above formula I and Ia as the active ingredient, and a suitable carrier. An effective amount of such compound for use in accordance with this invention is from about 0.01  $\mu$ g to about 1000  $\mu$ g per gm  
15 of composition, preferably from about 0.1  $\mu$ g to about 500  $\mu$ g per gram of composition, and may be administered topically, transdermally, orally, rectally, nasally, sublingually, or parenterally in dosages of from about 0.01 $\mu$ g/day to about 1000  $\mu$ g /day, and preferably from about 0.1  $\mu$ g/day to about 500  $\mu$ g/day.

The compounds I, particularly VIT-III, may be formulated as creams, lotions,  
20 ointments, topical patches, pills, capsules or tablets, suppositories, aerosols, or in liquid form as solutions, emulsions, dispersions, or suspensions in pharmaceutically innocuous and acceptable solvent or oils, and such preparations may contain in addition other pharmaceutically innocuous or beneficial components, such as stabilizers, antioxidants, emulsifiers, coloring agents, binders or taste-modifying agents.

25 The compounds I, particularly VIT-III, may be advantageously administered in amounts sufficient to effect the differentiation of promyelocytes to normal macrophages. Dosages as described above are suitable, it being understood that the amounts given are to

be adjusted in accordance with the severity of the disease, and the condition and response of the subject as is well understood in the art.

The formulations of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefore and optionally other 5 therapeutic ingredients. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

Formulations of the present invention suitable for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a 10 predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion.

Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and carrier such as cocoa butter, or in the form of an 15 enema.

Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredient which is preferably isotonic with the blood of the recipient.

Formulations suitable for topical administration include liquid or semi-liquid 20 preparations such as liniments, lotions, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops; or as sprays.

For nasal administration, inhalation of powder, self-propelling or spray 25 formulations, dispensed with a spray can, a nebulizer or an atomizer can be used. The formulations, when dispensed, preferably have a particle size in the range of 10 to 100 $\mu$ .

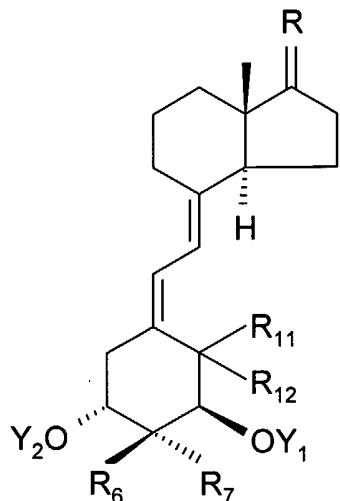
The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a patient as a physically and chemically stable unit dose comprising

5 either the active ingredient as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

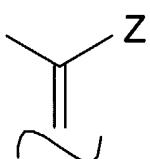
## CLAIMS

We claim:

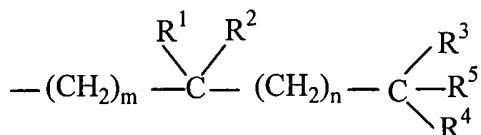
1. A compound having the formula:



5 where  $Y_1$  and  $Y_2$ , which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where  $R_{11}$  and  $R_{12}$  are each hydrogen or taken together are a methylene group, where  $R_6$  and  $R_7$ , which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or  $R_6$  and  $R_7$  when taken 10 together may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, or  $R_6$  and  $R_7$  when taken together may represent the group  $=CR_8R_9$  where  $R_8$  and  $R_9$ , which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken 15 together  $R_8$  and  $R_9$  may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, and where the group  $R$  represents a side chain represented by the structure



where the side chain and 17-ene double bond is in the E configuration and where Z is selected from Y, -OY, -CH<sub>2</sub>OY, -C≡CY and -CH=CHY, where the double bond in  
 20 the side chain may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, -COR<sup>5</sup> and a radical of the structure:



25 where m and n, independently, represent the integers from 0 to 5, where R<sup>1</sup> is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C<sub>1-5</sub>-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup>, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C<sub>1-5</sub> alkyl,  
 30 which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R<sup>1</sup> and R<sup>2</sup>, taken together, represent an oxo group, or an alkylidene group having a general formula C<sub>k</sub>H<sub>2k</sub>— where k is an integer, the group =CR<sup>2</sup>R<sup>3</sup>, or the group -(CH<sub>2</sub>)<sub>p</sub>—, where p is an integer from 2 to 5, and where R<sup>3</sup> and R<sup>4</sup>, taken together, represent an oxo group, or the group -(CH<sub>2</sub>)<sub>q</sub>—, where q is an integer from 2 to 5, and where R<sup>5</sup> represents hydrogen, hydroxy, protected hydroxy, or C<sub>1-5</sub> alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain  
 35 may be replaced by a nitrogen atom, or where any of the groups -CH(CH<sub>3</sub>)—, -(CH<sub>2</sub>)<sub>m</sub>—, -CR<sub>1</sub>R<sub>2</sub>— or -(CH<sub>2</sub>)<sub>n</sub>— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

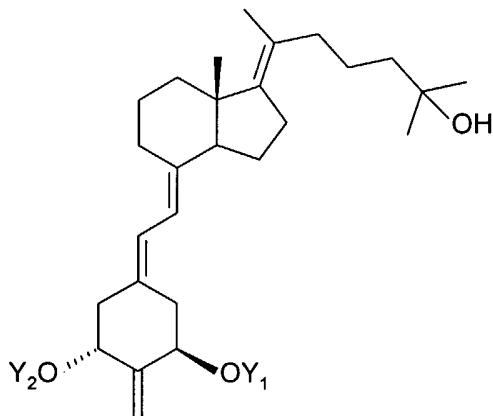
2. The compound of claim 1 wherein Y<sub>2</sub> is hydrogen.
3. The compound of claim 1 wherein Y<sub>1</sub> is hydrogen.
4. The compound of claim 1 wherein Y<sub>1</sub>, Y<sub>2</sub> and R<sup>5</sup> are hydrogen.

5. A pharmaceutical composition containing an effective amount of at least one compound as claimed in claim 1 together with a pharmaceutically acceptable excipient.

6. The pharmaceutical composition of claim 5 wherein said effective amount comprises from about 0.01  $\mu$ g to about 1000  $\mu$ g per gram of composition.

7. The pharmaceutical composition of claim 5 wherein said effective amount comprises from about 0.1  $\mu$ g to about 500  $\mu$ g per gram of composition.

8. A compound having the formula:



where  $Y_1$  and  $Y_2$ , which may be the same or different, are each selected from hydrogen or a hydroxy-protecting group.

