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(54) Title: 3-DESOXY-2-METHYLENE-19-NOR-VITAMIN D ANALOGS AND THEIR USES

(57) Abstract: This invention discloses 3-desoxy-2-methylene-19-nor-vitamin D analogs, and specifically (20S)-3-desoxy-2-methylene-1, a,25-dihydroxy-19-nor-vitamin D3 and (20R)-3- desoxy-2-methylene-1a,25-dihydroxy- 19-nor-vitamin D3 as well as pharmaceutical uses therefor. These compounds exhibit relatively high binding activity and pronounced activity in arresting the proliferation of undifferentiated cells and inducing their differentiation to monocytes thus evidencing use as anti-cancer agents especially for the treatment or prevention of osteosarcoma, leukemia, colon cancer, breast cancer, skin cancer or prostate cancer. These compounds also exhibit relatively high calcemic activity evidencing use in the treatment of bone diseases.

3-DESOXY-2-METHYLENE-19-NOR-VITAMIN D ANALOGS
AND THEIR USES

BACKGROUND OF THE INVENTION

[0001] This invention relates to vitamin D compounds, and more particularly to 3-Desoxy-2-Methylene-19-Nor-Vitamin D analogs and their pharmaceutical uses, and especially (20S)-3-desoxy-2-methylene-1 α ,25-dihydroxy-19-norvitamin D₃, its biological activities, and its pharmaceutical uses as well as (20R)-3-desoxy-2-methylene-1 α ,25-dihydroxy-19-norvitamin D₃, its biological activities, and its pharmaceutical uses. This latter compound can also be named simply as 3-desoxy-2-methylene-1 α ,25-dihydroxy-19-norvitamin D₃ since the 20-methyl substituent is in its natural or "R" orientation.

[0002] The natural hormone, 1 α ,25-dihydroxyvitamin D₃ and its analog in the ergosterol series, i.e. 1 α ,25-dihydroxyvitamin D₂ 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 α -hydroxyvitamin D₃, 1 α -hydroxyvitamin D₂, 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.

[0003] 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 some 19-nor-analogs (e.g., 1 α ,25-dihydroxy-19-nor-vitamin D₃) revealed a selective activity profile with high potency in inducing cellular differentiation, and reduced 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).

[0004] In U.S. Pat. No. 4,666,634, 2 β -hydroxy and alkoxy (e.g., ED-71) analogs of 1 α ,25-dihydroxyvitamin D₃ have been described and examined 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 1 α ,25-dihydroxyvitamin D₃ 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)).

[0005] 2-substituted analogs of 1 α ,25-dihydroxy-19-nor-vitamin D₃ 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.

[0006] 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 both carbon 1 (C-1) and carbon 3 (C-3), and a shortened side chain attached to carbon 20 (C-20) have also been synthesized and tested. 1 α -hydroxy-2-methylene-19-nor-pregnacalciferol is described in U.S. Patent 6,566,352 while 1 α -hydroxy-2-methylene-19-nor-homopregnacalciferol is described in U.S. Patent 6,579,861 and 1 α -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

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to vitamin D receptors and relatively high cell differentiation activity, but little if any calcemic activity as compared to 1 α ,25-dihydroxy vitamin D₃. Their biological activities make these compounds excellent candidates for a variety of pharmaceutical uses, as set forth in the '352, '861 and '622 patents.

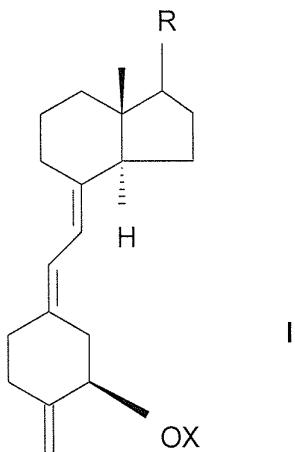
[0007] Analogs of the natural hormone 1 α ,25-dihydroxy vitamin D₃ characterized by the transposition of the A-ring exocyclic methylene group from carbon 10 (C-10) to carbon 2 (C-2) (e.g., 1 α ,25-dihydroxy-2-methylene-19-nor-vitamin D analogs) have been synthesized and tested [see Sicinski et al., *J. Med. Chem.*, 41, 4662 (1998); Sicinski et al., *Steroids* 67, 247 (2002); and, DeLuca et al., U.S. Pat. Nos. 5,843,928; 5,936,133 and 6,392,071]. Molecular mechanics studies performed on these analogs predict that a change of A-ring conformation may cause flattening of the cyclohexanediol ring. Molecular mechanics calculations and NMR studies also predict that the A-ring conformational equilibrium would be ca. 6:4 in favor of the conformer having an equatorial 1 α -OH. It was further predicted that introduction of the 2-methylene group into 19-nor-vitamin D carbon skeleton would change the character of its 1 α - and 3 β - A-ring hydroxyls. They would both be in allylic positions similar to the 1 α -hydroxyl group in the molecule of the natural hormone [i.e., 1 α ,25-(OH)₂D₃]. It was found that 1 α ,25-dihydroxy-2-methylene-19-nor-vitamin D analogs are characterized by significant biological potency. In addition, the biological potency of such analogs may be enhanced dramatically where "unnatural" (20S)-configuration is present.

SUMMARY OF THE INVENTION

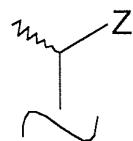
[0008] The present invention is aimed at vitamin D compounds characterized by the transposition of the A-ring exocyclic methylene group from carbon 10 (C-10) to carbon 2 (C-2) (e.g., 2-methylene-19-norvitamin D analogs). These analogs also lack a 3 β -OH group, but are characterized by the presence of a 1 α -OH group, that is important for biological activity. Accordingly, the present invention is directed toward 3-desoxy-2-methylene-19-nor-vitamin D analogs, and their pharmaceutical uses, and more specifically toward (20S)-3-desoxy-2-

methylene-1 α ,25-dihydroxy-19-norvitamin D₃, its biological activity, and various pharmaceutical uses for this compound as well as (20R)-3-desoxy-2-methylene-1 α ,25-dihydroxy-19-nor-vitamin D₃, its biological activity, and various pharmaceutical uses for this compound.

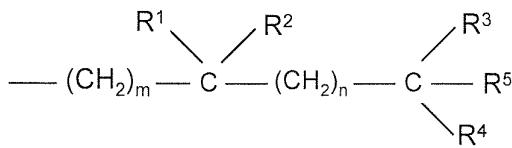
[0009] Structurally these 3-desoxy-2-methylene-19-nor-vitamin D analogs are characterized by the general formula I shown below:



where X is selected from the group consisting of hydrogen and a hydroxy-protecting group, and where the group R represents any of the typical side chains known for vitamin D type compounds. Thus, R may be hydrogen, an alkyl, hydroxyalkyl or fluoroalkyl group, or R may represent a side chain of the formula:



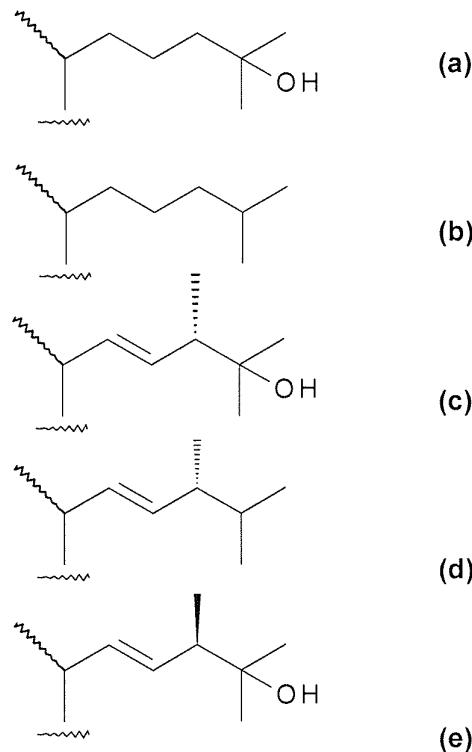
where the stereochemical center at carbon 20 may have the R or S configuration, and where Z in the above side chain structure is selected from Y, -OY, -CH₂OY, -C≡CY and -CH=CHY, where the double bond in the side chain may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, -COR⁵ and a radical of the structure:



where m and n, independently, represent the integers from 0 to 5, where R¹ is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C₁₋₅-alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R², R³, and R⁴, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C₁₋₅ alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R¹ and R², taken together, represent an oxo group, or an alkylidene group having a general formula C_kH_{2k}— where k is an integer, the group =CR²R³, or the group -(CH₂)_p—, where p is an integer from 2 to 5, and where R³ and R⁴, taken together, represent an oxo group, or the group -(CH₂)_q—, where q is an integer from 2 to 5, and where R⁵ represents hydrogen, hydroxy, protected hydroxy, or C₁₋₅ 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(CH₃)—, —(CH₂)_m—, —CR₁R₂— or —(CH₂)_n— at positions 20, 22, and 23, respectively, may be replaced by an oxygen or sulfur atom.

