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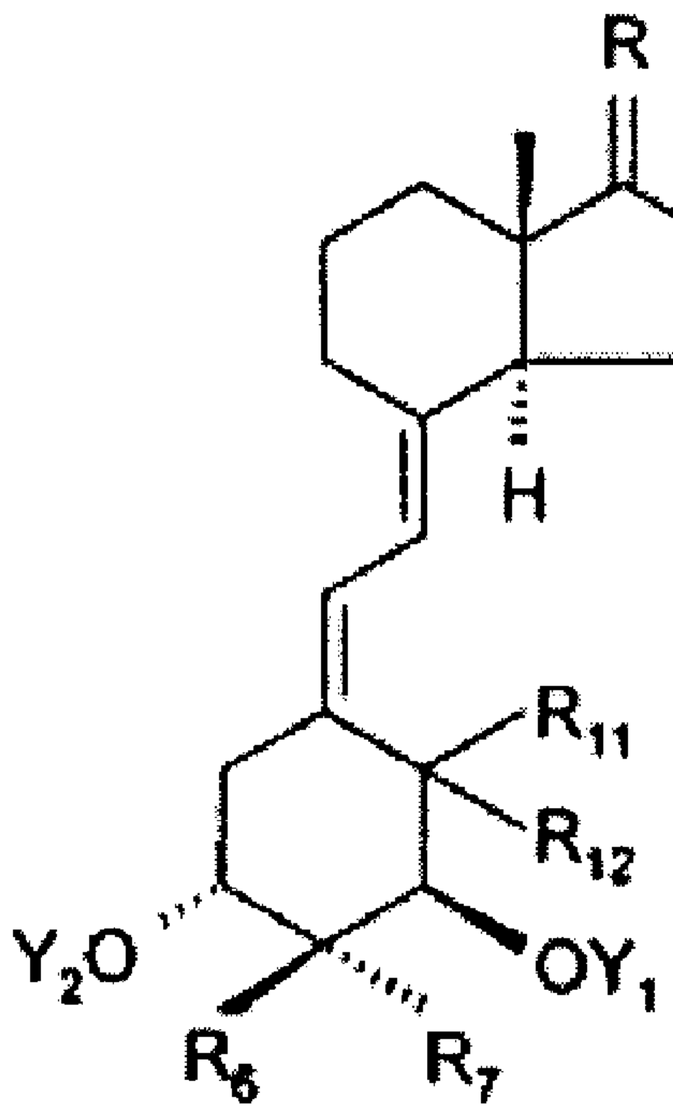
(54) Titre : ANALOGUES DE 17,20(E)-DESHYDRO VITAMINE D ET LEURS UTILISATIONS
(54) Title: 17,20(E)-DEHYDRO VITAMIN D ANALOGS AND THEIR USES



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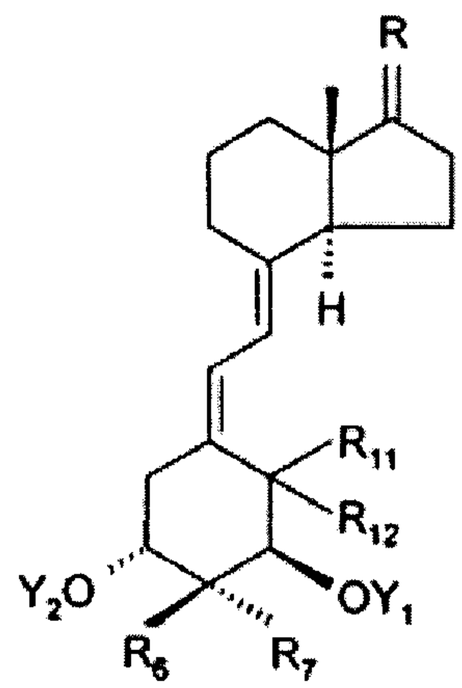
(57) Abrégé/Abstract:
This invention discloses 17,20(E)-dehydro-vitamin D analogs, and specifically 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 and pharmaceutical uses therefor. This compound has use as an anti-cancer agent, in the treatment of skin diseases and skin conditions and in the treatment of autoimmune disorders and inflammatory diseases as well as renal osteodystrophy and obesity. The compounds have the formula I: (see formula I) where Y_1 and Y_2 are each hydrogen or a hydroxy protecting group, where R_{11} and R_{12} are each hydrogen, where R_6 and R_7 are hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy or 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 are hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy or 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 typical side chains known for vitamin D type compounds.

ABSTRACT

This invention discloses 17,20(E)-dehydro-vitamin D analogs, and specifically 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 and pharmaceutical uses therefor. This compound has use as an anti-cancer agent, in the treatment of skin diseases and skin conditions and in the treatment of autoimmune disorders and inflammatory diseases as well as renal osteodystrophy and obesity. The compounds have the formula I:



I

where Y_1 and Y_2 are each hydrogen or a hydroxy protecting group, where R_{11} and R_{12} are each hydrogen, where R_6 and R_7 are hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy or 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 are hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy or 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 typical side chains known for vitamin D type compounds.

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

BACKGROUND OF THE INVENTION

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)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D_3, its biological activities, and its pharmaceutical uses.

The natural hormone, 1α,25-dihydroxyvitamin D_3 and its analog in the ergosterol series, i.e. 1α,25-dihydroxyvitamin D_2 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 1α-hydroxyvitamin D_3, 1α-hydroxyvitamin D_2, various side chain 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.

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., 1α,25-dihydroxy-19-nor-vitamin D_3) 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 (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, 2β-hydroxy and alkoxy (e.g., ED-71) analogs of 1α,25-dihydroxyvitamin D_3 have been described and examined by Chugai group as potential drugs for osteoporosis and as antitumor agents. See also Okano et al., Biochem. Biophys. Res. Commun. 163, 1444 (1989). Other 2-substituted (with hydroxyalkyl, e.g., ED-120, and fluoroalkyl groups) A-ring analogs of 1α,25-dihydroxyvitamin D_3 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)).

2-substituted analogs of 1α,25-dihydroxy-19-nor-vitamin D_3 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 binding sites in vitamin D receptors can accommodate different substituents at C-2 in the synthesized vitamin D analogs.

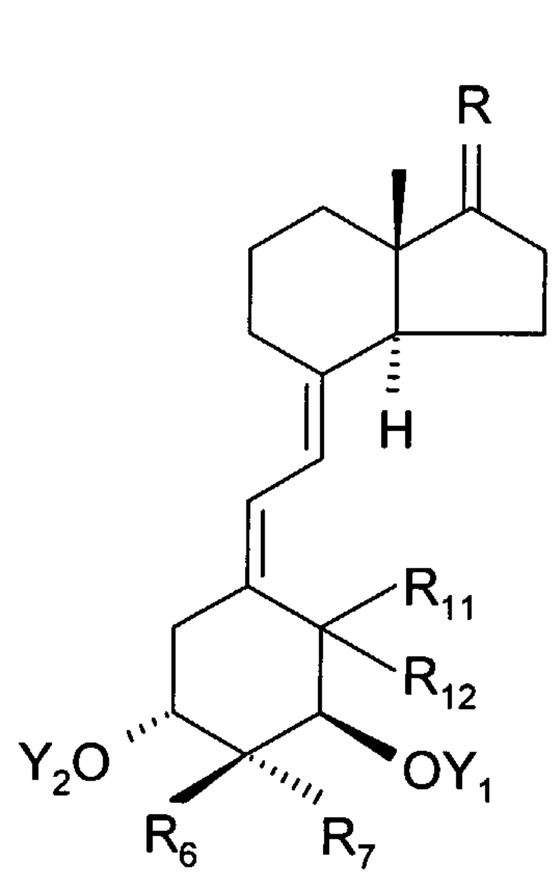
In a continuing effort to explore the 19-nor class of pharmacologically important vitamin D compounds, analogs which are characterized by the presence of a methylene substituent at carbon 2 (C-2), a hydroxyl group at carbon 1 (C-1), and a shortened side chain attached to carbon 20 (C-20) have also been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

and 1α-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 1α,25-dihydroxyvitamin D_3. Their biological activities make 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, and their pharmaceutical uses, and more specifically toward 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D_3, 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:

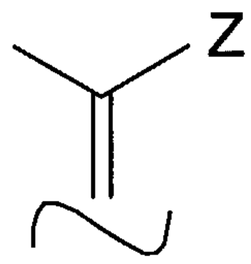


I

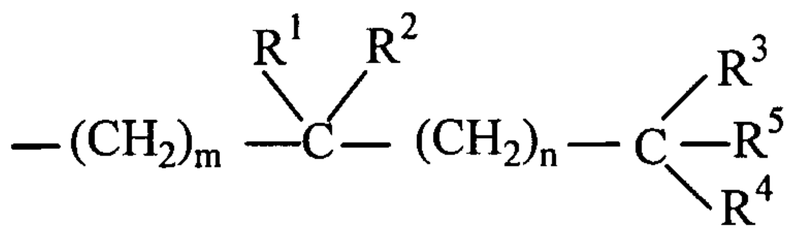
where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where R_{11} and R_{12} are each hydrogen or taken together are a methylene group, where R_6 and R_7, which may be the same or different, are each selected from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



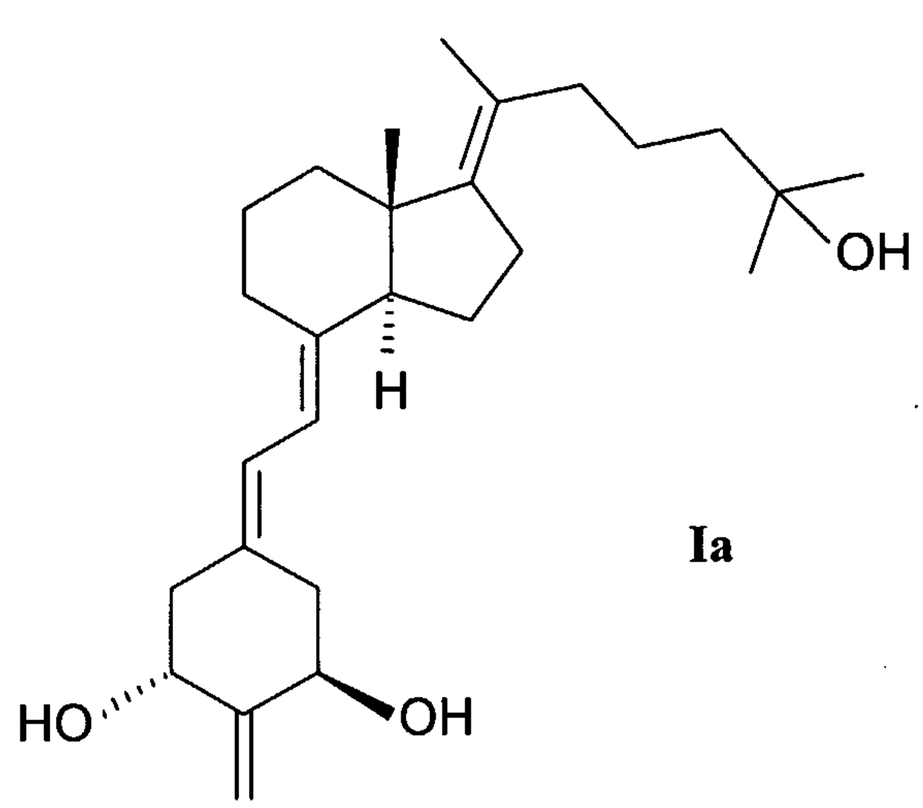
where the side chain and 17-ene double bond is in the E configuration and where Z is selected from Y, –OY, $–CH_2OY$, –C≡CY and –CH=CHY, where the double bond in the side chain may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, $-COR^5$ and a radical of the structure:



where m and n, independently, represent the integers from 0 to 5, where R^1 is 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^3, and R^4, independently, is selected from deuterium, deuteroalkyl, hydrogen, 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 R^1 and R^2, taken together, represent an oxo group, or an alkylidene group having a general formula C_kH_{2k}– where k is an integer, the group $=CR^2R^3$, or the group $-(CH_2)_p-$, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or the group $-(CH_2)_q-$, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} 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 $-CH(CH_3)-$, $-(CH_2)_m-$, $-CR_1R_2-$ or $-(CH_2)_n-$ at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

The preferred analog is 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D_3 which has the following formula **Ia**:



Ia

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 1α,25-dihydroxyvitamin D_3, and have very low ability to mobilize calcium from bone, as compared to 1α,25-dihydroxyvitamin D_3.