9. The compound of claim 8 wherein  $Y_2$  is hydrogen.

10. The compound of claim 8 wherein  $Y_1$  is hydrogen.

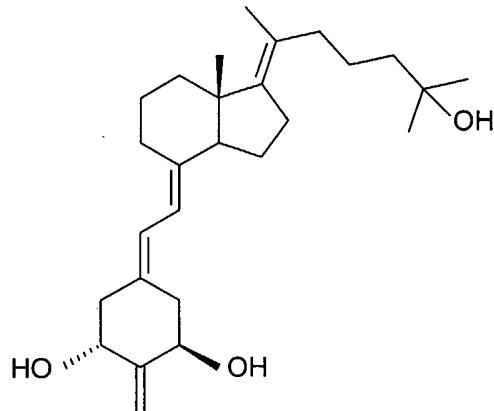
11. The compound of claim 8 wherein  $Y_1$  and  $Y_2$  are both t-butyldimethylsilyl.

12. A pharmaceutical composition containing an effective amount of at least one compound as claimed in claim 8 together with a pharmaceutically acceptable excipient.

13. The pharmaceutical composition of claim 12 wherein said effective amount comprises from about 0.01  $\mu$ g to about 1000  $\mu$ g per gram of composition.

14. The pharmaceutical composition of claim 12 wherein said effective amount comprise from about 0.1 $\mu$ g to about 500 $\mu$ g per gram of composition.

15. 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> having the formula:

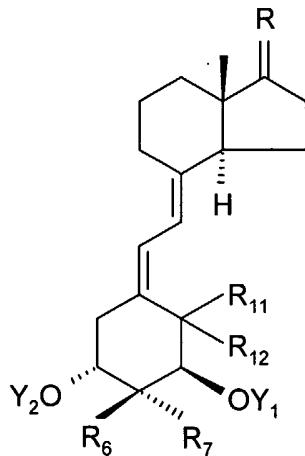


16. A pharmaceutical composition containing an effective amount of 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> together with a pharmaceutically acceptable excipient.

17. The pharmaceutical composition of claim 15 wherein said effective amount comprises from about 0.01 $\mu$ g to about 1000 $\mu$ g per gram of composition.

18. The pharmaceutical composition of claim 15 wherein said effective amount comprises from about 0.1 $\mu$ g to about 500 $\mu$ g per gram of composition.

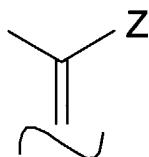
19. A method of treating psoriasis comprising administering to a subject with psoriasis an effective amount of a 17(20)-dehydro vitamin D analog having the formula:



where  $Y_1$  and  $Y_2$ , which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where  $R_{11}$  and  $R_{12}$  are each hydrogen or taken together are a methylene group, where  $R_6$  and  $R_7$ , which may be the same or different, are each selected from the group consisting of hydrogen,

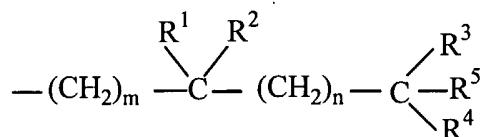
15 alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or  $R_6$  and  $R_7$  when taken together may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, or  $R_6$  and  $R_7$  when taken together may represent the group  $=CR_8R_9$  where  $R_8$  and  $R_9$ , which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken

20 together  $R_8$  and  $R_9$  may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, and where the group  $R$  represents a side chain represented by the structure



where the side chain and 17-ene double bond is in the E configuration and where  $Z$  is

25 selected from  $Y$ ,  $-OY$ ,  $-CH_2OY$ ,  $-C\equiv CY$  and  $-CH=CHY$ , where the double bond in the side chain may have the cis or trans geometry, and where  $Y$  is selected from hydrogen, methyl,  $-COR^5$  and a radical of the structure:



where  $m$  and  $n$ , independently, represent the integers from 0 to 5, where  $R^1$  is

30 selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and  $C_{1-5}$ -alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of  $R^2$ ,

R<sup>3</sup>, and R<sup>4</sup>, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C<sub>1-5</sub> alkyl, which may be straight-chain or branched, and  
35 optionally, bear a hydroxy or protected-hydroxy substituent, and where R<sup>1</sup> and R<sup>2</sup>, taken together, represent an oxo group, or an alkylidene group having a general formula C<sub>k</sub>H<sub>2k</sub>— where k is an integer, the group =CR<sup>2</sup>R<sup>3</sup>, or the group —(CH<sub>2</sub>)<sub>p</sub>—, where p is an integer from 2 to 5, and where R<sup>3</sup> and R<sup>4</sup>, taken together, represent an oxo group, or the group —(CH<sub>2</sub>)<sub>q</sub>—, where q is an integer from 2 to 5, and where R<sup>5</sup>  
40 represents hydrogen, hydroxy, protected hydroxy, or C<sub>1-5</sub> alkyl and wherein any of the CH—groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups —CH(CH<sub>3</sub>)—, —(CH<sub>2</sub>)<sub>m</sub>—, —CR<sub>1</sub>R<sub>2</sub>— or —(CH<sub>2</sub>)<sub>n</sub>— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

20. The method of claim 19 wherein the vitamin D analog is administered orally.

21. The method of claim 19 wherein the vitamin D analog is administered parenterally.

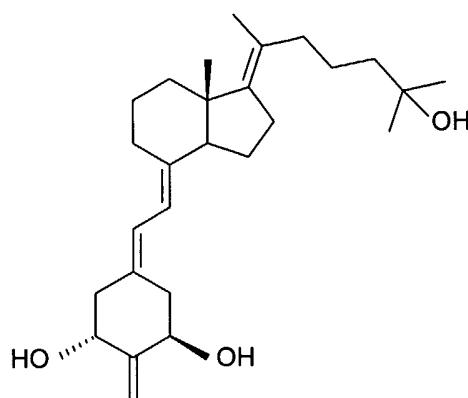
22. The method of claim 19 wherein the vitamin D analog is administered transdermally.

23. The method of claim 19 wherein the vitamin D analog is administered topically.

24. The method of claim 19 wherein the vitamin D analog is administered in a dosage of from about 0.01μg/day to about 1000μg/day.

25. A method of treating psoriasis comprising administering to a subject with psoriasis an effective amount of 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> having the formula:

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26. The method of claim 25 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered orally.

27. The method of claim 25 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered parenterally.

28. The method of claim 25 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered transdermally.

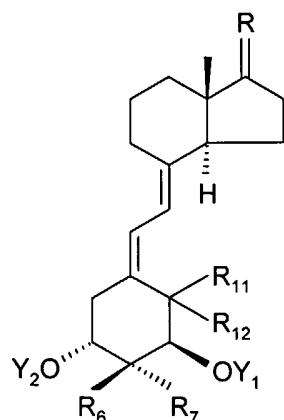
29. The method of claim 25 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered topically.

30. The method of claim 25 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered in a dosage of from about 0.01 $\mu$ g/day to about 1000 $\mu$ g/day.