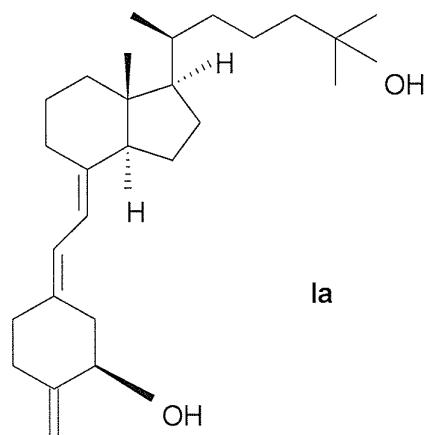
[0010] Specific important examples of side chains are the structures represented by formulas (a), (b), (c), (d) and (e) below with natural 20R-configuration, i.e., the side chain as it occurs in 25-hydroxyvitamin D₃ (a); vitamin D₃ (b); 25-hydroxyvitamin D₂ (c); vitamin D₂ (d); and the C-24 epimer of 25-hydroxyvitamin D₂ (e).

[0011] Additional important examples of side chains are the structures represented by formulas (a), (b), (c), (d) and (e) below having the 20-epi or (20S)-configuration, i.e., the side chain as it occurs in (20S)-25-hydroxyvitamin D₃ (a); (20S)-vitamin D₃ (b); (20S)-25-hydroxyvitamin D₂ (c); (20S)-vitamin D₂ (d); and the C-24 epimer of (20S)-25-hydroxyvitamin D₂ (e).

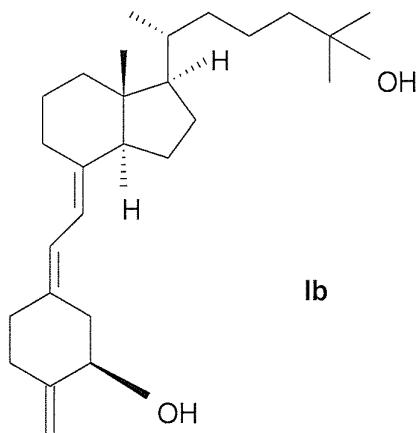


[0012] The wavy line to the carbon 20 indicates that carbon 20 may have either the R or S configuration.

[0013] The preferred analogs are (20S)-3-desoxy-2-methylene-1 α ,25-dihydroxy-19-nor-vitamin D₃ (referred to herein as "3-desoxy-2MD") which has the following formula **Ia**:



and (20R)-3-desoxy-2-methylene-1 α ,25-dihydroxy-19-nor-vitamin D₃ (referred to herein as "3D-MJ") which has the following formula **Ib**:



[0014] The above compounds of formula I, especially formula Ia and Ib, exhibit a desired, and highly advantageous, pattern of biological activity. These compounds are characterized by relatively high binding to vitamin D receptors, i.e. they bind with about the same affinity as 1 α ,25-dihydroxyvitamin D₃, and in bone cells their in vitro transcription activity is also substantially the same as 1 α ,25-dihydroxyvitamin D₃ in causing 24-hydroxylase gene transactivation. They are either about the same or slightly more potent causing differentiation of HL-60 cells into monocytes than 1,25(OH)₂D₃. They also exhibit either about the same or slightly more activity in their ability to mobilize calcium from bone, and similar or only slightly less activity in their ability to promote intestinal calcium transport, as compared to 1 α ,25-dihydroxyvitamin D₃.

[0015] The above compounds I, and particularly Ia and Ib, have relatively high binding affinity, are characterized by relatively high cell differentiation activity, and high bone calcium mobilization activity, but have slightly lower intestinal calcium transport activity. Thus, these compounds have potential as anti-cancer agents and provide therapeutic agents for the prevention or treatment of osteosarcoma, leukemia, colon cancer, breast cancer, skin cancer and prostate cancer. Because of their selective activity in the bone and relatively

high potency on cellular differentiation, 3-desoxy-2MD and 3D-MJ might also be useful in treatment of bone diseases, such as senile osteoporosis, postmenopausal osteoporosis, steroid-induced osteoporosis, low bone turnover osteoporosis, osteomalacia, and renal osteodystrophy.

[0016] One or more of the compounds may be present in a composition to treat or prevent the above-noted diseases in an amount from about 0.01 μ g/gm to about 1000 μ g/gm of the composition, preferably from about 0.1 μ g/gm to about 500 μ g/gm of the composition, and may be administered topically, transdermally, orally, rectally, nasally, sublingually, or parenterally in dosages of from about 0.01 μ g/day to about 1000 μ g/day, preferably from about 0.1 μ g/day to about 500 μ g/day.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Figures 1-5 illustrate various biological activities of (20S)-3-desoxy-2-methylene-1 α ,25-dihydroxy-19-nor-vitamin D₃, hereinafter referred to as "3-desoxy-2MD," as compared to the native hormone 1 α ,25-dihydroxyvitamin D₃, hereinafter "1,25(OH)₂D₃."

[0018] Figure 1 is a graph illustrating the relative activity of 3-desoxy-2MD and 1,25(OH)₂D₃ to compete for binding with [³H]-1,25-(OH)₂-D₃ to the full-length recombinant rat vitamin D receptor;

[0019] Figure 2 is a graph illustrating the percent HL-60 cell differentiation as a function of the concentration of 3-desoxy-2MD and 1,25(OH)₂D₃;

[0020] Figure 3 is a graph illustrating the in vitro transcription activity of 1,25(OH)₂D₃ as compared to 3-desoxy-2MD;

[0021] Figures 4A and 4B are bar graphs illustrating the bone calcium mobilization activity of 1,25(OH)₂D₃ as compared to 3-desoxy-2MD; and

[0022] Figures 5A and 5B are bar graphs illustrating the intestinal calcium transport activity of 1,25(OH)₂D₃ as compared to 3-desoxy-2MD.

[0023] Figures 6-10 illustrate various biological activities of (20R)-3-desoxy-2-methylene-1 α ,25-dihydroxy-19-nor-vitamin D₃, hereinafter referred to as “3D-MJ,” as compared to the native hormone 1 α ,25-dihydroxyvitamin D₃, hereinafter “1,25(OH)₂D₃.”

[0024] Figure 6 is a graph illustrating the relative activity of 3D-MJ and 1,25(OH)₂D₃ to compete for binding with [³H]-1,25-(OH)₂-D₃ to the full-length recombinant rat vitamin D receptor;

[0025] Figure 7 is a graph illustrating the percent HL-60 cell differentiation as a function of the concentration of 3D-MJ and 1,25(OH)₂D₃;

[0026] Figure 8 is a graph illustrating the in vitro transcription activity of 1,25(OH)₂D₃ as compared to 3D-MJ;

[0027] Figure 9 is a bar graph illustrating the bone calcium mobilization activity of 1,25(OH)₂D₃ as compared to 3D-MJ; and

[0028] Figure 10 is a bar graph illustrating the intestinal calcium transport activity of 1,25(OH)₂D₃ as compared to 3D-MJ.