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 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 prevent the above-noted diseases and disorders in an amount from about 0.01μg/gm to about 1000 μg/gm of the composition, preferably from about 0.1μg/gm to about 500μg/gm of the composition, and may be administered topically, transdermally, orally, rectally, nasally, sublingually, or parenterally in dosages of from about 0.01μg/day to about 1000μg/day, preferably from about 0.1μg/day to about 500 μg/day.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1-5 illustrate various biological activities of 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D_3, hereinafter referred to as "VIT-III," as compared to the native hormone 1α,25-dihydroxyvitamin D_3, hereinafter "$1,25(OH)_2D_3$."

Figure 1 is a graph illustrating the relative activity of VIT-III and $1,25(OH)_2D_3$ to compete for binding with $[^3H]$-$1,25$-$(OH)_2$-D_3 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 $1,25(OH)_2D_3$;

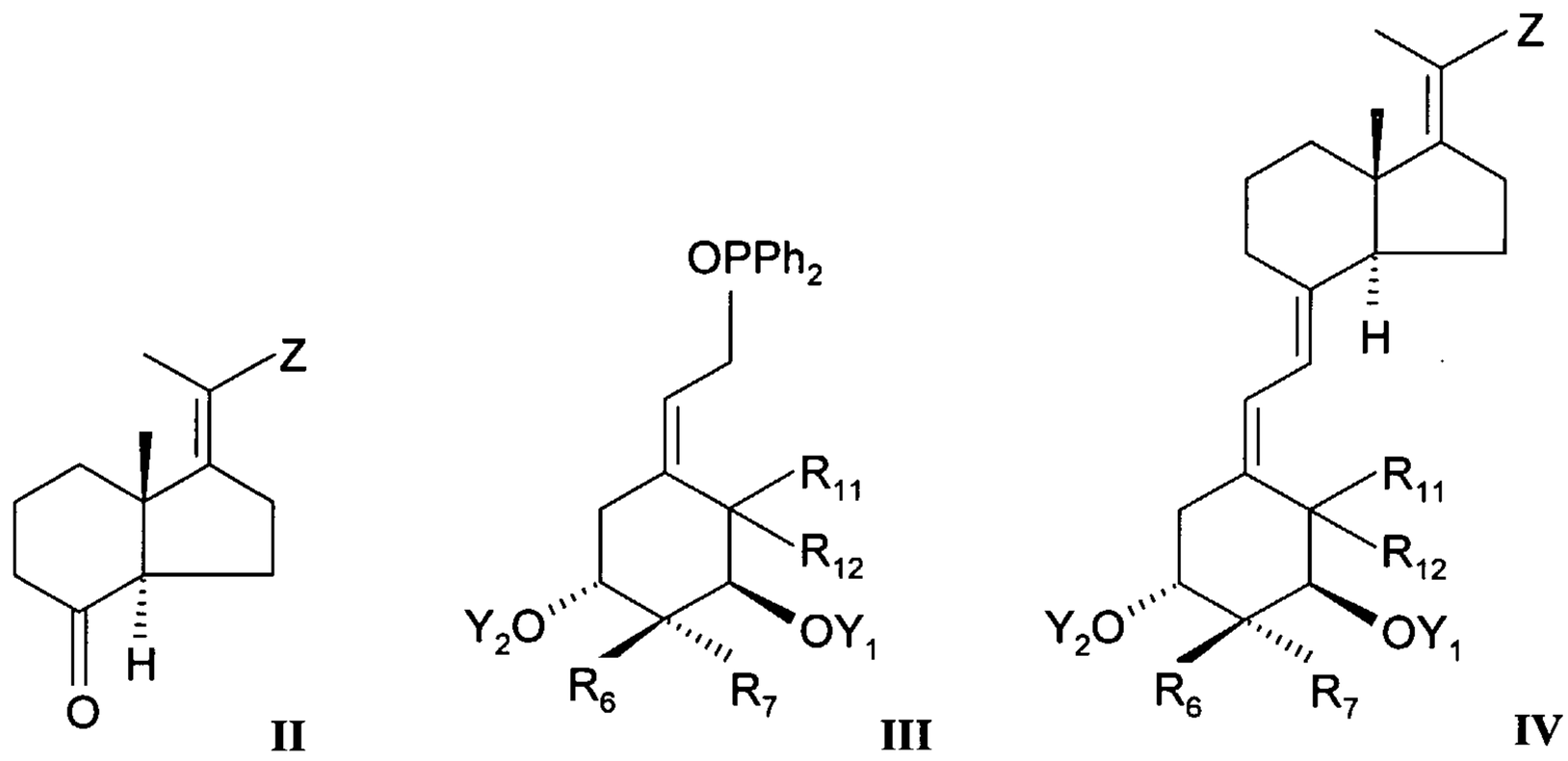
Figure 3 is a graph illustrating the in vitro transcription activity of $1,25(OH)_2D_3$ as compared to VIT-III;

Figure 4 is a bar graph illustrating the bone calcium mobilization activity of $1,25(OH)_2D_3$ as compared to VIT-III; and

Figure 5 is a bar graph illustrating the intestinal calcium transport activity of $1,25(OH)_2D_3$ 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:



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); Baggiolini 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 VIT-III).

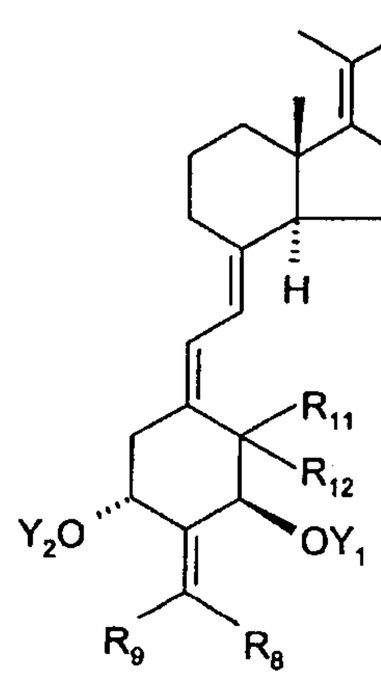
For the preparation of the required phosphine oxides of general structure III, a synthetic route has been developed starting from a methyl quinicate derivative which is easily obtained from commercial (IR,3R,4S,5R)-(-)-quinic acid as described by Perlman et al., Tetrahedron Lett. 32, 7663 (1991) and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

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".

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

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

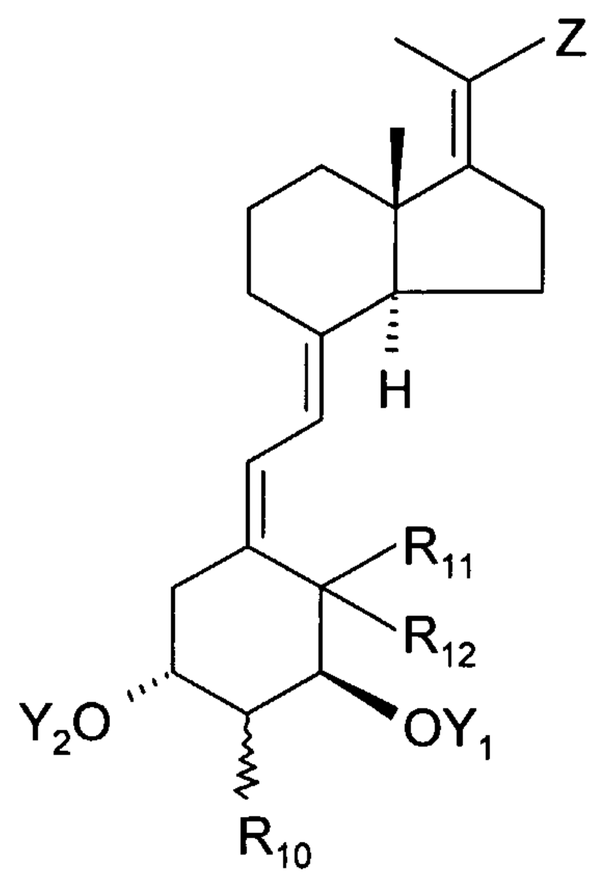


V

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 $-(CH_2)_x-$ 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:



VI

where Y_1, Y_2, R_{11}, R_{12} and Z are as previously defined herein, and R_{10} is selected from 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 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 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 or more of them may also be derivatived with a hydrolyzable group.

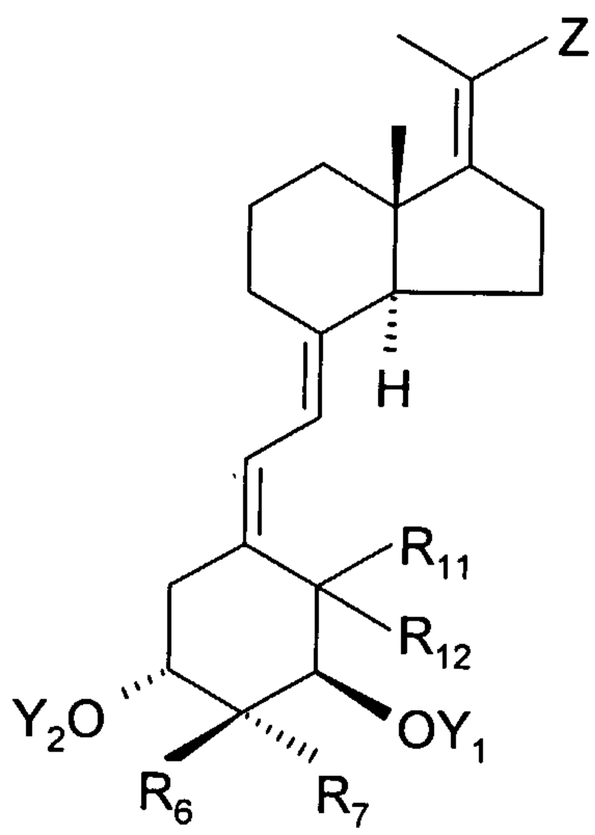
The "hydrolyzable group" present in the above-mentioned derivatives is preferably an acyl group, i.e. a group of the type Q^1CO-, where Q^1 represents hydrogen or a hydrocarbon radical of from 1 to 18 carbons that may be straight chain, cyclic, branched, saturated or unsaturated. Thus, for example, the hydrocarbon radical may be a 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-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:



VII

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 $CH_3(CH_2)_4CO$;

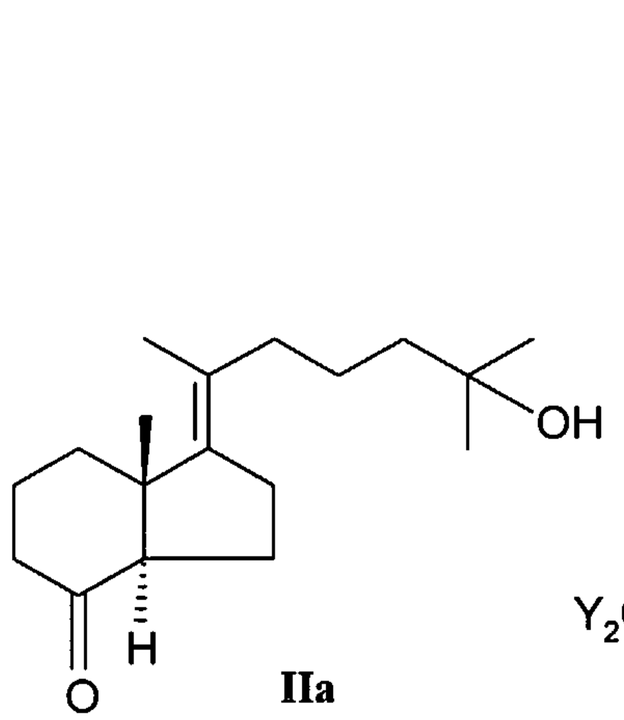
1,3,25-Trinonanoates where $Y_1=Y_2=Y_3$ and is $CH_3(CH_2)_7CO$; and

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

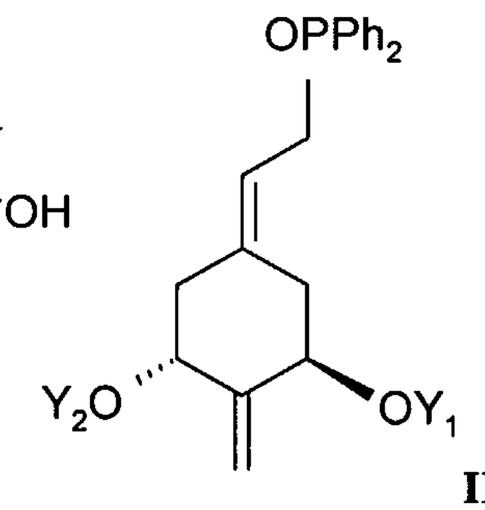
These compounds can be prepared by known methods. See for example WO97/11053 published March 27, 1999, and the previous description herein.