31. A method of treating a disease selected from the group consisting of leukemia, colon cancer, breast cancer, skin cancer or prostate cancer comprising administering to a subject with said disease an effective amount of a 17(20)-dehydro vitamin D analog having the formula:

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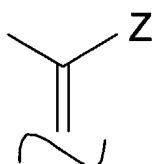
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where  $Y_1$  and  $Y_2$ , which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where  $R_{11}$  and  $R_{12}$  are each hydrogen or taken together are a methylene group, where  $R_6$  and  $R_7$ , which may

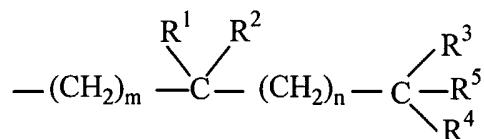
15 be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or  $R_6$  and  $R_7$  when taken together may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, or  $R_6$  and  $R_7$  when taken together may represent the group  $=CR_8R_9$  where  $R_8$  and  $R_9$ , which may be the same or different, are each selected from the group consisting of

20 hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together  $R_8$  and  $R_9$  may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, and where the group  $R$  represents a side chain represented by the structure



where the side chain and 17-ene double bond is in the E configuration and where  $Z$  is

25 selected from  $Y$ ,  $-OY$ ,  $-CH_2OY$ ,  $-C\equiv CY$  and  $-CH=CHY$ , where the double bond in the side chain may have the cis or trans geometry, and where  $Y$  is selected from hydrogen, methyl,  $-COR^5$  and a radical of the structure:



30 where  $m$  and  $n$ , independently, represent the integers from 0 to 5, where  $R^1$  is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and  $C_{1-5}$ -alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of  $R^2$ ,

R<sup>3</sup>, and R<sup>4</sup>, independently, is selected from deuterium, deuteroalkyl, hydrogen, 35 fluoro, trifluoromethyl and C<sub>1-5</sub> alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R<sup>1</sup> and R<sup>2</sup>, taken together, represent an oxo group, or an alkylidene group having a general formula C<sub>k</sub>H<sub>2k</sub>– where k is an integer, the group =CR<sup>2</sup>R<sup>3</sup>, or the group -(CH<sub>2</sub>)<sub>p</sub>–, where p is an integer from 2 to 5, and where R<sup>3</sup> and R<sup>4</sup>, taken together, represent an 40 oxo group, or the group -(CH<sub>2</sub>)<sub>q</sub>–, where q is an integer from 2 to 5, and where R<sup>5</sup> represents hydrogen, hydroxy, protected hydroxy, or C<sub>1-5</sub> alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups -CH(CH<sub>3</sub>)–, -(CH<sub>2</sub>)<sub>m</sub>–, -CR<sub>1</sub>R<sub>2</sub>– or -(CH<sub>2</sub>)<sub>n</sub>– at positions 20, 22, and 23, respectively, may be replaced by an oxygen or 45 sulfur atom.

32. The method of claim 31 wherein the vitamin D analog is administered orally.

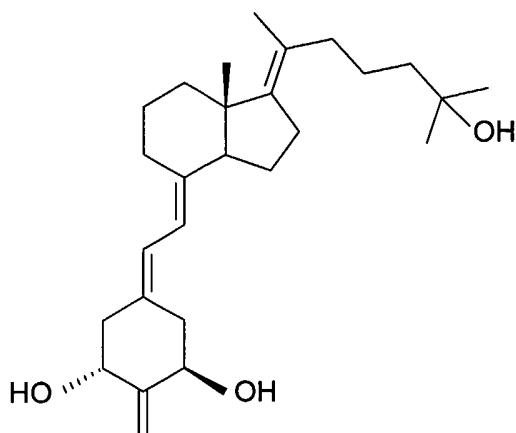
33. The method of claim 31 wherein the vitamin D analog is administered parenterally.

34. The method of claim 31 wherein the vitamin D analog is administered transdermally.

35. The method of claim 31 wherein the vitamin D analog is administered in a dosage of from about 0.01μg/day to about 1000μg/day.

36. A method of treating a disease selected from the group consisting of leukemia, colon cancer, breast cancer, skin cancer or prostate cancer comprising administering to a subject with said disease an effective amount of 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> having the formula:

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37. The method of claim 36 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered orally.

38. The method of claim 36 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered parenterally.

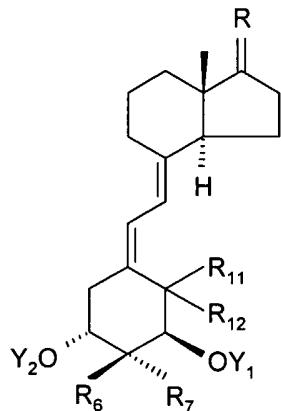
39. The method of claim 36 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered transdermally.

40. The method of claim 36 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered in a dosage of from about 0.01 $\mu$ g/day to about 1000 $\mu$ g/day.

41. A method of treating an autoimmune disease selected from the group consisting of multiple sclerosis, lupus, diabetes mellitus, hot versus graft rejection, and rejection of organ transplants, comprising administering to a subject with said disease an effective amount of a 17(20)-dehydro vitamin D analog having the

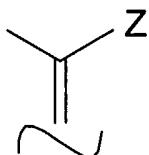
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formula:



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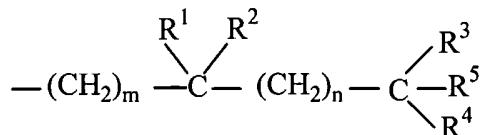
where  $Y_1$  and  $Y_2$ , which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where  $R_{11}$  and  $R_{12}$  are each hydrogen or taken together are a methylene group, where  $R_6$  and  $R_7$ , which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or  $R_6$  and  $R_7$  when taken together may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, or  $R_6$  and  $R_7$  when taken together may represent the group  $=CR_8R_9$  where  $R_8$  and  $R_9$ , which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together  $R_8$  and  $R_9$  may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, and where the group  $R$  represents a side chain represented by the structure



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where the side chain and 17-ene double bond is in the E configuration and where  $Z$  is selected from  $Y$ ,  $-OY$ ,  $-CH_2OY$ ,  $-C\equiv CY$  and  $-CH=CHY$ , where the double bond in the side chain may have the cis or trans geometry, and where  $Y$  is selected from hydrogen, methyl,  $-COR^5$  and a radical of the structure:

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where  $m$  and  $n$ , independently, represent the integers from 0 to 5, where  $R^1$  is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and  $C_{1-5}$ -alkyl, which may be straight chain or branched and,

35    optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup>, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C<sub>1-5</sub> alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R<sup>1</sup> and R<sup>2</sup>, taken together, represent an oxo group, or an alkylidene group having a general