DETAILED DESCRIPTION OF THE INVENTION

[0028a] Reference to any prior art in the specification is not an acknowledgment or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be understood, regarded as relevant, and/or combined with other pieces of prior art by a skilled person in the art.

[0028b] As used herein, except where the context requires otherwise, the term “comprise” and variations of the term, such as “comprising”, “comprises” and “comprised”, are not intended to exclude other additives, components, integers or steps.

[0029] 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, alkoxy carbonyl, acyl, alkylsilyl or alkylarylsilyl groups (hereinafter referred to simply as “silyl” groups), and alkoxyalkyl groups. Alkoxy carbonyl 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 oxanyl, 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. a group represented by "alkyl-O-." Alkoxyalkyl protecting groups are groupings such as methoxymethyl, ethoxymethyl, methoxyethoxymethyl, or tetrahydrofuryl 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.

[0030] 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 alkoxy carbonyl 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.

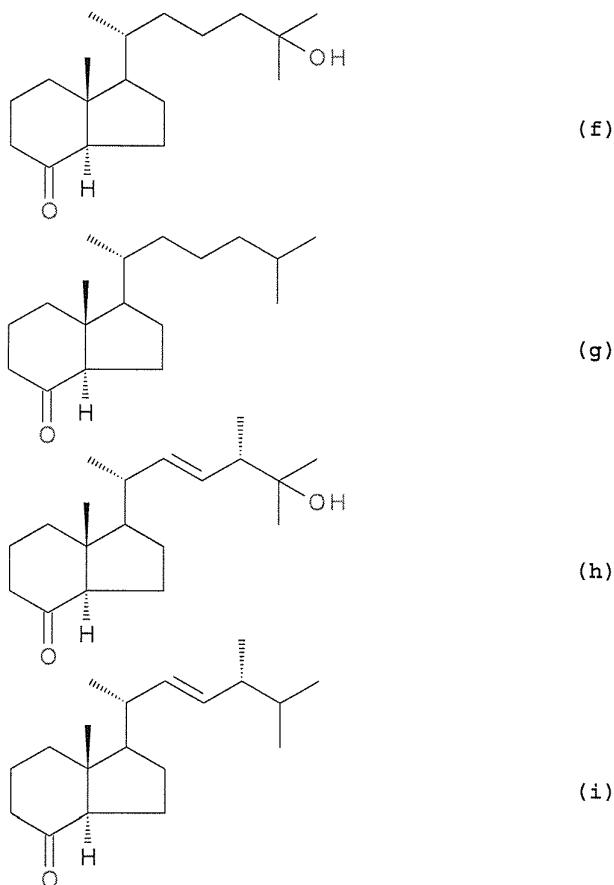
[0031] The preparation of 2-methylene-19-norvitamin D analogs of the basic structure **I** can be accomplished by a common general method, i.e., the condensation of a bicyclic Windaus-Grundmann type ketone **II** with the allylic phosphine oxide **III**:



[0032] In the structures **II** and **III**, substituents X and R represent the groups defined above; X being preferably a hydroxy-protecting group, it being also understood that any functionalities in R that might be sensitive, or that interfere with the condensation reaction, be suitable 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); Baggioolini 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)].

[0033] Hydrindanones of the general structure **II** are known, or can be prepared by known methods. Specific important examples of such known bicyclic ketones are the structures with the side chains (a), (b), (c) and (d) described above, i.e., 25-hydroxy Grundmann's ketone (f) [Baggiolini et al., *J. Org. Chem.*, 51, 3098 (1986)]; Grundmann's ketone (g) [Inhoffen et al., *Chem. Ber.*, 90, 664 (1957)]; 25-hydroxy Windaus ketone (h) [Baggiolini et al., *J. Org. Chem.*, 51, 3098 (1986)] and Windaus ketone (i) [Windaus et al., *Ann.*, 524, 297 (1936)]:



[0034] Regarding the preparation of the phosphine oxides of the structure **III**, alternative synthetic routes were established. As set forth in SCHEME 1, an achiral, commercially available acetal-ketone **1**, was enantioselectively hydroxylated to the hydroxy ketone **2**, using the method elaborated by Hayashi et al. [J. Org. Chem. 69, 5966 (2004)] and involving the reaction of a ketone with nitrosobenzene in the presence of a catalytic amount of *L*-proline. The introduced secondary hydroxyl was silylated and the protected compound **3** was subjected to the Wittig reaction with an ylide generated from methyltriphenylphosphonium bromide and *n*-butyllithium. In the resulting olefinic compound **4** the carbonyl group was deprotected in the reaction with the Lewis acid (FeCl_3) and the formed cyclohexanone **5** was subjected to a Peterson reaction leading to the mixture

of α,β -unsaturated esters **6** and **7**. Although possible at this stage, the separation of the geometric isomers was more easily achieved (by column chromatography) after the reduction step, providing the *E*- and *Z*-allylic alcohols **8** and **9**, respectively. The *Z*-isomer **9** was next transformed in the three-step procedure into the corresponding phosphine oxide **10**. Wittig-Horner coupling of the known Grundmann ketone **11** [see Sicinski et al., *J. Med. Chem.*, 41, 4662 (1998)] with the lithium phosphinoxy carbanion generated from the phosphine oxide **10** was subsequently carried out, producing the protected 19-norvitamin D compound, which after hydroxyls deprotection with tetrabutylammonium fluoride provided the desired (20*S*)-3-desoxy-2-methylene-1 *α* ,25-dihydroxy-19-nor-vitamin D₃ (**12**, 3-desoxy-2MD). This synthetic path is described in EXAMPLE I herein.

[0035] Alternately, Wittig-Horner coupling of the known Grundmann ketone **13** [see Sicinski et al., *J. Med. Chem.*, 37, 3730 (1994)] with the lithium phosphinoxy carbanion generated from the phosphine oxide **10** was carried out, producing the protected 19-norvitamin D compound, which after hydroxyls deprotection with tetrabutylammonium fluoride provided the desired (20*R*)-3-desoxy-2-methylene-1 *α* ,25-dihydroxy-19-nor-vitamin D₃ (14, 3D-MJ). This synthetic path is described in EXAMPLE II herein.

[0036] As it is evident from EXAMPLES I and II, other 19-norvitamin D analogs having the different side-chains may be synthesized by the methods set forth herein.

[0037] This invention is described by the following illustrative examples. In these examples specific products identified by Arabic numerals (e.g., 1, 2, 3, etc) refer to the specific structures so identified in the preceding description and in the SCHEME 1 or SCHEME 2.

EXAMPLES

[0038] Chemistry. Melting points (uncorrected) were determined on a Thomas-Hoover capillary melting-point apparatus. Optical rotations were measured in chloroform using a Perkin-Elmer 241 automatic polarimeter at 22 °C. Ultraviolet (UV) absorption spectra were recorded with a Perkin-Elmer Lambda 3B UV-VIS spectrophotometer in ethanol. ¹H

nuclear magnetic resonance (NMR) spectra were recorded in deuteriochloroform at 200, 400 and 500 MHz with a Varian Unity, Bruker DMX-400 and Bruker DMX-500 spectrometers, respectively. ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 50, 100 and 125 MHz with the same spectrometers in deuteriochloroform. Chemical shifts (δ) were reported downfield from internal Me_4Si (δ 0.00). Electron impact (EI) mass spectra were obtained with a Micromass AutoSpec (Beverly, MA) instrument. High-performance liquid chromatography (HPLC) was performed on a Waters Associates liquid chromatograph equipped with a Model 6000A solvent delivery system, a Model U6K Universal injector, and a Model 486 tunable absorbance detector. THF was freshly distilled before use from sodium benzophenone ketyl under argon.

EXAMPLE I

[0039] Preparation of (20*S*)-3-desoxy-2-methylene-1*α*,25-dihydroxy-19-nor-vitamin D₃ (**12**, 3-desoxy-2MD) from the phosphine oxide **10**.