17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 (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.

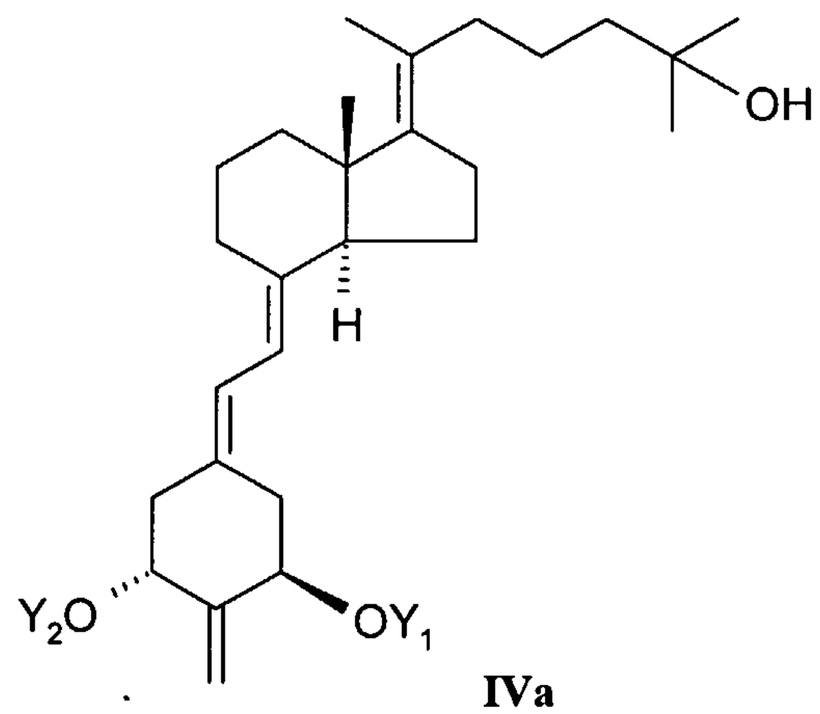
The preparation of 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 having the structure **Ia** can be accomplished by the condensation of a bicyclic Windaus-Grundmann type ketone **IIa** with the allylic phosphine oxide **IIIa** to the corresponding 17(20)-dehydro-vitamin D analog **IVa** followed by deprotection at C-1 and C-3 to provide Ia:



IIa



IIIa



IVa

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).

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, 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 oxalyl, malonyl, succinyl, glutaryl group, or an aromatic acyl group such as benzoyl, or a halo, nitro or alkyl substituted benzoyl group. The word "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 tetrahydrofuranyl and tetrahydropyranyl. Preferred silyl-protecting groups are 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 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.

SYNTHESIS

Des-A,B-23,24-dinorcholan-8β,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_3 was bubbled through the solution until a deep blue color developed and persisted (about 1h). The solution was treated with O_2 until the blue color faded (15 min). Then $NaBH_4$ (1.5 g, 39.7 mmol) was added. After 15 min. second portion of $NaBH_4$ (1.5 g, 39.7 mmol) was added and the reaction was allowed to warm to rt. Then the third portion of $NaBH_4$ (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 vaccuo and residue was dissolved in ethyl acetate. The organic phase was washed with 1N aqueous solution of HCl (100 mL), saturated $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic phase was dried (Na_2SO_4), 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 ^oC;^1H NMR (400 MHz, $CDCl_3$) δ: 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 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^+, 2), 194 (M^+-H_2O, 15), 179 (M^+-H_2O-CH_3, 18), 125 (43), 111 (100); exact mass calculated for $C_{13}H_{22}O$ [M - H_2O]$^+$ is 194.1671, measured is 194.1665.

Des-A,B-22-(*p*-toluenesulfonyloxy)-23,24-dinorcholan-8β-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_2Cl_2 (50 mL) and washed with saturated $CuSO_4$ solution (30 mL), 1N HCl (30 mL), and water (50 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by silica gel chromatography (25% ethyl acetate/hexane) yielded 1.7 g (4.64 mmol, 98%) of hydroxyl tosylate **3.** ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100MHz, $CDCl_3$) 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* (relative integration): 366 (M^+, 6), 194(14), 179(16), 125(30), 111(100); exact mass calculated for $C_{20}H_{30}SO_4Na$ ($M + Na^+$) is 389.1763, measured is 389.1768.

Des-A,B-8*β*-[(*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) 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 ^{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_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography (5% ethyl acetate/hexane) to give 1.94g (4.04 mmol, 99%) of **4.** ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100MHz, $CDCl_3$) δ: 114.5, 133.4, 129.8, 127.9, 74.8, 69.3, 52.3, 52.6, 42.2, 40.5, 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-8*β*-[(*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 $NaHCO_3$ (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 (Na_2SO_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**. H NMR (400 MHz, $CDCl_3$) δ: 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}C NMR (100MHz, $CDCl_3$) δ: 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.

Des-A,B-8*β*-[(*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. 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 O_2 was bubbled through the solution for additional 10 min. The reaction was quenched with water (15 mL) and extracted with ether (3 x 30 mL). The combined organic phases were dried (Na_2SO_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.** ^1H NMR (400 MHz, $CDCl_3$) δ: 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}C NMR (100MHz, $CDCl_3$) δ: 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.

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_2SO_4), 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. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (6H, s), 1.64 (2H, m), 1.96 (2H, m), 3.44 (2H, t, J = 6.68 Hz).

5-Bromo-2methyl-2[(*tert*-butyldimethylsilyl)oxy]-pentane (9). To a -50 ^{0}C cooled solution of alcohol **8** (3 g, 16.6 mmol) in anhydrous CH_2Cl_2 (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_2Cl_2 (3 x 40 mL), and combined organic phases were washed with 1N aqueous solution of NaOH (40 mL), dried (Na_2SO_4), 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.** ^{1}H NMR (400 MHz, $CDCl_3$) 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-8*β*,25-diols (15a and 15b):

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 ^{0}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 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_4Cl (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 (Na_2SO_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 temperature overnight and poured into ice-water and extracted with ether (3 x 20 mL). The organic layer was washed with saturated $CuSO_4$ solution (30 mL), 1N HCl (30 mL), water (50 mL). The organic phase was dried ($NaSO_4$), filtered and concentrated. Column Chromatography of crude mixture furnished 0.72 g (78%) of mixture of 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 ^{0}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, 36h; 50 mg, 48h)]. Methanol was evaporated and residue was diluted with ethyl acetate (30 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ solution (20 mL) water (20 mL), dried (Na_2CO_3) and evaporated. The residue was purified on column chromatography to yield 0.284 g (79%) of a mixture of olefin alcohols **14a, 14b, 15a, 15b, 16**. The olefin alcohols were separated on HPLC.

17(*E*)-Des-A,B-cholestan-17(20)-dehydro-8*β*,25-diol (15a). The olefin alcohols 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 μmol, 25%) was eluted at Rv = 50 mL. $[\alpha]^{25}_D$ -16.5^0 (c 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (3H, s), 1.20 (6H, s), 1.67 (3H, t, J = 1.84Hz), 4.14 (1H, m). ^{13}C NMR (100MHz, $CDCl_3$) δ: 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, 22.2, 19.1, 17.9, 17.2. MS *m/z* (relative intensity): 280 (M^+, 16), 262 (M-H_2O^+, 7), 229 (M-2xH_2O –CH_3^+, 16) 179(54), 161(100); Exact mass calculated for $C_{18}H_{32}O_2$ $[M+Na]^+$ 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 μmol) in anhydrous CH_2Cl_2 (5 mL) was added PDC (40 mg, 107 μmol) 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 filtrate was concentrated and applied on a Sep-Pak™ cartridge and eluted with ethyl acetate/hexane (20/80) to give 17 mg, (61.1 μmol, 86%) of ketone as colorless oil. To a -50 °C cooled solution of ketone (17 mg, 61.1 μmol) in anhydrous CH_2Cl_2 (5 mL) was added 2,6-lutidine (9 μL, 7.86 mg, 73.3 μmol) folowed by TESOTf (17 μL, 19.4 mg, 73.3 μmol). The solution was stirred at 0 °C for 15 min and water (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 5 mL), and combined organic phases were dried (Na_2SO_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 μmol, 60%) was eluted at R_v = 20 mL as colorless oil. $[\alpha]^{25}_D$ -14.4 (c 0.73, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 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}C NMR (100MHz, $CDCl_3$) δ: 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 M^+, 377($[M-CH_3]^+$, 3) 363($[M-C_2H_5]^+$, 9), 204(100), 189((18), 161(45). Exact mass calculated for $C_{24}H_{44}O_2Si$ $[M+Na]^+$ is 415.3008, found 415.3016.

17(*E*)-1α,25 Dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D_3 (20a). To a solution of phosphine oxide **18** (0.051 g, 87.6 μmol) in anhydrous THF (500 μL) at -25 ^{0}C was slowly added PhLi 1.2M in cyclohexane/ether (70/30) (80 μL, 8.1 mg, 96.4 μmol) under argon with stirring. The solution turned deep orange. The mixture was stirred at that temperature for 20 min and cooled to -78 °C. A precooled (-78 °C) solution of ketone **17a** (14 mg, 35.7 μmol) in anhydrous THF (100 μL) was added slowly. The mixture was stirred under argon atmosphere at -78 °C for 3h and at 0 °C for 18h. Ethyl acetate was added and organic phase was washed with brine, dried

(Na_2SO_4) 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 μmol, 29%) was eluted at R_v = 20 mL as colorless oil. UV (in hexane) λ_{max} 243.1, 252, 262.2 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 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^+, 624(59), 366(32), 91(100); Exact mass calculated for $C_{45}H_{84}O_3Si_3$ $[M+Na]^+$ is 779.5626, found 779.5648.

The protected vitamin **19a** (7.7 mg, 10.2 μmol) was dissolved in anhydrous THF (500 μL) and treated with TBAF (0.102 mL, 26.7 mg, 102 μmol) 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 μmol, 69%) was collected at R_v = 42 mL as white solid: UV (in EtOH) λ_{max} 242.9, 251, 261.2 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 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^+, 36), 396($[M-H_2O]^+$, 6), 381($[M-H_2O-CH_3]^+$, 8) 285(70), 149(61), 69(100).

17(*Z*)-Des-A,B-cholest-17(20)-dehydro-8*β*,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 Rv = 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 μmol) in anhydrous CH_2Cl_2 (5 mL) was added PDC (55 mg, 145.7 μmol) 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 μmol, 89%) as colorless oil. To a -50 °C cooled solution of ketones 30.2 mg (30.2 mg, 108.6 μmol) in anhydrous CH_2Cl_2 (10 mL) was added 2,6-lutidine (16 μL, 13.9 mg, 130.3 μmol) followed by TESOTf (30 μL, 34.5 mg, 130.3 μmol). The solution was stirred at 0 °C for 15min and water (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 5 mL), and combined organic phases were dried (Na_2SO_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 μmol, 18%) was eluted at R_v = 34mL as colorless oil. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 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}CNMR (100MHz, $CDCl_3$) δ: 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 M^+, 363 ($[M - C_2H_5]^+$, 10), 334 ($[M - 2xC_2H_5]^+$, 1), 204 (100).