40    formula C<sub>k</sub>H<sub>2k</sub>– where k is an integer, the group =CR<sup>2</sup>R<sup>3</sup>, or the group –(CH<sub>2</sub>)<sub>p</sub>–, where p is an integer from 2 to 5, and where R<sup>3</sup> and R<sup>4</sup>, taken together, represent an oxo group, or the group –(CH<sub>2</sub>)<sub>q</sub>–, where q is an integer from 2 to 5, and where R<sup>5</sup> represents hydrogen, hydroxy, protected hydroxy, or C<sub>1-5</sub> alkyl and wherein any of the CH–groups at positions 20, 22, or 23 in the side chain may be replaced by a

45    nitrogen atom, or where any of the groups –CH(CH<sub>3</sub>)–, –(CH<sub>2</sub>)<sub>m</sub>–, –CR<sub>1</sub>R<sub>2</sub>– or –(CH<sub>2</sub>)<sub>n</sub>– at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

42.    The method of claim 41 wherein the vitamin D analog is administered orally.

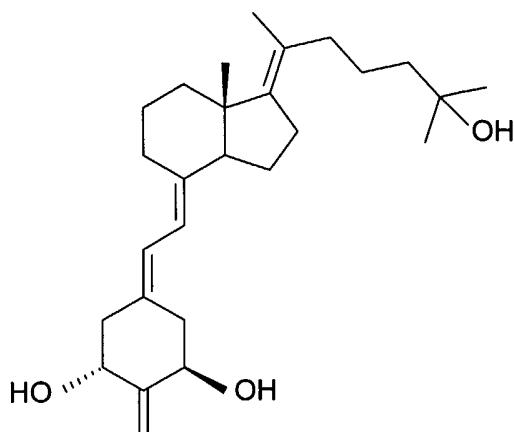
43.    The method of claim 41 wherein the vitamin D analog is administered parenterally.

44.    The method of claim 41 wherein the vitamin D analog is administered transdermally.

45.    The method of claim 41 wherein the vitamin D analog is administered in a dosage of from about 0.01μg/day to about 1000μg/day.

46.    A method of treating an autoimmune disease selected from the group consisting of multiple sclerosis, lupus, diabetes mellitus, host versus graft rejection, and rejection of organ transplants, comprising administering to a subject with said disease an effective amount of 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-

5    methylene-19-nor-vitamin D<sub>3</sub> having the formula:



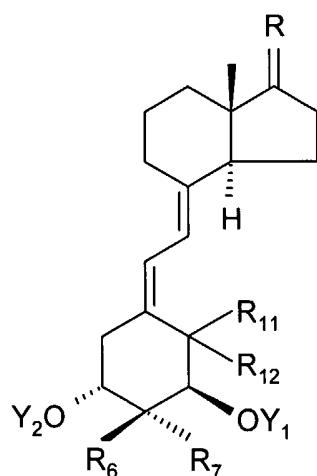
47. The method of claim 46 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered orally.

48. The method of claim 46 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered parenterally.

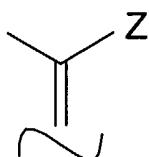
49. The method of claim 46 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered transdermally.

50. The method of claim 46 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered in a dosage of from about 0.01 $\mu$ g/day to about 1000 $\mu$ g/day.

51. A method of treating an inflammatory disease selected from the group consisting of rheumatoid arthritis, asthma, and inflammatory bowel diseases, comprising administering to a subject with said disease an effective amount of a 17(20)-dehydro vitamin D analog having the formula:

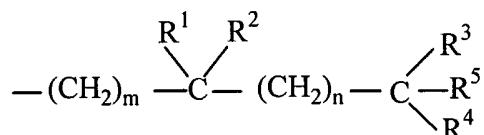


where  $Y_1$  and  $Y_2$ , which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where  $R_{11}$  and  $R_{12}$  are each hydrogen or taken together are a methylene group, where  $R_6$  and  $R_7$ , which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or  $R_6$  and  $R_7$  when taken together may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, or  $R_6$  and  $R_7$  when taken together may represent the group  $=CR_8R_9$  where  $R_8$  and  $R_9$ , which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together  $R_8$  and  $R_9$  may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, and where the group  $R$  represents a side chain represented by the structure



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where the side chain and 17-ene double bond is in the E configuration and where  $Z$  is selected from  $Y$ ,  $-OY$ ,  $-CH_2OY$ ,  $-C\equiv CY$  and  $-CH=CHY$ , where the double bond in the side chain may have the cis or trans geometry, and where  $Y$  is selected from hydrogen, methyl,  $-COR^5$  and a radical of the structure:



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where  $m$  and  $n$ , independently, represent the integers from 0 to 5, where  $R^1$  is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and  $C_{1.5}$ -alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of  $R^2$ ,

35 R<sup>3</sup>, and R<sup>4</sup>, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C<sub>1-5</sub> alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R<sup>1</sup> and R<sup>2</sup>, taken together, represent an oxo group, or an alkylidene group having a general formula C<sub>k</sub>H<sub>2k</sub>– where k is an integer, the group =CR<sup>2</sup>R<sup>3</sup>, or the group –(CH<sub>2</sub>)<sub>p</sub>–, 40 where p is an integer from 2 to 5, and where R<sup>3</sup> and R<sup>4</sup>, taken together, represent an oxo group, or the group –(CH<sub>2</sub>)<sub>q</sub>–, where q is an integer from 2 to 5, and where R<sup>5</sup> represents hydrogen, hydroxy, protected hydroxy, or C<sub>1-5</sub> alkyl and wherein any of the CH–groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups –CH(CH<sub>3</sub>)–, –(CH<sub>2</sub>)<sub>m</sub>–, –CR<sub>1</sub>R<sub>2</sub>– or 45 –(CH<sub>2</sub>)<sub>n</sub>– at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

52. The method of claim 51 wherein the vitamin D analog is administered orally.

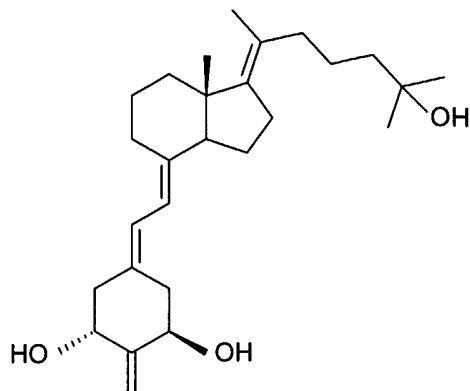
53. The method of claim 51 wherein the vitamin D analog is administered parenterally.

54. The method of claim 51 wherein the vitamin D analog is administered transdermally.

55. The method of claim 51 wherein the vitamin D analog is administered in a dosage of from about 0.01μg/day to about 1000μg/day.