[0040] (a) α -Hydroxylation of a ketal-ketone **1** (SCHEME 1). (*R*)-7-Hydroxy-1,4-dioxa-spiro[4.5]decan-8-one (**2**). To a stirred solution of 1,4-cyclohexanedione monoethylene ketal (**1**; 3.00 g, 19.23 mmol) and *L*-proline (0.97 g, 8.42 mmol) in CHCl_3 (10 mL), a solution of nitrosobenzene (3.60 g, 33.65 mmol) in CHCl_3 (16 mL) was slowly added at 4 °C over 24 h by a syringe pump. Then the mixture was stirred at room temperature for additional 2 h. Reaction was quenched with brine, and the organic materials were extracted with ethyl acetate, dried (MgSO_4) and concentrated in vacuum. Purification by column chromatography on silica (0.5→20% ethyl acetate/hexane gradient) gave an oily α -hydroxy ketone **2** (1.45 g, 44%). Purity of the product was checked by HPLC (4.6 mm × 25 cm Chiralcell OD-H column, 1.5 mL/min) using hexane/2-propanol (99:1) solvent system: it was found to have enantiomeric excess (*ee*) higher than 97% (R_V = 7.5 mL; for the *S*-enantiomer R_V = 6.0 mL).

[0041] **2**: $[\delta]_D$ +27° (*c* 0.65, CHCl_3); ^1H NMR (200 MHz, CDCl_3) δ 1.85 (1H, t, *J* = 12.4 Hz, 6 β -H), 2.05 (2H, m, 10-H₂), 2.50 (br m, 6 α - and 9 β -H), 2.70 (1H, dt, *J* = 6.8, 13.2 Hz, 9 α -H), 3.46 (1H, s, OH), 4.03 (4H, m, -O-CH₂CH₂-O-), 4.38 (1H, dd, *J* = 12.4, 6.8 Hz,

7 α -H); HRMS (ESI) exact mass calculated for C₈H₁₂O₄Na (M⁺ + Na) 195.0633, found 195.0628.

[0042] (b) Protection of α -hydroxy ketone **2**. (R)-7-[(*tert*-Butyldiphenylsilyl)oxy]-1,4-dioxa-spiro[4.5]decan-8-one (**3**). *tert*-Butyldiphenylsilyl chloride (3.55 mL, 3.75 g, 13.65 mmol) was added to a solution of α -hydroxy ketone **2** (1.60 g, 13.65 mmol) and imidazole (2.32 g, 33.9 mmol) in anhydrous DMF (9 mL). The mixture was stirred at room temperature for 18 h. The reaction was quenched with brine and extracted with hexane. The combined organic phases were dried (MgSO₄) and concentrated under reduced pressure. Column chromatography on silica (1→4% hexane/ethyl acetate gradient) provided the protected compound **3** (3.35 g, 88%) as a colorless oil.

[0043] **3**: ¹H NMR (200 MHz, CDCl₃) δ 1.10 (9H, s, Si-*t*-Bu), 1.8-2.1 (4H, br m, 6- and 10-H₂), 2.35 (2H, m, 9-H₂), 3.62 (1H, m, one of -O-CH₂CH₂-O-), 3.82 (3H, m, three of -O-CH₂CH₂-O-), 4.40 (1H, dd, J = 11.8, 7.6 Hz, 7 α -H), 7.38 (6H, m, Ar-H), 7.67 (4H, m, Ar-H); ¹³C NMR (50 MHz, CDCl₃) δ 19.4, 27.1, 34.7, 35.9, 43.8, 64.5, 64.7, 73.8, 107.6, 127.8, 129.9, 133.3, 134.1, 136.0, 207.7; HRMS (ESI) exact mass calculated for C₂₄H₃₀O₄SiNa (M⁺ + Na) 433.1811, found 433.1800.

[0044] (c) Wittig reaction of the ketone **3**. (R)-7-[(*tert*-Butyldiphenylsilyl)oxy]-8-methylene-1,4-dioxa-spiro[4.5]decane (**4**). To methyltriphenylphosphonium bromide (2.5 g, 6.99 mmol) in anhydrous THF (20 mL) at 0 °C was added dropwise *n*-BuLi (1.6 M in hexanes; 8.8 mL, 14.08 mmol). After 15 min another portion of phosphonium salt (2.5 g, 6.99 mmol) was added, and the solution was stirred at 0 °C for 10 min, and at room temperature for 20 min. The orange-red mixture was then cooled to -78 °C and siphoned to the precooled (-78 °C) solution of the ketone **3** (2.85 g, 6.93 mmol) in anhydrous THF (7 mL). The reaction mixture was stirred at -78 °C for 4 h and then at room temperature for 1 h. The mixture was poured into brine and extracted with hexane. Organic extracts were dried (MgSO₄), and evaporated to give an orange oily residue which was purified by flash chromatography on

silica. Elution with hexane/ethyl acetate (97:3) gave pure 4-methylene compound **4** (2.62 g, 93%) as a colorless oil.

[0045] **4**: ^1H NMR (200 MHz, CDCl_3) δ 1.01 (9H, s, Si-*t*-Bu), 1.43 (2H, m, 10-H₂), 1.62 (2H, m, 6-H₂), 2.19 (2H, m, 9-H₂), 3.36 (1H, m, one of -O-CH₂CH₂-O-), 3.73 (3H, m, three of -O-CH₂CH₂-O-), 4.30 (1H, dd, J = 11.0, 5.0 Hz, 7 α -H), 4.88 and 5.31 (1H and 1H, each br s, =CH₂), 7.35 (6H, m, Ar-H), 7.70 (4H, m, Ar-H); ^{13}C NMR (50 MHz, CDCl_3) δ 14.5, 19.5, 22.9, 30.0, 31.8, 36.3, 44.5, 64.1, 64.3, 71.2, 106.6, 109.2, 127.7, 129.8, 134.1, 134.8, 135.9, 136.2, 149.3; HRMS (ESI) exact mass calcd for $\text{C}_{25}\text{H}_{32}\text{O}_3\text{SiNa}$ ($\text{M}^+ + \text{Na}$) 431.2019, measured 431.2028.

[0046] (d) Deprotection of a carbonyl group in the ketal **4**. (*R*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-4-methylene-cyclohexanone (**5**). To a solution of ketal **4** (160 mg, 0.392 mmol) in methylene chloride (11 mL) at room temperature $\text{FeCl}_3 \times 6\text{H}_2\text{O}$ (547 mg, 2.02 mmol) was added. The resulting dark yellow suspension was stirred for 50 min and quenched by the addition of water. The aqueous layer was extracted with methylene chloride, the combined organic layers were dried (MgSO_4) and concentrated under reduced pressure. Column chromatography on silica of the resulting yellow residue using hexane/ethyl acetate (95:5) yielded ketone **5** (141 mg, 99%) as a colorless oil.

[0047] **5**: ^1H NMR (500 MHz, CDCl_3) δ 1.05 (9H, s, Si-*t*-Bu), 2.32-2.52 (5H, br m, 2 β -H, 5-H₂ and 6-H₂), 2.83 (1H, m, 2 α -H), 4.47 (1H, br t, J ~ 6 Hz, 3 α -H), 4.90 (2H, s, =CH₂), 7.40 (6H, m, Ar-H), 7.65 (4H, m, Ar-H); ^{13}C NMR (125 MHz, CDCl_3) δ 19.6, 27.1, 32.8, 36.9, 44.8, 72.8, 107.1, 108.2, 128.0, 129.8, 133.0, 133.3, 135.1, 207.7; HRMS (ESI) exact mass calculated for $\text{C}_{23}\text{H}_{28}\text{O}_2\text{SiNa}$ ($\text{M}^+ + \text{Na}$) 387.1757, found 387.1746.