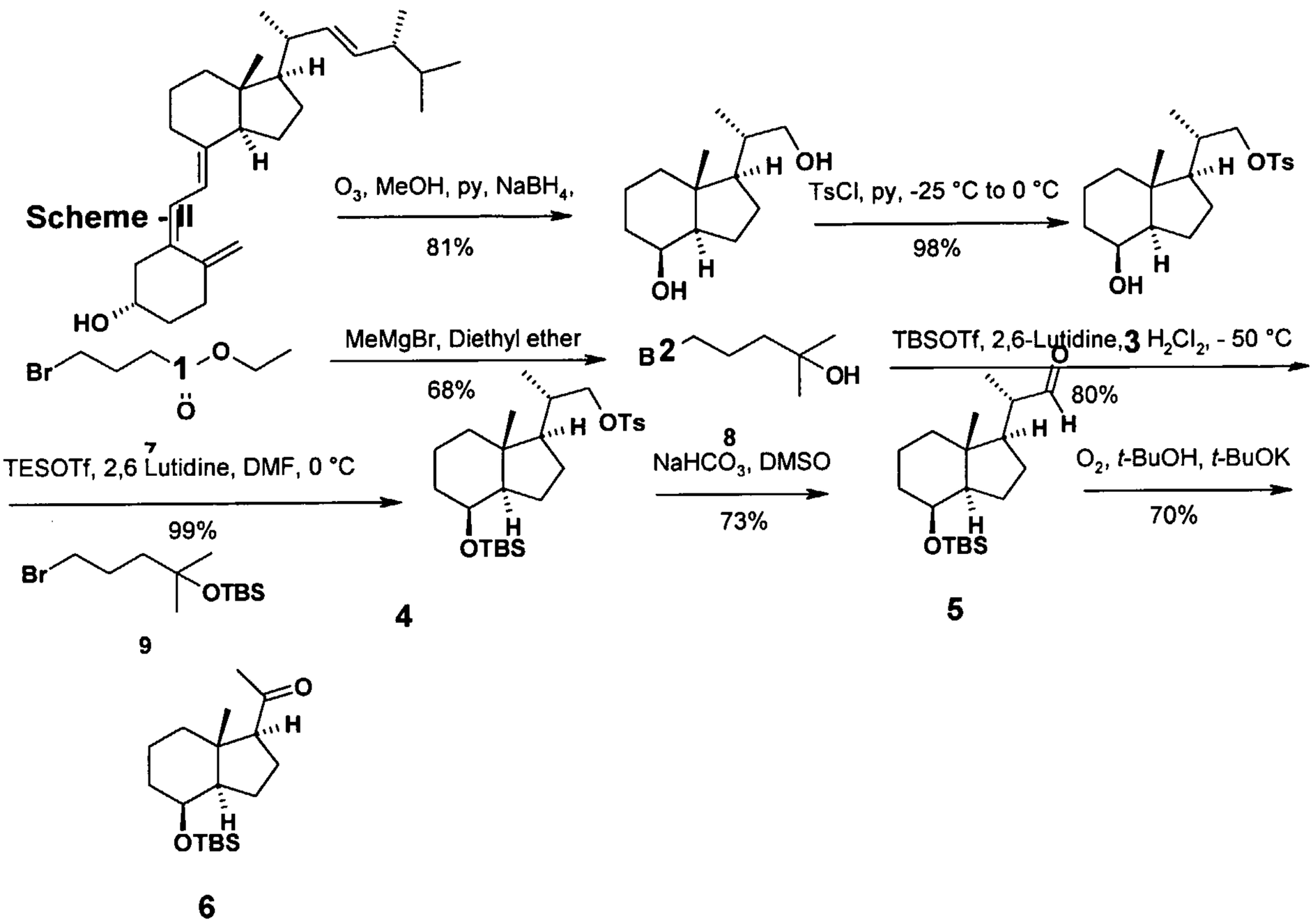
17(*Z*)-1α,25 Dihydroxy-17(20)-dehydro-2-methylene-19-norvitamin D_3 (20b). To a solution of phosphine oxide **10** (62 mg, 106.5 μmol) in anhydrous THF (750 μL) at -25 ^{0}C was slowly added PhLi 1.8 M in Di-n-butyl ether (59 μL, 8.9mg, 106.5 μmol) under argon with stirring. The solution turned deep orange. The mixture was stirred at that temperature for 20 min and cooled to -78 °C. A precooled (-78 °C) solution of ketone **17b** (7.7 mg, 19.6 μmol) in anhydrous THF (100 μL) was added slowly. The mixture was stirred under argon atmosphere at -78 °C for 3h and at 0 °C for 18h.

Ethyl acetate was added and organic phase was washed with brine, dried (Na_2SO_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 μmol, 86%) was eluted at R_v = 19 mL as colorless oil. $[\alpha]^{25}_D$ -9.35 (c 0.64, $CHCl_3$); UV (in hexane): λ_{max} 244.4, 253.2, 263.2 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 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 = 11.1Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 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 M^+, 366(2), 263(100); Exact mass calculated for $C_{45}H_{84}O_3Si_3[M+Na]^+$ is 779.5626, found 779.5647.

The protected vitamin **19b** (12.8 mg, 16.9 mmol) was dissolved in anhydrous THF (500 μL) and treated with TBAF (170 μL, 44.2 mg, 169 μmol) 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 μmol, 62%) was eluted at R_v = 33 mL. UV (in ethanol): λ_{max} 244.1, 252.5, 262.1nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 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, 4.44Hz), 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 (M^+, 90), 399 ($M\text{-}CH_3^+$, 17), 381 $[M\text{-}CH_3\text{-}H_2O]^+$, 18), 363 ($[M\text{-}CH_3\text{-}2 \times H_2O]^+$, 7), 285 (86), 243 (35), 91 (100); exact mass calculated for $C_{27}H_{42}O_3$ ($[M+Na]^+$) is 437.3032, measured is 437.3026.

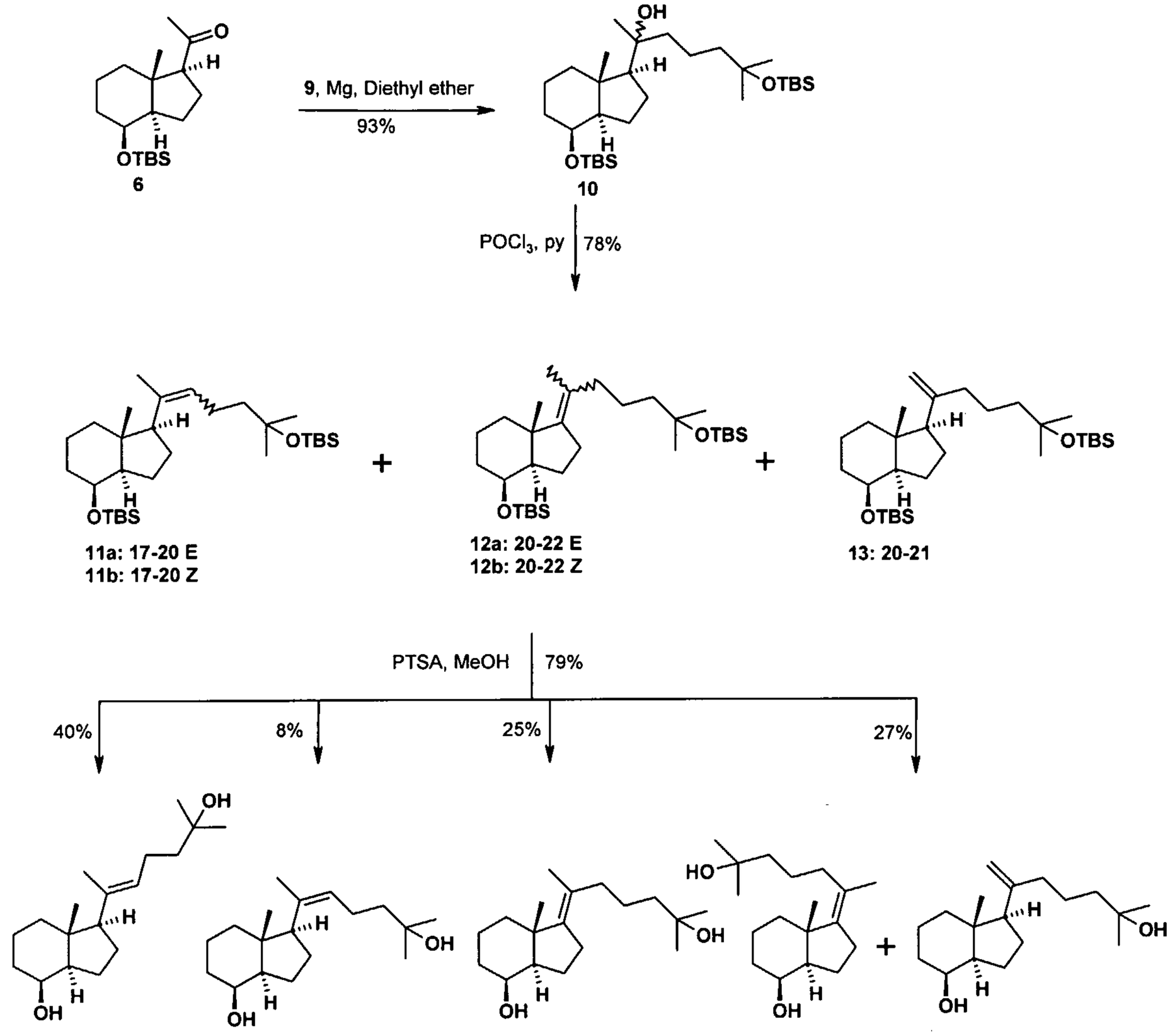
SCHEMES

Scheme - I



Scheme - II

Scheme - III


O
H
OTBS
H
6
9, Mg, Diethyl ether
93%
OH
H
OTBS
OTBS
10
POCl3, py
78%
H
OTBS
OTBS
11a: 17-20 E
11b: 17-20 Z
+
OTBS
H
OTBS
12a: 20-22 E
12b: 20-22 Z
+
H
OTBS
OTBS
13: 20-21
PTSA, MeOH
79%
40%
8%
25%
27%
OH
H
OH
14a: 20-22E
OH
H
OH
14b: 20-22Z
OH
H
OH
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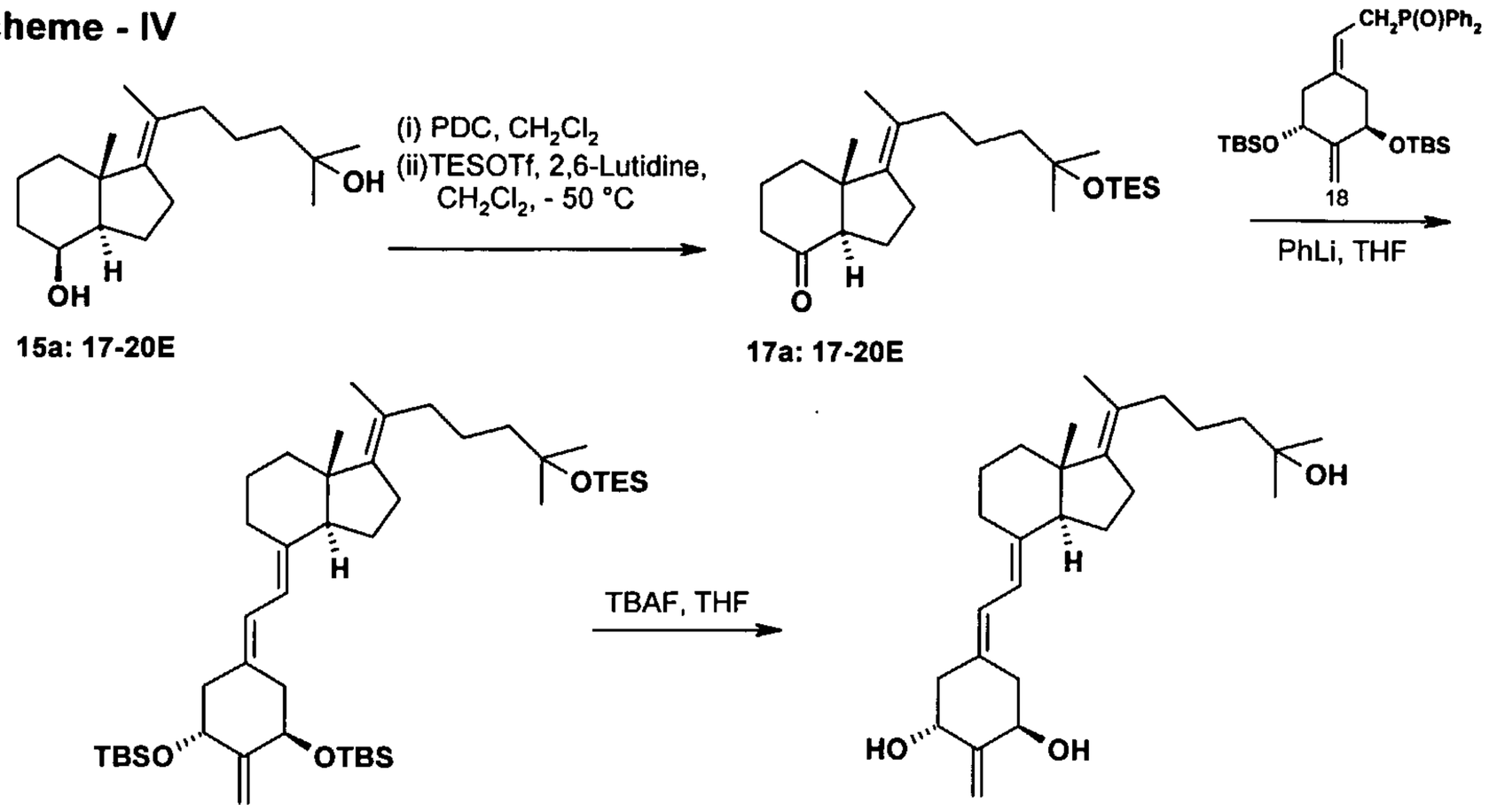
HO
H
OH
15b: 17-20Z
+
H
OH
OH
16: 20-21