56. A method of treating an inflammatory disease selected from the group consisting of rheumatoid arthritis, asthma, and inflammatory bowel diseases, comprising administering to a subject with said disease an effective amount of 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> having the formula:

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57. The method of claim 56 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered orally.

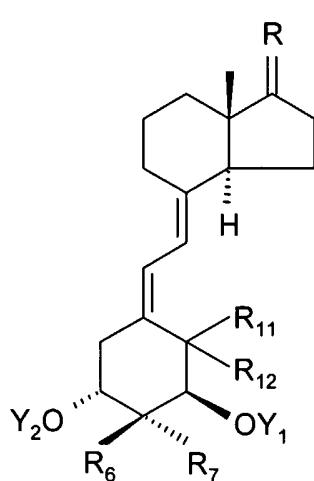
58. The method of claim 56 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered parenterally.

59. The method of claim 56 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered transdermally.

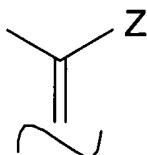
60. The method of claim 56 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered in a dosage of from about 0.01 $\mu$ g/day to about 1000 $\mu$ g/day.

61. A method of treating a skin condition selected from the group consisting of wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration and insufficient sebum secretion which comprises administering to a subject with said skin condition an effective amount of a 17(20)-dehydro vitamin D analog having the formula:

10



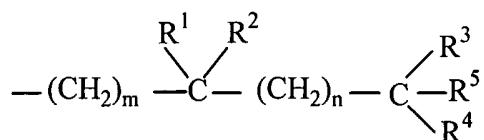
where  $Y_1$  and  $Y_2$ , which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where  $R_{11}$  and  $R_{12}$  are each hydrogen or taken together are a methylene group, where  $R_6$  and  $R_7$ , which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or  $R_6$  and  $R_7$  when taken together may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, or  $R_6$  and  $R_7$  when taken together may represent the group  $=CR_8R_9$  where  $R_8$  and  $R_9$ , which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together  $R_8$  and  $R_9$  may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, and where the group  $R$  represents a side chain represented by the structure



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where the side chain and 17-ene double bond is in the E configuration and where  $Z$  is selected from  $Y$ ,  $-OY$ ,  $-CH_2OY$ ,  $-C\equiv CY$  and  $-CH=CHY$ , where the double bond in the side chain may have the cis or trans geometry, and where  $Y$  is selected from hydrogen, methyl,  $-COR^5$  and a radical of the structure:

30



where  $m$  and  $n$ , independently, represent the integers from 0 to 5, where  $R^1$  is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and  $C_{1-5}$ -alkyl, which may be straight chain or branched and, 35 optionally, bear a hydroxy or protected-hydroxy substituent, and where each of  $R^2$ ,

R<sup>3</sup>, and R<sup>4</sup>, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C<sub>1-5</sub> alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R<sup>1</sup> and R<sup>2</sup>, taken together, represent an oxo group, or an alkylidene group having a general formula C<sub>k</sub>H<sub>2k</sub>– where k is an integer, the group =CR<sup>2</sup>R<sup>3</sup>, or the group –(CH<sub>2</sub>)<sub>p</sub>–, where p is an integer from 2 to 5, and where R<sup>3</sup> and R<sup>4</sup>, taken together, represent an oxo group, or the group –(CH<sub>2</sub>)<sub>q</sub>–, where q is an integer from 2 to 5, and where R<sup>5</sup> represents hydrogen, hydroxy, protected hydroxy, or C<sub>1-5</sub> alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups –CH(CH<sub>3</sub>)–, –(CH<sub>2</sub>)<sub>m</sub>–, –CR<sub>1</sub>R<sub>2</sub>– or –(CH<sub>2</sub>)<sub>n</sub>– at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

62. The method of claim 61 wherein the vitamin D analog is administered orally.

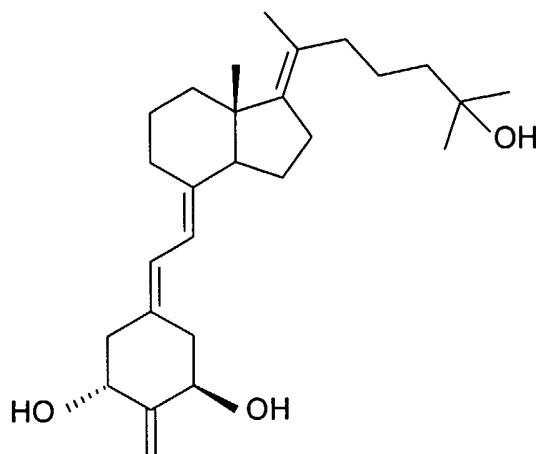
63. The method of claim 61 wherein the vitamin D analog is administered parenterally.

64. The method of claim 61 wherein the vitamin D analog is administered transdermally.

65. The method of claim 61 wherein the vitamin D analog is administered topically.

66. The method of claim 61 wherein the vitamin D analog is administered in a dosage of from about 0.01μg/day to about 1000μg/day.

67. A method of treating a skin condition selected from the group consisting of wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration and insufficient sebum secretion which comprises administered to a subject with said skin condition an effective amount of 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> having the formula:



68. The method of claim 67 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered orally.

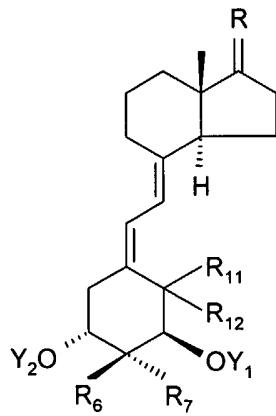
69. The method of claim 67 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered parenterally.

70. The method of claim 67 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered transdermally.

71. The method of claim 67 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered topically.

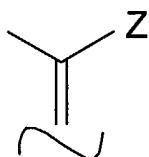
72. The method of claim 67 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered in a dosage of from about 0.01 $\mu$ g/day to about 1000 $\mu$ g/day.