[0048] (e) Peterson reaction of the ketone **5**. [(*R*)-3'-[*tert*-Butyldiphenylsilyl)oxy]-4'-methylene-cyclohexylidene]acetic acid methyl ester (mixture of **6** and **7**). To a solution of diisopropylamine (48.5 μL , 376 μmol) in anhydrous THF (260 μL) was added *n*-BuLi (2.5 M in hexanes; 148 μL , 367 μmol) under argon at -78 °C with stirring, and methyl

(trimethylsilyl)acetate (60 μ L, 367 μ mol) was then added. After 15 minutes keto compound **5** (63 mg, 172.8 μ mol) in anhydrous THF (300 μ L + 80 μ L) was added dropwise. The solution was stirred at -78 °C for 2 hours, and the reaction was quenched with saturated NH₄Cl, poured into brine and extracted with ethyl acetate. The combined organic extracts were dried (MgSO₄) and evaporated. The residue was dissolved in hexane and applied on a silica Sep-Pak cartridge. Elution with hexane/ethyl acetate (98:2) gave unsaturated esters **6** and **7** (65 mg, 90%) as a colorless oil.

[0049] **6** and **7** (mixture of isomers) ¹H NMR (200 MHz, CDCl₃; selected signals) δ 1.15 and 1.17 (5H and 4H, each s, 2 \times Si-*t*-Bu), 2.1–3.3 (6H, br m, 2'-, 5'- and 6'-H₂), 3.69 and 3.73 (1.67H and 1.33H, each s, 2 \times COOCH₃), 4.29 (1H, m, 3' α -H), 4.82, 4.90, 4.93, 5.12 (0.56H, 0.56H, 0.44H and 0.44H, each br s, =CH₂), 5.48 and 5.83 (0.44H and 0.56H, each br s, CH-COOMe), 7.45 (6H, m, Ar-H), 7.75 (4H, m, Ar-H); HRMS (ESI) exact mass calculated for C₂₆H₃₂O₃SiNa (M⁺ + Na) 443.2019, found 443.2035.

[0050] (f) Reduction of the esters **6** and **7**. (*E*)- and (*Z*)-2-[(*R*)-3'-[(*tert*-Butyldiphenylsilyl)oxy]-4'-methylene-cyclohexylidene]ethanols (**8** and **9**). Diisobutylaluminium hydride (1.5 M in toluene; 1.9 mL, 2.85 mmol) was slowly added to a stirred solution of allylic esters **6** and **7** (165 mg, 0.392 mmol) in toluene:methylene chloride (2:1; 8 mL) at -78 °C under argon. Stirring was continued at -78 °C for 1 h and at -40 °C for 30 min. The mixture was quenched by slow addition of potassium-sodium tartrate (2N, 4 mL), aqueous HCl (2N, 4 mL) and H₂O (14 mL), and extracted with ethyl acetate. Combined organic layers were washed with brine, dried (MgSO₄) and evaporated. The residue was passed through a silica Sep-Pak cartridge with hexane/ethyl acetate (9:1). The obtained mixture of allylic alcohols was separated by HPLC (9.4 mm \times 25 cm Zorbax-Sil column, 4 mL/min) using hexane/ethyl acetate (8:2) solvent system: the *Z*-isomer **9** (82 mg, 53%) was collected at R_V = 35 mL and the *E*-isomer **8** (60 mg, 39%) at R_V = 41 mL.

[0051] **8** (minor *E*-isomer): ¹H NMR (500 MHz, CDCl₃) δ 1.08 (9H, s, Si-*t*-Bu), 1.96 (1H, ~dt, J ~ 5, 12.5 Hz, 6' β -H), 2.07 (1H, dd, J = 12.5, 8.5 Hz, 2' β -H), 2.08 (1H, m, 5' α -H),

2.13 (1H, dd, $J = 12.5, 4.5$ Hz, 2' α -H), 2.31 (1H, dt, $J = 12.5, 4.5$ Hz, 6' α -H), 2.48 (1H, dt, $J = 12.5, 5.5$ Hz, 5' β -H), 4.09 (2H, d, $J = 7.0$ Hz, -CH₂OH), 4.14 (1H, dd, $J = 8.5, 4.5$ Hz, 3' α -H), 4.82 and 5.10 (1H and 1H, each br s, =CH₂), 5.16 (1H, t, $J = 7.5$ Hz, 2-H), 7.39 (6H, m, Ar-H), 7.65 (4H, m, Ar-H); ¹³C NMR (125 MHz, CDCl₃) δ 19.3, 27.0, 29.3, 32.7, 46.6, 58.7, 74.0, 107.2, 123.6, 127.5, 129.6, 133.8, 134.5, 135.8, 139.7, 149.6; HRMS (ESI) exact mass calculated for C₂₅H₃₂O₂SiNa (M⁺ + Na) 415.2070, found 415.2059.

[0052] **9 (major Z-isomer):** ¹H NMR (500 MHz, CDCl₃) δ 1.09 (9H, s, Si-*t*-Bu), 1.99 (2H, m, 2' β - and 5' α -H), 2.11 (2H, m, 6' α - and 6' β -H), 2.25 (1H, dd, $J = 13.0, 4.5$ Hz, 2' α -H), 2.48 (1H, dt, $J = 12.5, 5.5$ Hz, 5' β -H), 3.62 (1H, dd, $J = 10.0, 7.2$ Hz, one of -CH₂OH), 3.71 (1H, dd, $J = 10.0, 7.0$ Hz, one of -CH₂OH), 4.09 (1H, dd, $J = 9.0, 4.5$ Hz, 3' α -H), 4.82 and 5.10 (1H and 1H, each br s, =CH₂), 5.37 (1H, t, $J = 7.0$ Hz, 2-H), 7.39 (6H, m, Ar-H), 7.65 (4H, m, Ar-H); ¹³C NMR (125 MHz, CDCl₃) δ 19.3, 27.0, 33.4, 37.3, 38.8, 58.3, 73.7, 107.1, 123.6, 127.6, 129.7, 133.7, 134.5, 135.8, 139.4, 149.6; HRMS (ESI) exact mass calculated for C₂₅H₃₂O₂SiNa (M⁺ + Na) 415.2070, found 415.2067.

[0053] (g) Preparation of the phosphine oxide **10**. [2-[(*Z*)-(R)-3'--[*tert*-Butyldiphenylsilyl)oxy]-4'-methylene-cyclohexylidene]ethyl]diphenyl phosphine oxide (**10**). To a solution of an allylic alcohol **9** (24 mg, 61 μ mol) in anhydrous THF (0.6 mL) was added *n*-BuLi (2.5 M in hexanes; 24 μ L, 60 μ mol) under argon at 0 °C. A solution of a freshly recrystallized tosyl chloride (11.2 mg, 61 μ mol) in anhydrous THF (110 μ L) was then added to the allylic alcohol - *n*-BuLi solution. The mixture was stirred at 0 °C for 5 min and set aside at 0 °C. In another dry flask with air replaced by argon, *n*-BuLi (2.5 M in hexanes; 49 μ L, 123 μ mol) was added to a solution of Ph₂PH (22 μ L, 124 μ mol) in anhydrous THF (180 μ L) at 0°C with stirring. The red solution was siphoned under argon pressure to the solution of tosylate until the orange color persisted (ca. one-half of the solution was added). The resulting mixture was stirred for an additional 30 min at 0 °C and quenched by addition of H₂O (10 μ L). Solvents were evaporated under reduced pressure, the residue was redissolved

in methylene chloride (0.6 mL), and stirred with 10% H₂O₂ (0.2 mL) at 0 °C for 1 h. The organic layer was separated, washed with cold aqueous sodium sulfite and water, dried (MgSO₄), and evaporated. The residue was subjected to flash chromatography on silica. Elution with hexane/ethyl acetate (9:1) gave the unreacted allylic alcohol **9** (8 mg), further elution with hexane/ethyl acetate (6:4) gave the phosphine oxide **10** (17 mg, 48%; 72% considering the recovered **9**).