Scheme - IV



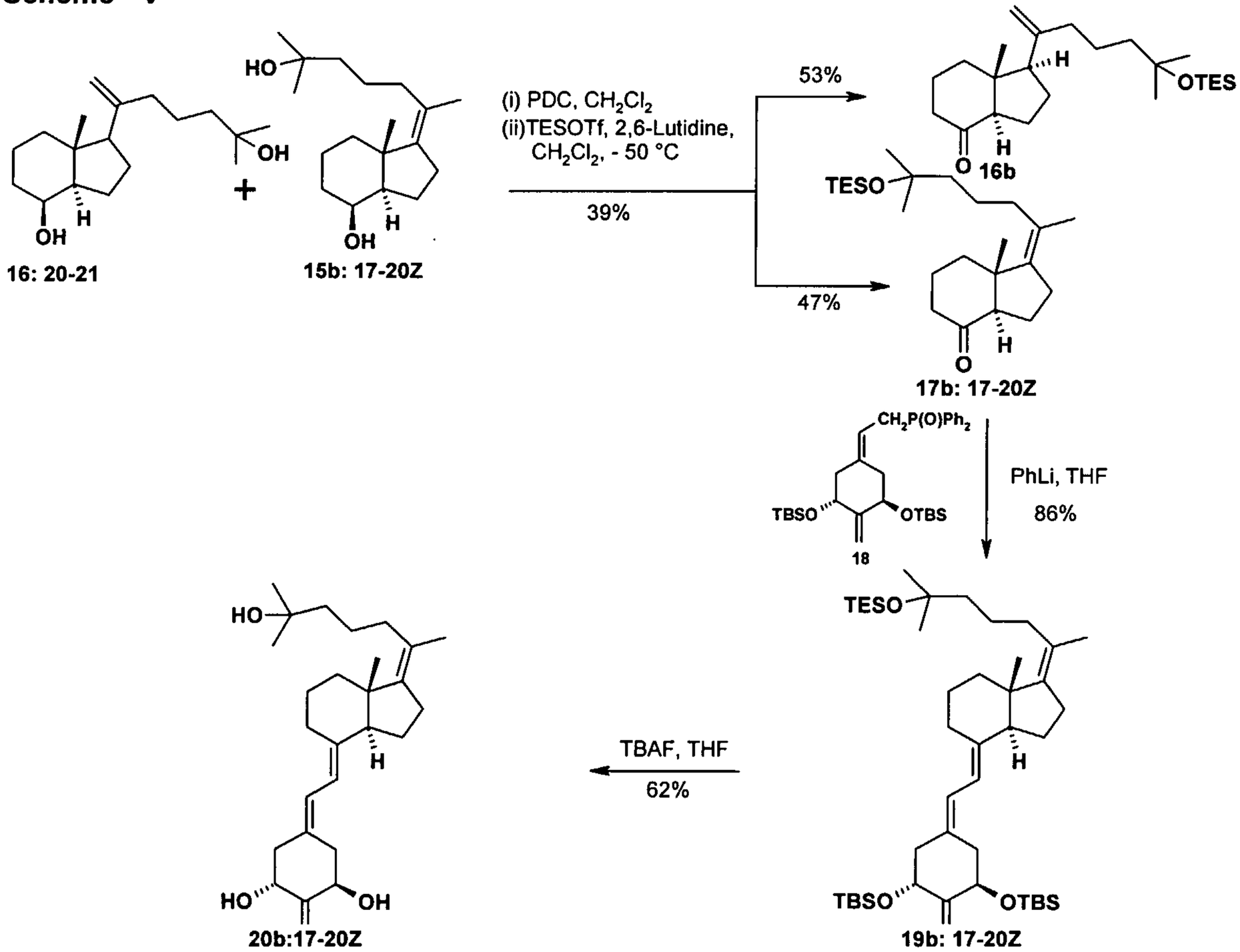
15a: 17-20E

17a: 17-20E

19a: 17-20E

20a: 17-20E

Scheme - V



16: 20-21

15b: 17-20Z

17b: 17-20Z

20b:17-20Z

19b: 17-20Z

BIOLOGICAL ACTIVITY OF 17(E)-1α,25-DIHYDROXY-17(20)-DEHYDRO-2-METHYLENE-19-NORVITAMIN D_3

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 1α,25-dihydroxy-19-nor-vitamin D_3 in its E configuration had little or no effect on binding to the full length recombinant rat vitamin D receptor, as compared to 1α,25-dihydroxyvitamin D_3. The compound VIT-III bound equally well to the receptor as compared to the standard 1,25-$(OH)_2D_3$ (Figure 1). It might be expected from these results that compound VIT-III would have equivalent biological activity. Surprisingly, 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_3 (1,25$(OH)_2D_3$), the natural hormone, in stimulating intestinal calcium transport.

Figure 4 demonstrates that VIT-III has very little bone calcium mobilization activity, as compared to 1,25$(OH)_2D_3$.

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$(OH)_2D_3$ on HL-60 cell differentiation, making it an excellent candidate for the treatment of psoriasis and cancer, 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 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 1α,25-dihydroxyvitamin D_3 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.

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

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

Vitamin D Receptor Binding

Test Material

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 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 $TEDK_{50}$ (50 mM Tris, 1.5 mM EDTA, pH7.4, 5 mM DTT, 150 mM KCl) with 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 ($1,25(OH)_2D_3$: molar extinction coefficient = 18,200 and λ_{max} = 265 nm). Radiolabeled ligand (^{3}H-$1,25(OH)_2D_3$, ~159 Ci/mmole) was added in ethanol at a final concentration of 1 nM.

Assay Conditions

Radiolabeled and unlabeled ligands were added to 100 mcl of the diluted protein at a final ethanol concentration of ≤10%, mixed and incubated overnight on ice to reach binding equilibrium. The following day, 100 mcl of hydroxylapatite slurry (50%) was added to each tube and mixed at 10-minute intervals for 30 minutes. The hydroxylapaptite 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 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

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 (≤ 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_2.

Assay Conditions

HL60 cells were plated at 1.2×10^5 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. 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).

<u>In vitro Transcription Assay</u>

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., "A Highly Sensitive Method For Large-Scale Measurements Of 1,25-Dihydroxyvitamin D3", Analytical Biochemistry, Vol. 255, Issue 1, pp. 148-154 (1998). Cells were given a range of doses. Sixteen hours after dosing the cells were harvested and luciferase activities were measured using a luminometer. RLU = relative lucerifase units.

Antagonism was tested by adding a combination of $1,25(OH)_2D_3$ and the compound in the same well keeping the final ethanol concentration the same.

<u>Intestinal Calcium Transport and Bone Calcium Mobilization</u>

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 transport analysis using the everted gut sac method.

Antagonism was tested by administering a combination of $1,25(OH)_2D_3$ and the compound to the animal simultaneously.

INTERPRETATION OF DATA

VDR binding, HL60 cell differentiation, and transcription activity. VIT-III ($K_i=3.8x10^{-10}M$) is equivalent to the natural hormone 1α,25-dihydroxyvitamin D_3 ($K_i=1.1x10^{-10}M$) in its ability to compete with $[^3H]$-$1,25(OH)_2D_3$ for binding to the full-length recombinant rat vitamin D receptor (Figure 1). There is also little difference between VIT-III ($EC_{50}=1.7x10^{-8}M$) in its ability (efficacy or potency) to promote HL60 differentiation as compared to 1α,25-dihydroxyvitamin D_3 ($EC_{50}=2.8x10^{-8}M$) (See Figure 2). Also, compound VIT-III ($EC_{50}=3.1x10^{-11}M$) has about the same transcriptional activity in bone cells as 1α,25-dihydroxyvitamin D_3 ($EC_{50}=2.3x10^{-10}M$) (See Figure 3). These results suggest 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 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.

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 $1,25(OH)_2D_3$ in intestine and bone were tested. As expected, the

native hormone ($1,25(OH)_2D_3$) 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 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-II1 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 $1,25(OH)_2D_3$ 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 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 $1,25(OH)_2D_3$; and (3) it is easily synthesized. Since VIT-III has significant 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 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 0.01μg to 1000μg per day of the compounds I, particularly VIT-III, preferably from about 0.1μg to about 500 μg per day, is appropriate for prevention and/or treatment purposes, such dose being adjusted 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. 1α-hydroxyvitamin D_2 or D_3, or 1α,25-dihydroxyvitamin D_3 -- in situations where different degrees of bone mineral mobilization and calcium transport 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 μg to about 1000 μg per gm of composition, preferably from about 0.1 μg to about 500 μg per gram of composition, and may be administered topically, transdermally, orally, rectally, nasally, sublingually, or parenterally in dosages of from about 0.01μg/day to about 1000 μg /day, and preferably from about 0.1 μg/day to about 500 μg/day.

The compounds I, particularly VIT-III, may be formulated as creams, lotions, 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.

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 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 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 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.

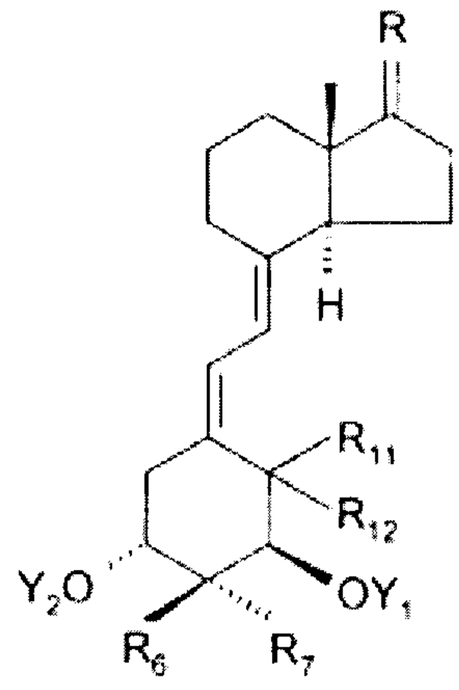
Formulations suitable for topical administration include liquid or semi-liquid preparations such as liniments, lotions, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops; or as sprays.

For nasal administration, inhalation of powder, self-propelling or spray 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 100µ.

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

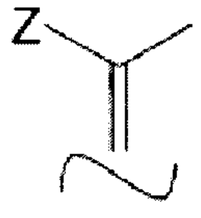
CLAIMS:

1. A compound having the formula:

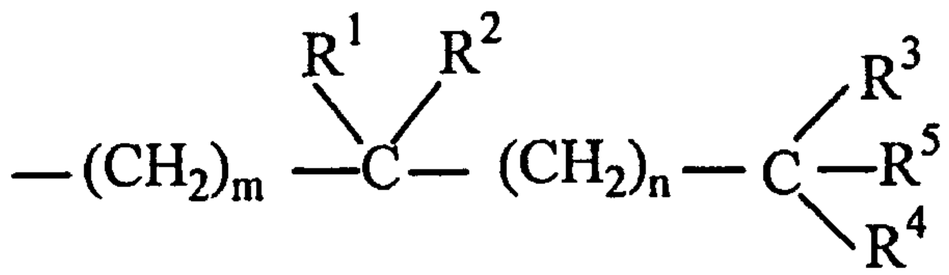


I

where Y_1 and Y_2, which may be the same or different, are hydrogen or a hydroxy-protecting group, where R_{11} and R_{12} are each hydrogen, where R_6 and R_7, which may be the same or different, are hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy or 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 hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy or 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

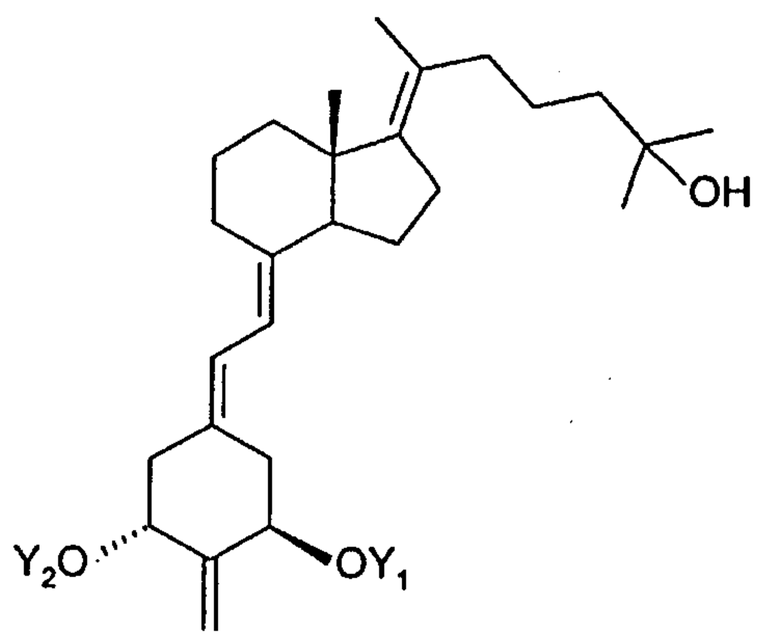


where the side chain and 17-ene double bond is in the E configuration and where Z is Y, -OY, $-CH_2OY$, $-C\equiv CY$ or $-CH=CHY$, where the double bond in the side chain may have the cis or trans geometry, and where Y is hydrogen, $-COR^5$ or a radical of the structure:



where m and n, independently, represent the integers from 0 to 5, where R^1 is hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, or 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^3, and R^4, independently, is deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl or C_{1-5} alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, or where R^1 and R^2, taken together, represent an oxo group, the group $=CR^4R^3$, or the group $-(CH_2)_p-$, where p is an integer from 2 to 5, or where R^3 and R^4, taken together, represent an oxo group, or the group $-(CH_2)_q-$, where q is an integer from 2 to 5, and where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl and wherein any of the CH- groups at positions 22 or 23 in the side chain may be replaced by a nitrogen atom, or where any of the groups $-(CH_2)_m-$, $-CR_1R_2-$ or $-(CH_2)_n-$ at positions 22 and 23, respectively, may be replaced by an oxygen or sulfur atom.