73. A method of treating renal osteodystrophy comprising administering to a subject with renal osteodystrophy an effective amount of a 17(20)-dehydro vitamin D analog having the formula:



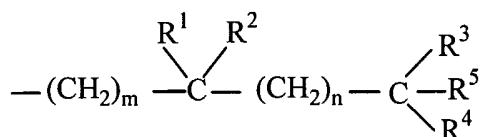
10 where  $Y_1$  and  $Y_2$ , which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where  $R_{11}$  and  $R_{12}$  are each hydrogen or taken together are a methylene group, where  $R_6$  and  $R_7$ , which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or  $R_6$  and  $R_7$  when taken together may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, or  $R_6$  and  $R_7$  when taken together may represent the group  $=CR_8R_9$  where  $R_8$  and  $R_9$ , which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together  $R_8$  and  $R_9$  may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, and where the group  $R$  represents a side chain represented by the structure

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20 where the side chain and 17-ene double bond is in the E configuration and where  $Z$  is selected from  $Y$ ,  $-OY$ ,  $-CH_2OY$ ,  $-C\equiv CY$  and  $-CH=CHY$ , where the double bond in the side chain may have the cis or trans geometry, and where  $Y$  is selected from

25 hydrogen, methyl,  $-COR^5$  and a radical of the structure:



30 where  $m$  and  $n$ , independently, represent the integers from 0 to 5, where  $R^1$  is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro,

trifluoromethyl, and C<sub>1-5</sub>-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup>, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C<sub>1-5</sub> alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R<sup>1</sup> and R<sup>2</sup>, taken together, represent an oxo group, or an alkylidene group having a general formula C<sub>k</sub>H<sub>2k</sub>– where k is an integer, the group =CR<sup>2</sup>R<sup>3</sup>, or the group –(CH<sub>2</sub>)<sub>p</sub>–, where p is an integer from 2 to 5, and where R<sup>3</sup> and R<sup>4</sup>, taken together, represent an oxo group, or the group –(CH<sub>2</sub>)<sub>q</sub>–, where q is an integer from 2 to 5, and where R<sup>5</sup> represents hydrogen, hydroxy, protected hydroxy, or C<sub>1-5</sub> alkyl and wherein any of the CH-groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups –CH(CH<sub>3</sub>)–, –(CH<sub>2</sub>)<sub>m</sub>–, –CR<sub>1</sub>R<sub>2</sub>– or –(CH<sub>2</sub>)<sub>n</sub>– at positions 20, 22, and 23, respectively, may be replaced by an oxygen or 45 sulfur atom.

74. The method of claim 73 wherein the vitamin D analog is administered orally.

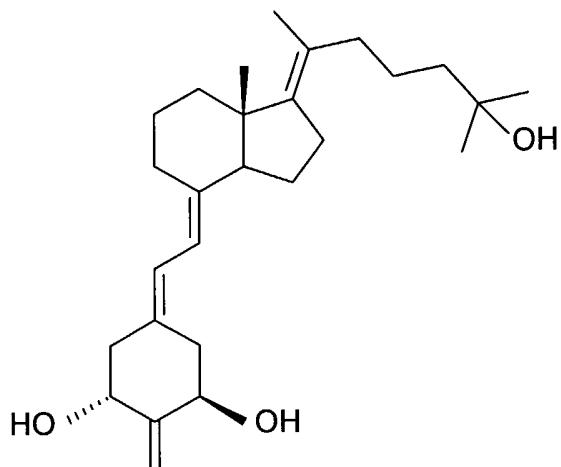
75. The method of claim 73 wherein the vitamin D analog is administered parenterally.

76. The method of claim 73 wherein the vitamin D analog is administered transdermally.

77. The method of claim 73 wherein the vitamin D analog is administered in a dosage of from about 0.01μg/day to about 1000μg/day.

78. A method of treating renal osteodystrophy comprising administering to a subject with renal osteodystrophy an effective amount of 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> having the formula:

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79. The method of claim 78 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered orally.

80. The method of claim 78 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered parenterally.

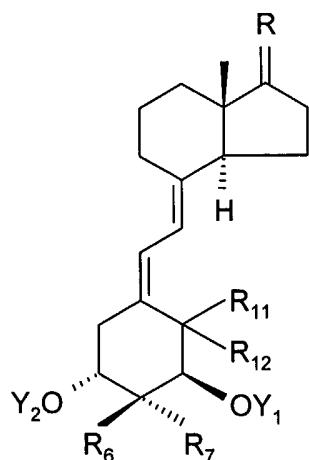
81. The method of claim 78 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered transdermally.

82. The method of claim 78 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered in a dosage of from about 0.01 $\mu$ g/day to about 1000 $\mu$ g/day.

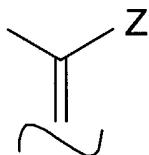
83. A method of treating or preventing obesity of an animal, inhibiting adipocyte differentiation, inhibiting SCD-1 gene transcription, and/or reducing body fat in an animal comprising administering to an animal in need thereof an effective amount of a 17(20)-dehydro vitamin D analog having the formula:

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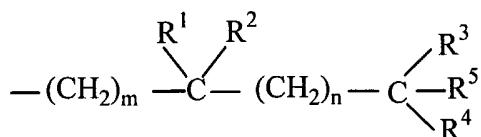


where  $Y_1$  and  $Y_2$ , which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where  $R_{11}$  and  $R_{12}$  are each hydrogen or taken together are a methylene group, where  $R_6$  and  $R_7$ , which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or  $R_6$  and  $R_7$  when taken together may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, or  $R_6$  and  $R_7$  when taken together may represent the group  $=CR_8R_9$  where  $R_8$  and  $R_9$ , which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together  $R_8$  and  $R_9$  may represent the group  $-(CH_2)_x-$  where  $x$  is an integer from 2 to 5, and where the group  $R$  represents a side chain represented by the structure



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where the side chain and 17-ene double bond is in the E configuration and where  $Z$  is selected from  $Y$ ,  $-OY$ ,  $-CH_2OY$ ,  $-C\equiv CY$  and  $-CH=CHY$ , where the double bond in the side chain may have the cis or trans geometry, and where  $Y$  is selected from hydrogen, methyl,  $-COR^5$  and a radical of the structure:



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where  $m$  and  $n$ , independently, represent the integers from 0 to 5, where  $R^1$  is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and  $C_{1-5}$ -alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of  $R^2$ ,

35 R<sup>3</sup>, and R<sup>4</sup>, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C<sub>1-5</sub> alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R<sup>1</sup> and R<sup>2</sup>, taken together, represent an oxo group, or an alkylidene group having a general formula C<sub>k</sub>H<sub>2k</sub>– where k is an integer, the group =CR<sup>2</sup>R<sup>3</sup>, or the group –(CH<sub>2</sub>)<sub>p</sub>–, 40 where p is an integer from 2 to 5, and where R<sup>3</sup> and R<sup>4</sup>, taken together, represent an oxo group, or the group –(CH<sub>2</sub>)<sub>q</sub>–, where q is an integer from 2 to 5, and where R<sup>5</sup> represents hydrogen, hydroxy, protected hydroxy, or C<sub>1-5</sub> alkyl and wherein any of the CH–groups at positions 20, 22, or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups –CH(CH<sub>3</sub>)–, –(CH<sub>2</sub>)<sub>m</sub>–, –CR<sub>1</sub>R<sub>2</sub>– or 45 –(CH<sub>2</sub>)<sub>n</sub>– at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

84. The method of claim 83 wherein the vitamin D analog is administered orally.

85. The method of claim 83 wherein the vitamin D analog is administered parenterally.

86. The method of claim 83 wherein the vitamin D analog is administered transdermally.

87. The method of claim 83 wherein the vitamin D analog is administered in a dosage of from about 0.01μg/date to about 1000μg/day.