[0054] **10:** ¹H NMR (500 MHz, CDCl₃) δ 1.07 (9H, s, Si-*t*-Bu), 1.47 (1H, br t, J ~ 11 Hz, 2'α-H), 1.77 (1H, dt, J = 4.8, 12.3 Hz, 6'α-H), 1.90 (1H, br m, 6'β-H), 2.05 (2H, br m, 2'β- and 5'β-H), 2.42 (1H, dt, J = 12.5, 4.3 Hz, 5'α-H), 2.51 (2H, dt, J = 7.3, 15.0 Hz, one of 1-H₂) and 2.57 (2H, dt, J = 7.7, 15.0 Hz, one of 1-H₂), 3.91 (1H, dd, J = 10.0, 5.0 Hz, 3'β-H), 4.83 and 5.21 (1H and 1H, each br s, =CH₂), 5.22 (1H, m, 2-H), 7.2-7.5 (16H, br m, Ar-H), 7.61 (2H, dd, J = 8.0, 1.5 Hz, Ar-H), 7.72 (2H, dd, J = 8.0, 1.5 Hz, Ar-H); HRMS (ESI) exact mass calculated for C₃₇H₄₁O₂PSiNa (M⁺ + Na) 599.2512, found 599.2524.

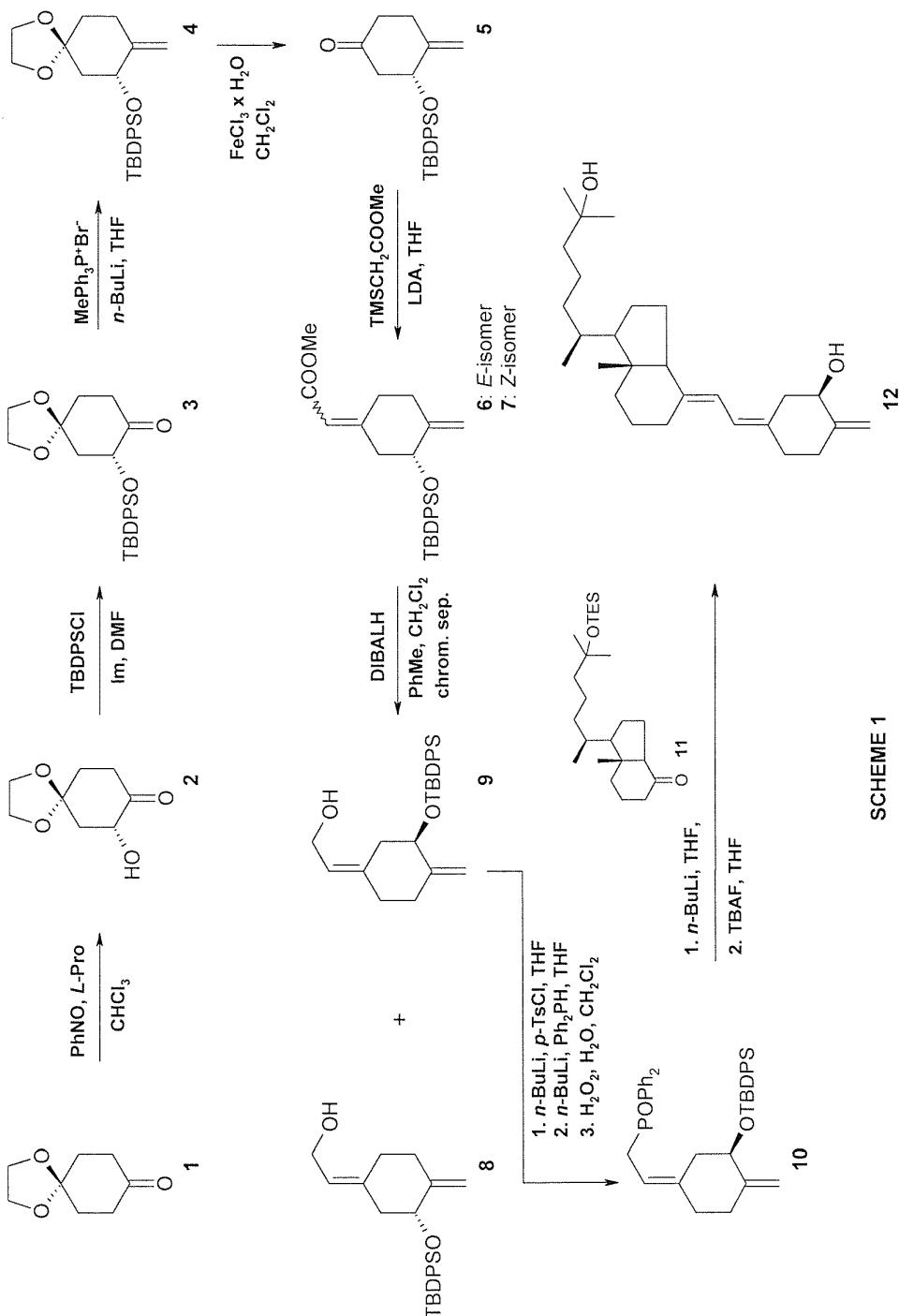
[0055] (h) Wittig- Horner reaction of the phosphine oxide **10** and the Grundmann ketone **11**. (20*S*)-3-desoxy-1*α*,25-dihydroxy-2-methylene-19-nor-vitamin D₃ (**12**). To a solution of the phosphine oxide **10** (17 mg, 29.4 μmol) in anhydrous THF (250 μL) at 0 °C was slowly added *n*-BuLi (2.5 M in hexanes; 12 μL, 30 μmol) under argon with stirring. The solution turned red. The mixture was cooled to -78 °C, and precooled (-78 °C) solution of protected hydroxy ketone **11** (3 mg, 7.62 μmol) in anhydrous THF (60 μL + 40 μL) was slowly added. The mixture was stirred under argon at -78 °C for 1 h and at 0 °C for 19 h. Ethyl acetate was added, and the organic layer was washed with brine, dried (MgSO₄) and evaporated. The residue was dissolved in hexane, applied on a silica Sep-Pak cartridge and washed with hexane/diethyl ether (98:2) to give the silylated 19-norvitamin derivative (5.0 mg, 87%).

[0056] The product was dissolved in THF (380 μL) and tetrabutylammonium fluoride (1.0 M in THF; 318 μL, 318 μmol) was added under argon at room temperature. The stirring was continued for 18 h, brine was added and the mixture was extracted with ethyl acetate.

The organic extracts were dried (MgSO_4) and evaporated. The residue was purified by HPLC (9.4 mm \times 25 cm Zorbax-Sil column, 4 mL/min) using hexane/2-propanol (93:7) solvent system; 19-norvitamin **12** (2.9 mg, 75%) was collected at R_V = 22.5 mL. Analytical sample of the vitamin was obtained after HPLC (9.4 mm \times 25 cm Zorbax Eclipse XDB-C18 column, 4 mL/min) using methanol/water (94:6) solvent system (R_V = 22.5 mL).

[0057] **12:** UV (EtOH) λ_{max} 244, 252, 261 nm; ^1H NMR (500 MHz, CDCl_3) δ 0.549 (3H, s, 18- H_3), 0.857 (3H, d, J = 6.5 Hz, 21- H_3), 1.215 (6H, s, 26- and 27- H_3), 2.15-2.35 (3H, m), 2.47 (1H, dd, J = 12.8, 5.0 Hz, 3 α -H), 2.81 (1H, br dd, J = 13.4, 4.5 Hz, 9 β -H), 2.92 (1H, dd, J = 12.9, 4.5 Hz, 10 β -H), 4.11 (1H, m, $w/2$ = 15 Hz, 1 β -H), 4.83 and 4.98 (1H and 1H, each br s, = CH_2), 5.88 and 6.27 (1H and 1H, each d, J = 11.2 Hz, 7- and 6-H); HRMS (ESI) exact mass calculated for $\text{C}_{27}\text{H}_{44}\text{O}_2\text{Na}$ ($\text{M}^+ + \text{Na}$) 423.3239, found 423.3232.

[0058] SCHEME 1 is set forth below.



SCHEME 1

EXAMPLE II

[0059] Preparation of (20R)-3-desoxy-2-methylene-1 α ,25-dihydroxy-19-nor-vitamin D₃ (14, 3D-MJ) from the phosphine oxide **10**.