2. A compound having the formula:



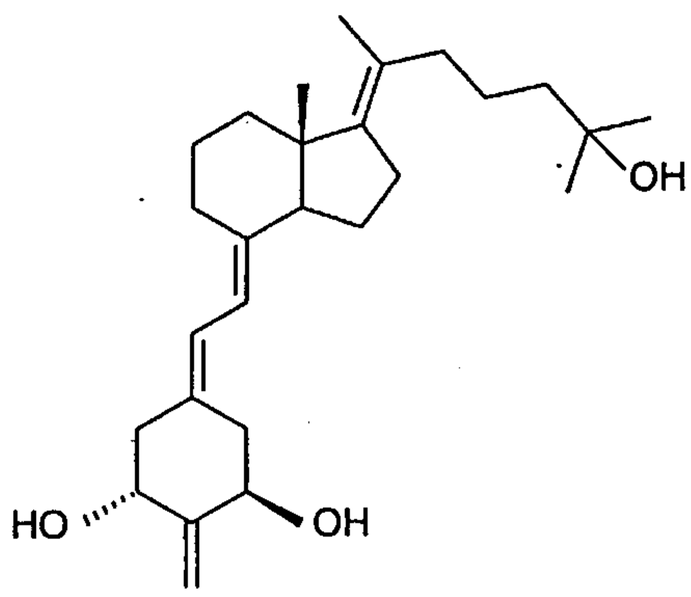
where Y_1 and Y_2, which may be the same or different, are each hydrogen or a hydroxy-protecting group.

3. The compound of claim 1 or 2, wherein Y_2 is hydrogen.

4. The compound of claim 1 or 2, wherein Y_1 is hydrogen.

5. The compound of claim 1 or 2, wherein Y_1 and Y_2 are both t-butyldimethylsilyl.

6. 17(E)-1α,25-dihydroxy-17(20)-dehydro-2-methylene-19-nor-vitamin D_3 having the formula:



7. A pharmaceutical composition containing a compound as defined in any one of claims 1-6 together with a pharmaceutically acceptable excipient.

8. The pharmaceutical composition of claim 7 containing said compound in an amount of from 0.01 μg to 1000 μg per gram of composition.

9. The pharmaceutical composition of claim 8 containing said compound in an amount of from 0.1 μg to 500 μg per gram of composition.

10. The use of a compound as defined in any one of claims 1-6, in the manufacture of a therapeutic product or products for the treatment of psoriasis.

11. The use as defined in claim 10, wherein said products are formulated for oral administration.

12. The use as defined in claim 10, wherein said products are formulated for parenteral administration.

13. The use as defined in claim 10, wherein said products are formulated for transdermal administration.

14. The use as defined in claim 10, wherein said products are formulated for topical administration.

15. The use as defined in any one of claims 10-14, wherein said products contain said compound in an amount from 0.01µg to 1000µg per gram of product.

16. The use as defined in claim 15, wherein said products contain said compound in an amount from 0.1µg to 500µg per gram of product.

17. The use as defined in any one of claims 10-14, wherein said products are formulated as daily dosage units each containing said compound in an amount from 0.01µg to 1000µg.

18. The use as defined in claim 17, wherein said products are formulated as daily dosage units each containing said compound in an amount from 0.1µg to 500µg.

19. The use of a therapeutically effective amount of a compound as defined in any one of claims 1- 6 in the treatment of psoriasis.

20. The use of a composition as defined in claim 7 in the treatment of psoriasis, wherein said composition is formulated into daily dosage units each containing said compound in a therapeutically effective amount of from 0.01µg to 1000µg.

21. The use of a compound as defined in any one of claims 1- 6, in the manufacture of a

therapeutic product or products for the treatment of a disease in the form of leukemia, colon cancer, breast cancer, skin cancer or prostate cancer.

22. The use as defined in claim 21, wherein said products are formulated for oral administration.

23. The use as defined in claim 21, wherein said products are formulated for parenteral administration.

24. The use as defined in claim 21, wherein said products are formulated for transdermal administration.

25. The use as defined in any one of claims 21-24, wherein said products contain said compound in an amount from 0.01μg to 1000μg per gram of product.

26. The use as defined in claim 25, wherein said products contain said compound in an amount from 0.1μg to 500μg per gram of product.

27. The use as defined in any one of claims 21-24, wherein said products are formulated as daily dosage units each containing said compound in an amount from 0.01μg to 1000μg.

28. The use as defined in claim 27, wherein said products are formulated as daily dosage units each containing said compound in an amount from 0.1μg to 500μg.

29. The use of a therapeutically effective amount of a compound as defined in any one of claims 1-6 in the treatment of a disease in the form of leukemia, colon cancer, breast cancer, skin cancer or prostate cancer.

30. The use of a composition as defined in claim 7 in the treatment of a disease in the form of leukemia, colon cancer, breast cancer, skin cancer or prostate cancer, wherein said

composition is formulated into daily dosage units each containing said compound in a therapeutically effective amount of from 0.01µg to 1000µg.

31. The use of a compound as defined in any one of claims 1-6 in the manufacture of a therapeutic product or products for the treatment of an autoimmune disease in the form of multiple sclerosis, lupus, diabetes mellitus, host versus graft rejection, or rejection of organ transplants.

32. The use as defined in claim 31, wherein said products are formulated for oral administration.

33. The use as defined in claim 31, wherein said products are formulated for parenteral administration.

34. The use as defined in claim 31, wherein said products are formulated for transdermal administration.

35. The use as defined in any one of claims 31-34, wherein said products contain said compound in an amount from 0.01µg to 1000µg per gram of product.

36. The use as defined in claim 35, wherein said products contain said compound in an amount from 0.1µg to 500µg per gram of product.

37. The use as defined in any one of claims 31-34, wherein said products are formulated as daily dosage units each containing said compound in an amount from 0.01µg to 1000µg.

38. The use as defined in claim 37, wherein said products are formulated as daily dosage units each containing said compound in an amount from 0.1µg to 500µg.

39. The use of a therapeutically effective amount of a compound as defined in any one of claims 1- 6 in the treatment of an autoimmune disease in the form of multiple sclerosis, lupus, diabetes mellitus, host versus graft rejection, and rejection of organ transplants.

40. The use of a composition as defined in claim 7 in the treatment of an autoimmune disease in the form of multiple sclerosis, lupus, diabetes mellitus, host versus graft rejection, and rejection of organ transplants, wherein said composition is formulated into daily dosage units each containing said compound in a therapeutically effective amount of from 0.01µg to 1000µg.

41. The use of a compound as defined in any one of claims 1-6, in the manufacture of a therapeutic product or products for the treatment of an inflammatory disease in the form of rheumatoid arthritis, asthma, or inflammatory bowel disease.

42. The use as defined in claim 41, wherein said products are formulated for oral administration.

43. The use as defined in claim 41, wherein said products are formulated for parenteral administration.

44. The use as defined in claim 41, wherein said products are formulated for transdermal administration.

45. The use as defined in any one of claims 41-44, wherein said products contain said compound in an amount from 0.01µg to 1000µg per gram of product.

46. The use as defined in claim 45, wherein said products contain said compound in an amount from 0.1µg to 500µg per gram of product.

47. The use as defined in any one of claims 41-44, wherein said products are formulated as daily dosage units each containing said compound in an amount from 0.01μg to 1000μg.

48. The use as defined in claim 47, wherein said products are formulated as daily dosage units each containing said compound in an amount from 0.1μg to 500μg.

49. The use of a therapeutically effective amount of a compound as defined in any one of claims 1- 6 in the treatment of an inflammatory disease in the form of rheumatoid arthritis, asthma, or inflammatory bowel disease.

50. The use of a composition as defined in claim 7 in the treatment of an inflammatory disease in the form of rheumatoid arthritis, asthma, or inflammatory bowel disease, wherein said composition is formulated into daily dosage units each containing said compound in a therapeutically effective amount of from 0.01μg to 1000μg.

51. The use of a compound as defined in any one of claims 1-6, in the manufacture of a therapeutic product or products for the treatment of a skin condition in the form of wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration or insufficient sebum secretion.

52. The use as defined in claim 51, wherein said products are formulated for oral administration.

53. The use as defined in claim 51, wherein said products are formulated for parenteral administration.

54. The use as defined in claim 51, wherein said products are formulated for transdermal administration.

55. The use as defined in claim 51, wherein said products are formulated for topical administration.

56. The use as defined in any one of claims 51-55, wherein said products contain said compound in an amount from 0.01µg to 1000µg per gram of product.

57. The use as defined in claim 56, wherein said products contain said compound in an amount from 0.1µg to 500µg per gram of product.

58. The use as defined in any one of claims 51-55, wherein said products are formulated as daily dosage units each containing said compound in an amount from 0.01µg to 1000µg.

59. The use as defined in claim 58, wherein said products are formulated as daily dosage units each containing said compound in an amount from 0.1µg to 500µg.

60. The use of a therapeutically effective amount of a compound as defined in any one of claims 1- 6 in the treatment of a skin condition in the form of wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration or insufficient sebum secretion.

61. The use of a composition as defined in claim 7 in the treatment of a skin condition in the form of wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration or insufficient sebum secretion, wherein said composition is formulated into daily dosage units each containing said compound in a therapeutically effective amount of from 0.01µg to 1000µg.

62. The use of a compound as defined in any one of claims 1- 6, in the manufacture of a therapeutic product or products for the treatment of renal osteodystrophy.

63. The use as defined in claim 62, wherein said products are formulated for oral administration.

64. The use as defined in claim 62, wherein said products are formulated for parenteral administration.

65. The use as defined in claim 62, wherein said products are formulated for transdermal administration.

66. The use as defined in any one of claims 62-65, wherein said products contain said compound in an amount from 0.01μg to 1000μg per gram of product.

67. The use as defined in claim 66, wherein said products contain said compound in an amount from 0.1μg to 500μg per gram of product.

68. The use as defined in any one of claims 62-65, wherein said products are formulated as daily dosage units each containing said compound in an amount from 0.01μg to 1000μg.

69. The use as defined in claim 68, wherein said products are formulated as daily dosage units each containing said compound in an amount from 0.1μg to 500μg.

70. The use of a therapeutically effective amount of a compound as defined in any one of claims 1- 6 in the treatment of renal osteodystrophy.

71. The use of a composition as defined in claim 7 in the treatment of renal osteodystrophy, wherein said composition is formulated into daily dosage units each containing said compound in a therapeutically effective amount of from 0.01μg to 1000μg.

72. The use of a compound as defined in any one of claims 1- 6, in the manufacture of a therapeutic product or products for the treatment or prevention of obesity of an animal, inhibiting adipocyte differentiation, inhibiting SCD-1 gene transcription or reducing body fat in said animal.

73. The use as defined in claim 72, wherein said products are formulated for oral administration.

74. The use as defined in claim 72, wherein said products are formulated for parenteral administration.

75. The use as defined in claim 72, wherein said products are formulated for transdermal administration.

76. The use as defined in any one of claims 72-75, wherein said products contain said compound in an amount from 0.01μg to 1000μg per gram of product.