88. The method of claim 83 wherein the animal is a human.

89. The method of claim 83 wherein the animal is a domestic animal.

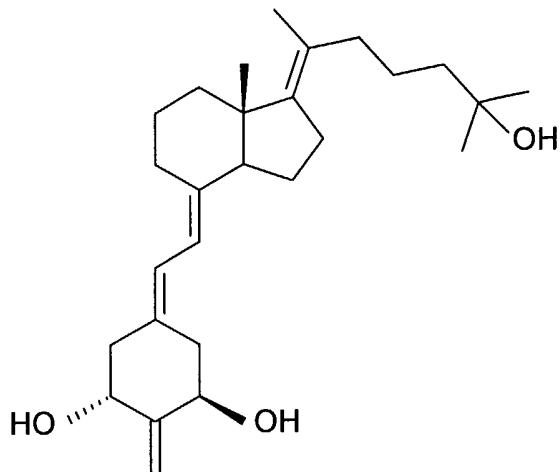
90. The method of claim 83 wherein the animal is an agricultural animal.

91. A method of treating or preventing obesity of an animal, inhibiting adipocyte differentiation, inhibiting SCD-1 gene transcription, and/or reducing body

fat in an animal comprising administering to an animal in need thereof an effective amount of 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub>

5 having the formula:

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92. The method of claim 91 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered orally.

93. The method of claim 91 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered parenterally.

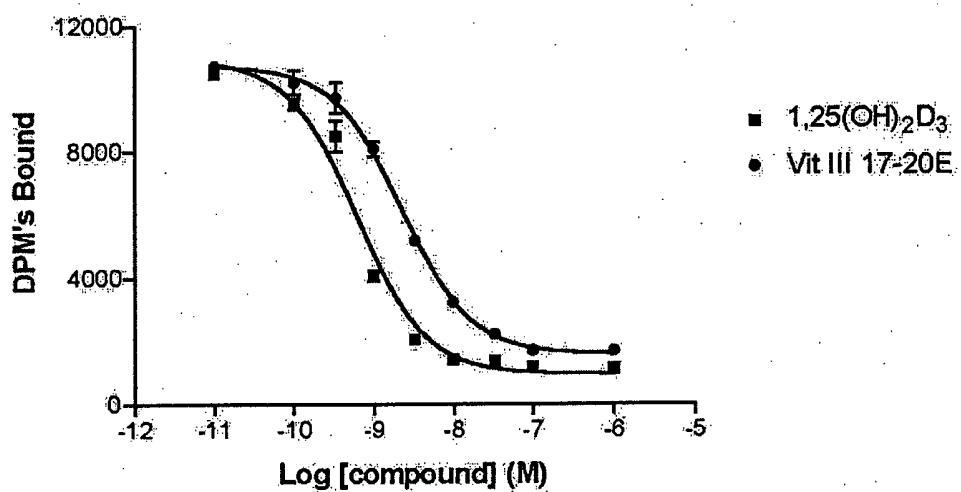
94. The method of claim 91 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered transdermally.

95. The method of claim 91 wherein 17(E)-1 $\alpha$ ,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D<sub>3</sub> is administered in a dosage of from about 0.01 $\mu$ g/day to about 1000 $\mu$ g/day.

96. The method of claim 91 wherein the animal is a human.

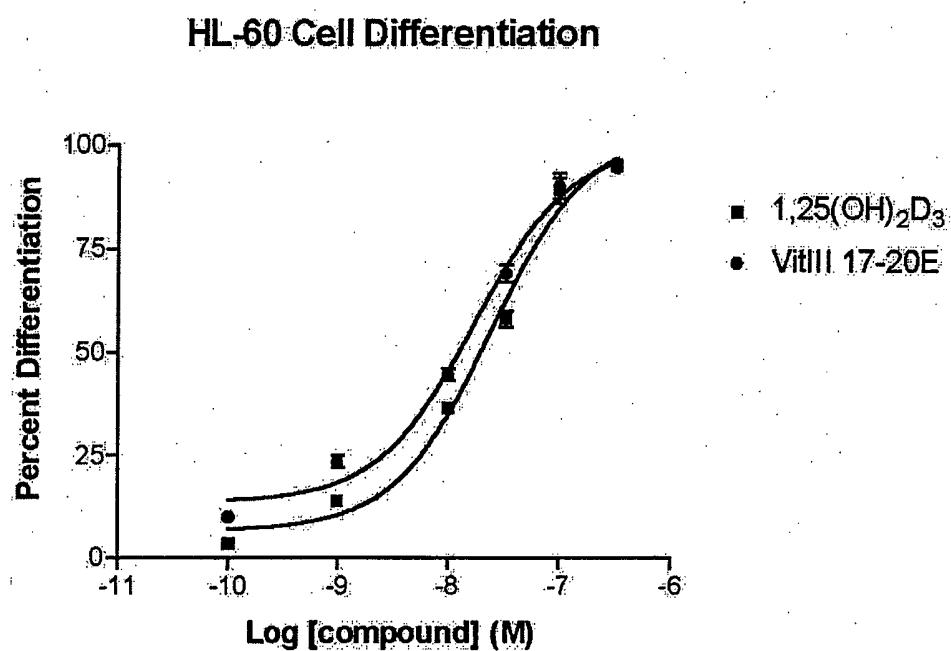
97. The method of claim 91 wherein the animal is a domestic animal.