[0060] As illustrated in SCHEME 2, the preparation of phosphine oxide **10** is the same as that described in EXAMPLE I via steps (a) through (g).

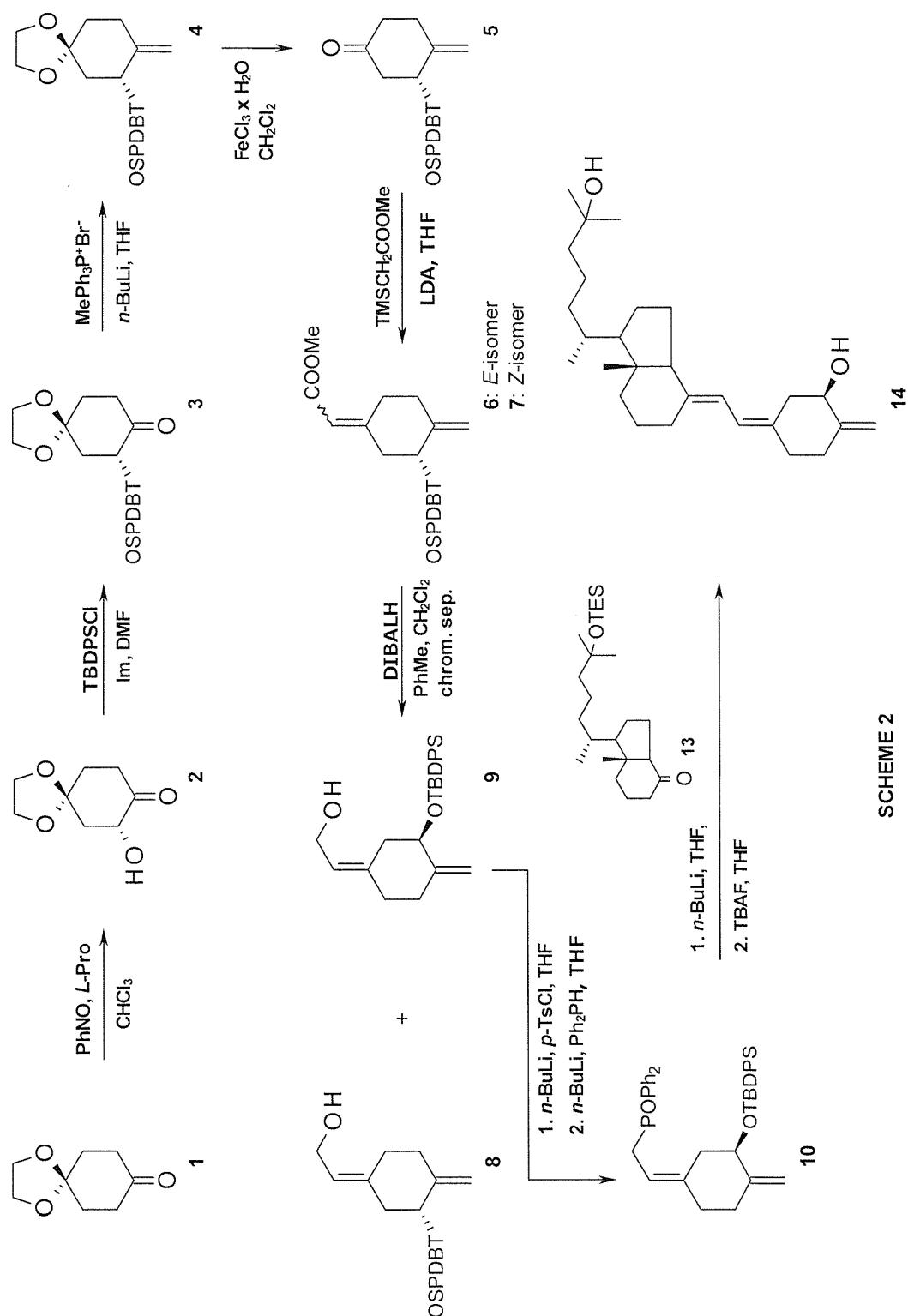
[0061] (h) Wittig- Horner reaction of the phosphine oxide **10** and the Grundmann ketone **13**. 3-Desoxy-1 α ,25-dihydroxy-2-methylene-19-nor-vitamin D₃ (**14**). To a solution of the phosphine oxide **10** (7 mg, 12.13 μ mol) in anhydrous THF (200 μ L) at 0 °C was slowly added *n*-BuLi (1.6 M in hexanes; 13 μ L, 21 μ mol) under argon with stirring. The solution turned red. The mixture was cooled to -78 °C, and precooled (-78 °C) solution of protected hydroxy ketone **13** (5 mg, 12.66 μ mol) in anhydrous THF (100 μ L + 50 μ L) was slowly added. The mixture was stirred under argon at -78 °C for 1 h and at 0 °C for 19 h. Ethyl acetate was added, and the organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in hexane, applied on a silica Sep-Pak cartridge and washed with hexane/diethyl ether (98:2) to give the silylated 19-norvitamin derivative (4.0 mg, 42%).

[0062] The product was dissolved in THF (350 μ L) and tetrabutylammonium fluoride (1.0 M in THF; 318 μ L, 318 μ mol) was added under argon at room temperature. The stirring was continued for 18 h, brine was added and the mixture was extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by HPLC (9.4 mm × 25 cm Zorbax-Sil column, 4 mL/min) using hexane/2-propanol (95:5) solvent system; 19-norvitamin **14** (1.97 mg, 93%) was collected at R_V = 21 mL. Analytical sample of the vitamin was obtained after HPLC (9.4 mm × 25 cm Zorbax Eclipse XDB-C18 column, 4 mL/min) using methanol/water (93:7) solvent system (R_V = 40 mL).

[0063] **14**: UV (EtOH) λ_{max} 244.0, 251.5, 260.5 nm; ¹H NMR (500 MHz, $CDCl_3$) δ 0.550 (3H, s, 18-H₃), 0.939 (3H, d, *J* = 6.5 Hz, 21-H₃), 1.219 (6H, s, 26- and 27-H₃), 1.95-2.05 (2H,

m), 2.14 (1H, m), 2.23-2.35 (2H, m), 2.47 (1H, dd, $J = 12.9, 4.5$ Hz), 2.81 (1H, dd, $J = 12.5, 3.5$ Hz, 9 β -H), 2.92 (1H, dd, $J = 12.9, 4.5$ Hz), 4.11 (1H, narr m, 1 β -H), 4.83 i 4.98 (1H i 1H, each br s, =CH₂), 5.87 and 6.27 (1H and 1H, each d, $J = 11.3$ Hz, 7- and 6-H); HRMS (ESI)) exact mass calculated for C₂₇H₄₄O₂Na (M⁺ + Na) 423.3239, found 423.3243.

[0064] SCHEME 2 is set forth below.



BIOLOGICAL ACTIVITY OF (20S)-3-DESOXY-2-METHYLENE-1 α ,25-DIHYDROXY-19-NORVITAMIN D₃ (3-DESOXY-2MD)

[0065] The introduction of a methylene group to the 2-position, the removal of the methylene substituent at carbon 10 and the hydroxyl group at carbon 3, and orienting the methyl group at carbon 20 in its epi or S configuration had little or no effect on binding to the full length recombinant rat vitamin D receptor, as compared to 1 α ,25-dihydroxyvitamin D₃. The compound 3-desoxy-2MD bound with about the same affinity to the receptor as compared to the standard 1,25-(OH)₂D₃ (Figure 1). It might be expected from these results that compound 3-desoxy-2MD would have equivalent biological activity. Surprisingly, however, compound 3-desoxy-2MD is a highly selective analog with unique biological activity.

[0066] Figures 5A and 5B show that 3-desoxy-2MD has relatively low activity as compared to that of 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃), the natural hormone, in stimulating intestinal calcium transport. 3-desoxy-2MD is at least one half log less potent than 1,25(OH)₂D₃ in promoting active calcium transport across the gut.