77. The use as defined in claim 76, wherein said products contain said compound in an amount from 0.1μg to 500μg per gram of product.

78. The use as defined in any one of claims 72-75, wherein said products are formulated as daily dosage units each containing said compound in an amount from 0.01μg to 1000μg.

79. The use as defined in claim 78, wherein said products are formulated as daily dosage units each containing said compound in an amount from 0.1μg to 500μg.

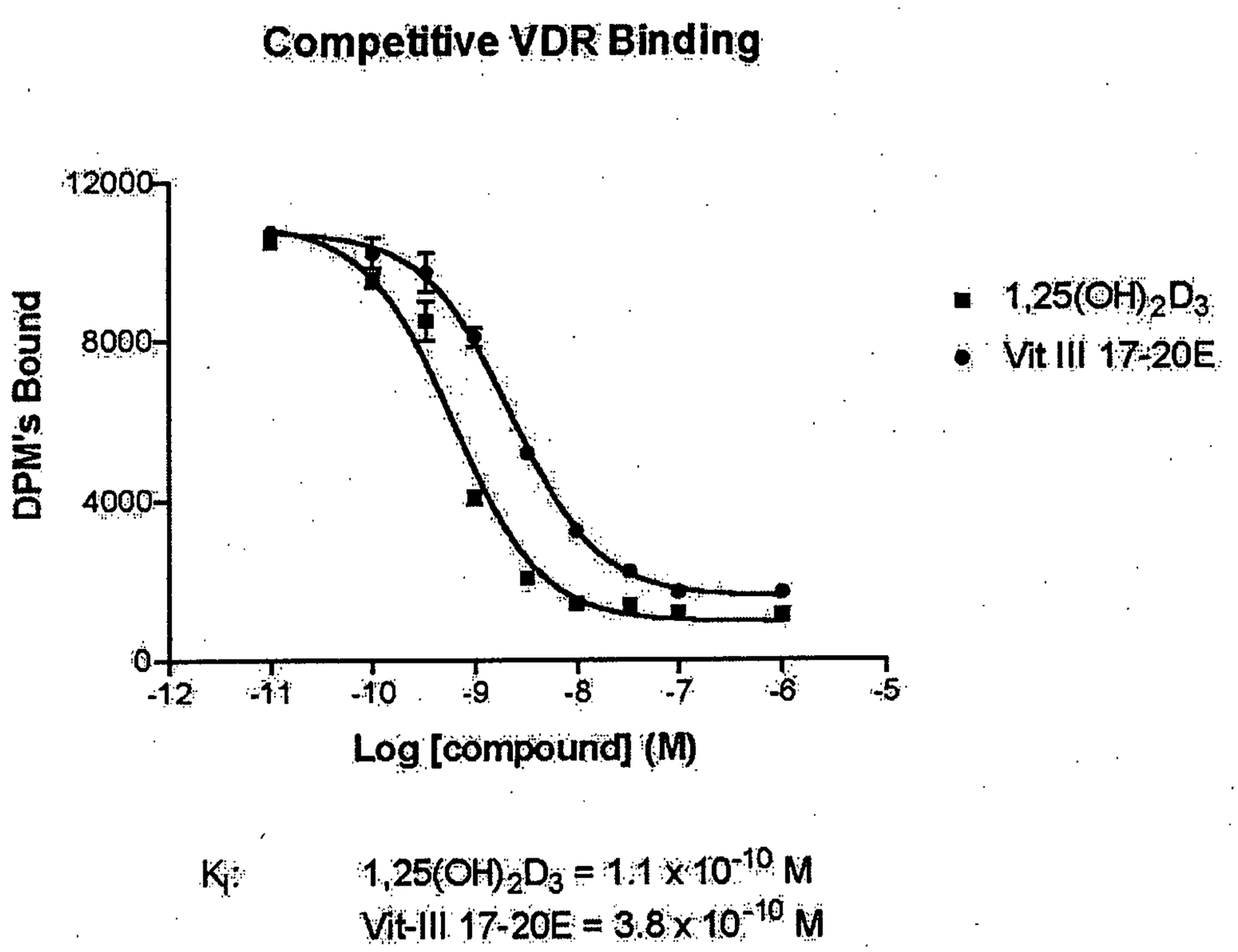
80. The use of a therapeutically effective amount of a compound as defined in any one of claims 1- 6 in the treatment of or prevention of obesity of an animal, inhibiting adipocyte differentiation, inhibiting SCD-1 gene transcription or reducing body fat in said animal.

81. The use of a composition as defined in claim 7 in the treatment of or prevention of obesity of an animal, inhibiting adipocyte differentiation, inhibiting SCD-1 gene transcription or reducing body fat in said animal, wherein said composition is formulated into daily dosage units each containing said compound in a therapeutically effective amount of from 0.01μg to 1000μg.

82. The use as defined in claim 80 or 81, wherein the animal is a human.

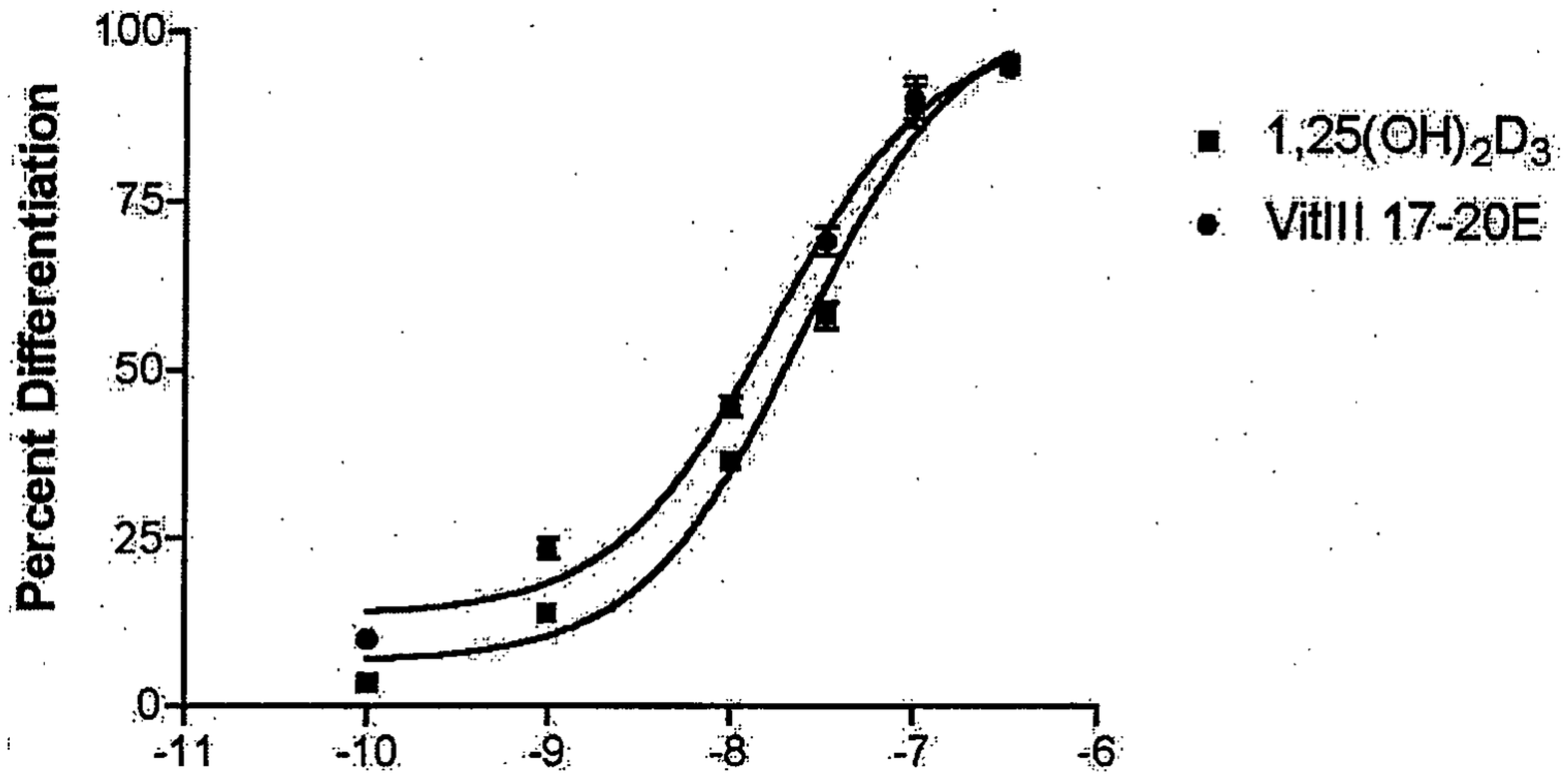
83. The use as defined in 80 or 81, wherein the animal is a domestic animal.