98. The method of claim 91 wherein the animal is an agricultural animal.

**Competitive VDR Binding**

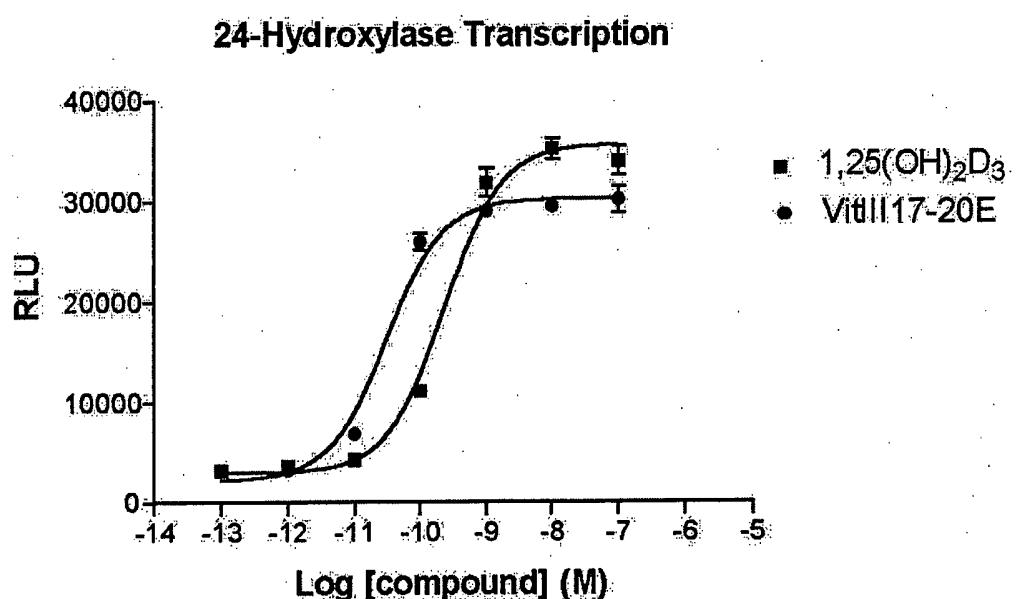
$$K_D = 1,25(\text{OH})_2\text{D}_3 = 1.1 \times 10^{-10} \text{ M}$$
$$K_D = \text{Vit-III 17-20E} = 3.8 \times 10^{-10} \text{ M}$$

**Figure 1**



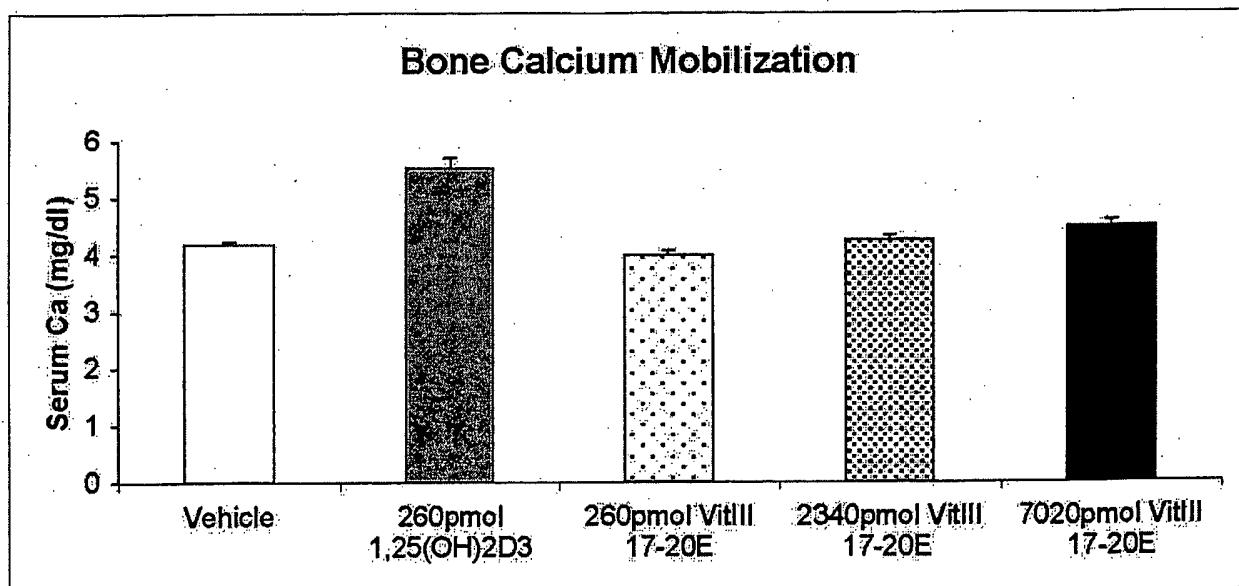
EC<sub>50</sub>: 1,25(OH)<sub>2</sub>D<sub>3</sub> =  $2.5 \times 10^{-8}$  M  
Vit III 17-20E =  $1.7 \times 10^{-8}$  M

**Figure 2**

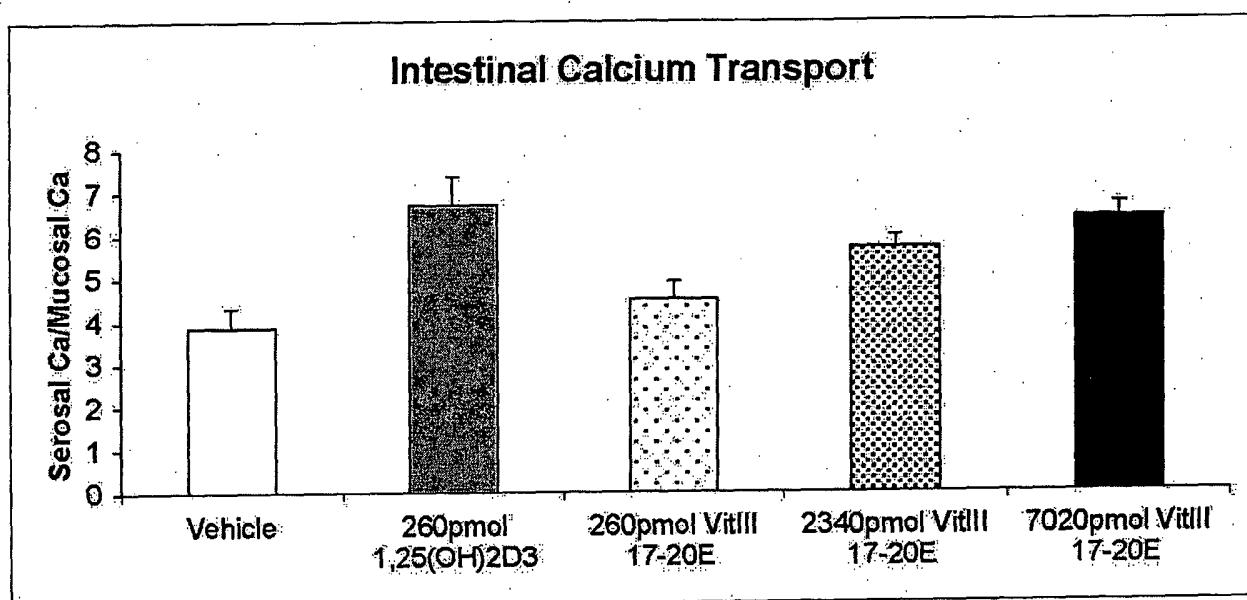


EC<sub>50</sub>: 1,25(OH)<sub>2</sub>D<sub>3</sub> =  $2.3 \times 10^{-10}$  M  
Vit-III 17-20E =  $3.1 \times 10^{-11}$  M

**Figure 3**



**Figure 4**



**Figure 5**