84. The use as defined in claim 80 or 81, wherein the animal is an agricultural animal.



K_i: $1,25(OH)_2D_3 = 1.1 \times 10^{-10}$ M
Vit-III 17-20E = 3.8×10^{-10} M

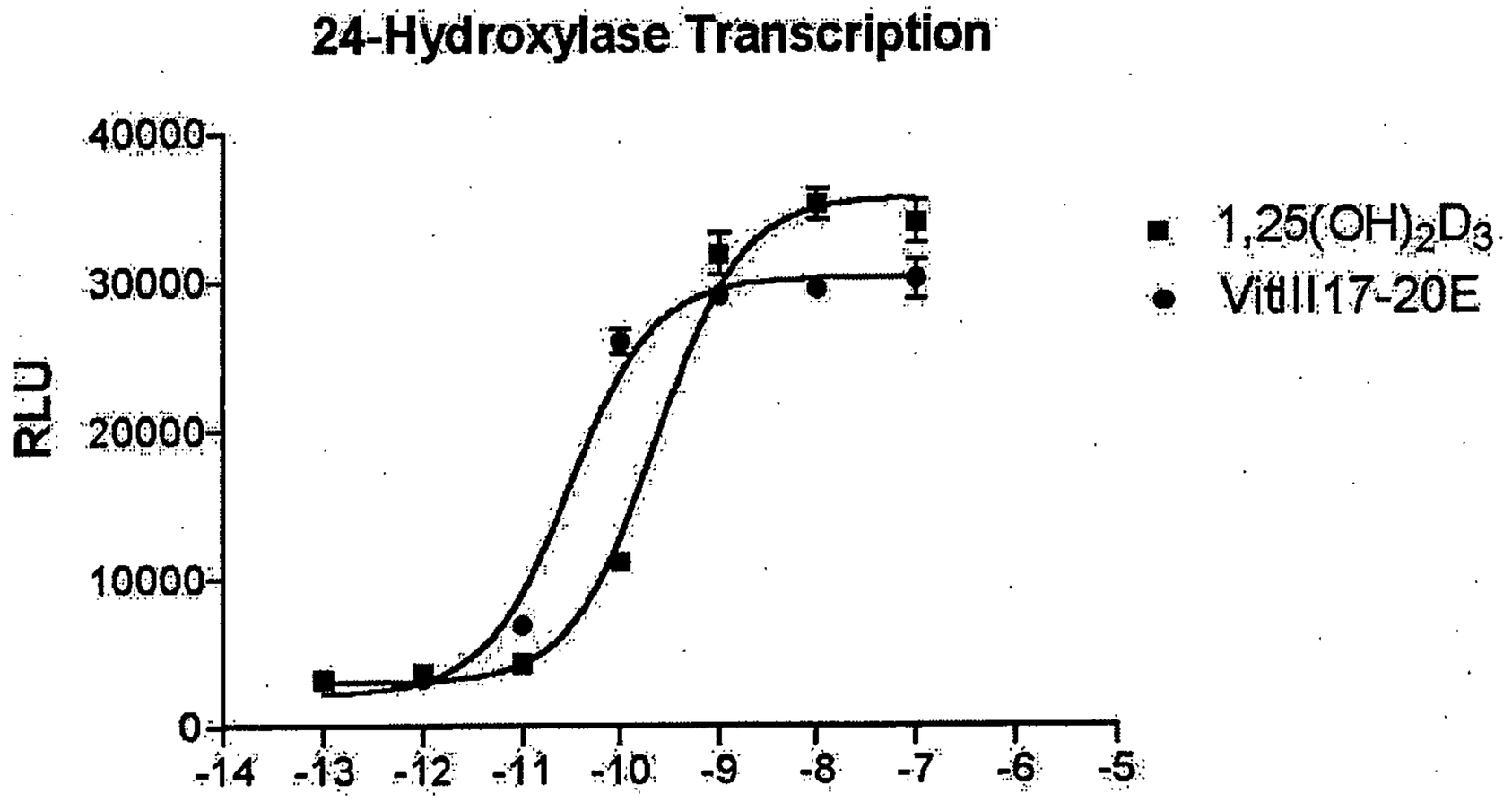
Figure 1



EC_{50}: $1,25(OH)_2D_3 = 2.5 \times 10^{-8}$ M

Vit III 17-20E = 1.7×10^{-8} M

Figure 2



EC_{50}: $1,25(OH)_2D_3 = 2.3 \times 10^{-10}$ M

Vit-III 17-20E = 3.1×10^{-11} M

Figure 3

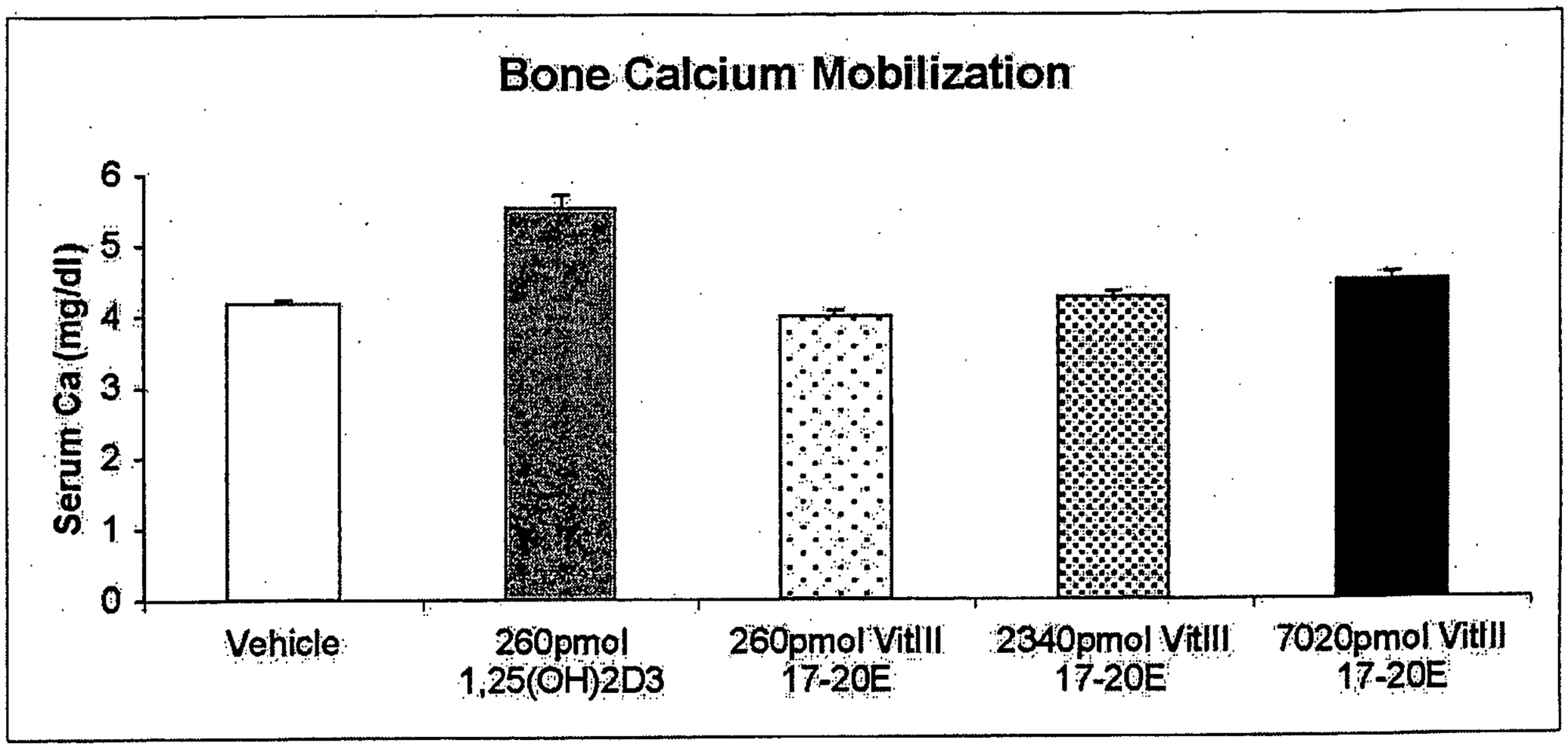

Bone Calcium Mobilization
Serum Ca (mg/dl)
0
1
2
3
4
5
6
Vehicle
260pmol 1,25(OH)2D3
260pmol VitIII 17-20E
2340pmol VitIII 17-20E
7020pmol VitIII 17-20E

Figure 4

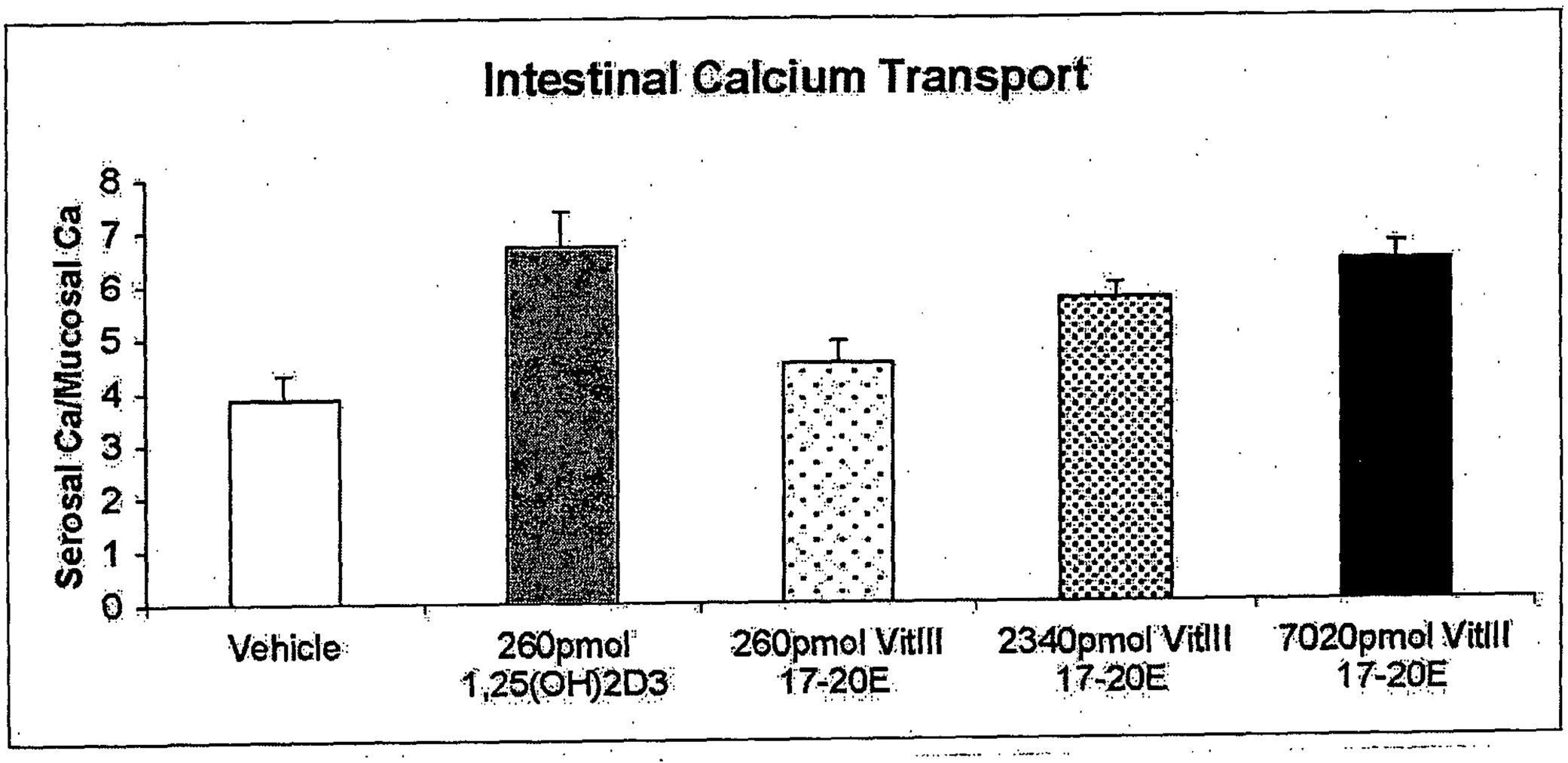
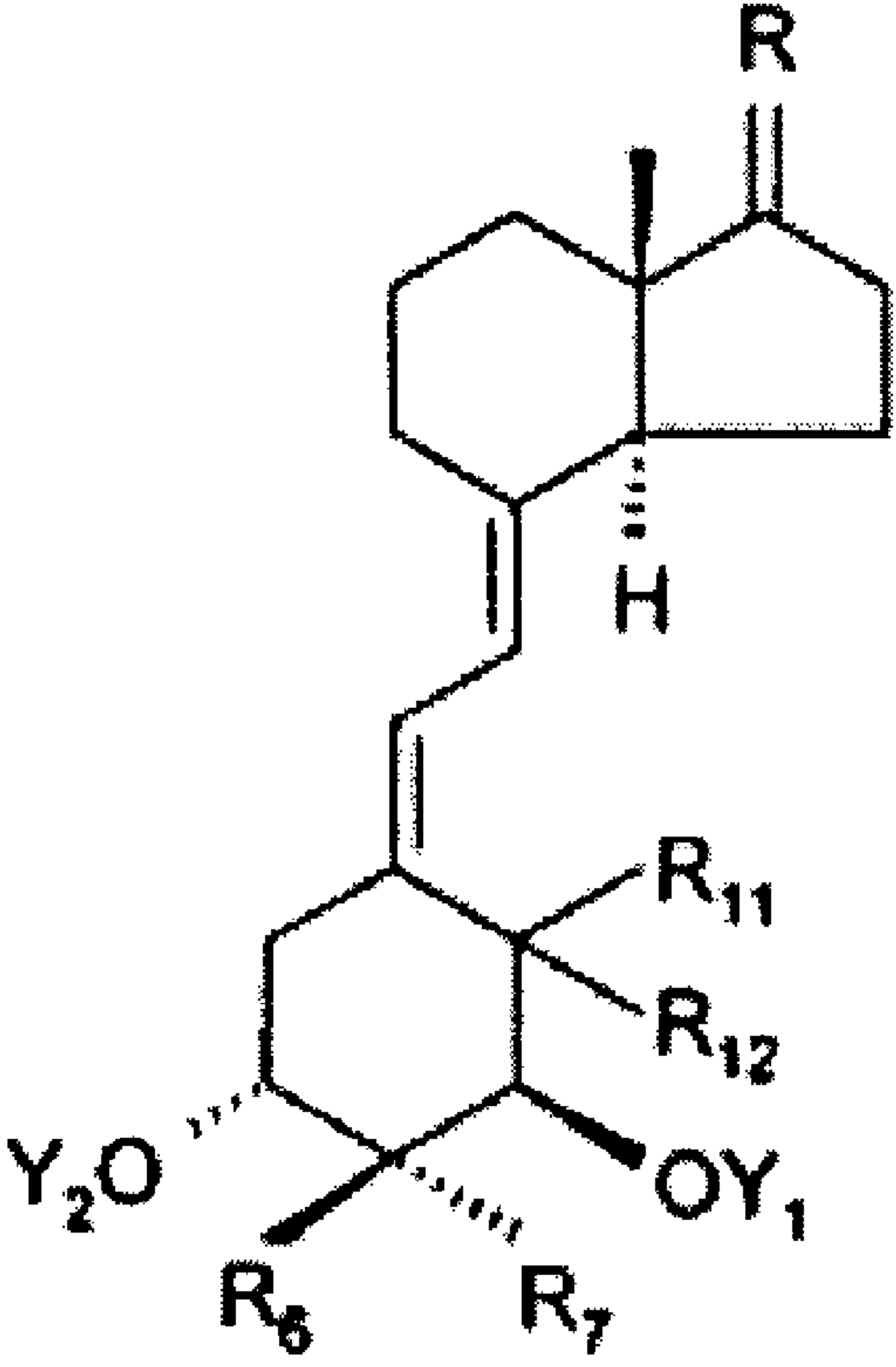

Intestinal Calcium Transport
Serosal Ca/Mucosal Ca
0
1
2
3
4
5
6
7
8
Vehicle
260pmol 1,25(OH)2D3
260pmol VitIII 17-20E
2340pmol VitIII 17-20E
7020pmol VitIII 17-20E

Figure 5



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