[0067] Figures 4A and 4B demonstrate that 3-desoxy-2MD has relatively high bone calcium mobilization activity, as compared to 1,25(OH)₂D₃. 3-desoxy-2MD is at least 10 times more potent than the native hormone in releasing bone calcium stores.

[0068] Figure 2 illustrates that 3-desoxy-2MD is about 3 times more potent than 1,25(OH)₂D₃ on HL-60 cell differentiation, making it an excellent candidate for the treatment of a cancer, especially for the prevention or treatment of osteosarcoma, leukemia, colon cancer, breast cancer, skin cancer and prostate cancer.

[0069] Figure 3 illustrates that the compound 3-desoxy-2MD has about the same transcriptional activity as 1 α ,25-dihydroxyvitamin D₃ in bone cells. In bone cells, 3-desoxy-2MD is as potent as 1,25(OH)₂D₃ in increasing transcription of the 24-hydroxylase gene. This result, together with the cell differentiation activity of Figure 2, suggests that 3-desoxy-2MD will be very effective in treating the above referred to cancers because it has direct

cellular activity in causing cell differentiation, gene transcription, and in suppressing cell growth.

EXPERIMENTAL METHODS

[0070] The compounds of the invention were prepared and studied using the following methods.

Vitamin D Receptor Binding

[0071] Test Material

[0072] Protein Source

[0073] 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 TEDK₅₀ (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.

[0074] Study Drugs

[0075] Unlabeled ligands were dissolved in ethanol and the concentrations determined using UV spectrophotometry (1,25(OH)₂D₃: molar extinction coefficient = 18,200 and λ_{max} = 265 nm). Radiolabeled ligand (³H-1,25(OH)₂D₃, ~159 Ci/mmol) was added in ethanol at a final concentration of 1 nM.

[0076] Assay Conditions

[0077] Radiolabeled and unlabeled ligands were added to 100 μ l of the diluted protein at a final ethanol concentration of $\leq 10\%$, mixed and incubated overnight on ice to reach binding equilibrium. The following day, 100 μ 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% Triton 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

[0078] Test Material

[0079] Study Drugs

[0080] 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 ($\leq 0.2\%$) present in the cell cultures.

[0081] Cells

[0082] 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% CO₂.

[0083] Assay Conditions

[0084] 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).

In vitro Transcription Assay

[0085] 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 luminometer. RLU = relative luciferase units.

Intestinal Calcium Transport and Bone Calcium Mobilization

[0086] 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.

INTERPRETATION OF DATA

[0087] VDR binding, HL60 cell differentiation, and transcription activity. 3-desoxy-2MD ($K_i=2\times 10^{-10} M$) has about the same activity as the natural hormone $1\alpha,25$ -

dihydroxyvitamin D₃ ($K_i=1\times10^{-10}M$) in its ability to compete with [³H]-1,25(OH)₂D₃ for binding to the full-length recombinant rat vitamin D receptor (Figure 1). 3-desoxy-2MD is also 3 times more potent ($EC_{50}=7\times10^{-10}M$) in its ability (efficacy or potency) to promote HL60 differentiation as compared to 1 α ,25-dihydroxyvitamin D₃ ($EC_{50}=2\times10^{-9}M$) (See Figure 2). Also, compound 3-desoxy-2MD ($EC_{50}=3\times10^{-10}M$) has about the same transcriptional activity in bone cells as 1 α ,25-dihydroxyvitamin D₃ ($EC_{50}=3\times10^{-10}M$) (See Figure 3). These data also indicate that 3-desoxy-2MD will have significant activity as an anti-cancer agent, especially for preventing or treating osteosarcoma, leukemia, colon cancer, breast cancer, skin cancer and prostate cancer because it has direct cellular activity in causing cell differentiation and in suppressing cell growth.

[0088] 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 3-desoxy-2MD and 1,25(OH)₂D₃ in intestine and bone were tested. As expected, the native hormone (1,25(OH)₂D₃) increased serum calcium levels at the dosages tested (Figs. 4A and 4B). Figures 4A and 4B also show that 3-desoxy-2MD has significantly more activity in mobilizing calcium from bone than 1,25(OH)₂D₃. Administration of 3-desoxy-2MD at 780 pmol/day for 4 consecutive days resulted in higher mobilization of bone calcium (about 10 times more potent) than the native hormone at the same 780 pmol/day dose in releasing bone calcium stores.

[0089] Intestinal calcium transport was evaluated in the same groups of animals using the everted gut sac method (Figures 5A and 5B). These results show that the compound 3-desoxy-2MD is about one half log less potent in promoting intestinal calcium transport activity when administered at the recommended lower dosages, as compared to 1,25(OH)₂D₃. Thus, it may be concluded that 3-desoxy-2MD has relatively low intestinal calcium transport activity at the tested doses.

[0090] These results further illustrate that 3-desoxy-2MD is an excellent candidate for numerous human therapies as described herein. 3-desoxy-2MD is an excellent candidate for

treating a cancer because: (1) it has significant VDR binding, transcription activity and cellular differentiation activity; (2) it has relatively low intestinal calcium absorption liability unlike $1,25(\text{OH})_2\text{D}_3$; and (3) it is easily synthesized. Because of its selective activity in the bone and increased potency on cellular differentiation, 3-desoxy-2MD might also be useful in treatment of bone diseases, such as senile osteoporosis, postmenopausal osteoporosis, steroid-induced osteoporosis, low bone turnover osteoporosis, osteomalacia, and renal osteodystrophy.

BIOLOGICAL ACTIVITY OF (20R)-3-DESOXY-2-METHYLENE- $1\alpha,25$ -DIHYDROXY-19-NOR-VITAMIN D₃ (3D-MJ)

[0091] The introduction of a methylene group to the 2-position, the removal of the methylene substituent at carbon 10 and the hydroxyl group at carbon 3, and orienting the methyl group at carbon 20 in its natural or R configuration had little or no effect on binding to the full length recombinant rat vitamin D receptor, as compared to $1\alpha,25$ -dihydroxyvitamin D₃. The compound 3D-MJ bound with about the same affinity to the receptor as compared to the standard $1,25(\text{OH})_2\text{D}_3$ (Figure 6). It might be expected from these results that compound 3D-MJ would have equivalent biological activity. Surprisingly, however, compound 3D-MJ is a highly selective analog with unique biological activity.

[0092] Figure 10 shows that 3D-MJ has relatively high activity in stimulating intestinal calcium transport. 3D-MJ has about the same potency as $1,25(\text{OH})_2\text{D}_3$ in promoting active calcium transport across the gut.

[0093] Figure 9 demonstrates that 3D-MJ has relatively high bone calcium mobilization activity, as compared to $1,25(\text{OH})_2\text{D}_3$. 3D-MJ has about the same potency as the native hormone in releasing bone calcium stores.

[0094] Figure 7 illustrates that 3D-MJ has about the same potency as $1,25(\text{OH})_2\text{D}_3$ on HL-60 cell differentiation, making it an excellent candidate for the treatment of a cancer, especially for the prevention or treatment of osteosarcoma, leukemia, colon cancer, breast cancer, skin cancer and prostate cancer.

[0095] Figure 8 illustrates that the compound 3D-MJ has about the same transcriptional activity as 1 α ,25-dihydroxyvitamin D₃ in bone cells. In bone cells, 3D-MJ is as potent as 1,25(OH)₂D₃ in increasing transcription of the 24-hydroxylase gene. This result, together with the cell differentiation activity of Figure 7, suggests that 3D-MJ will be very effective in treating the above referred to cancers because it has direct cellular activity in causing cell differentiation, gene transcription, and in suppressing cell growth.

INTERPRETATION OF DATA

[0096] VDR binding, HL60 cell differentiation, and transcription activity. 3D-MJ ($K_i=7\times10^{-10}$ M) has about the same activity as the natural hormone 1 α ,25-dihydroxyvitamin D₃ ($K_i=1\times10^{-10}$ M) in its ability to compete with [³H]-1,25(OH)₂D₃ for binding to the full-length recombinant rat vitamin D receptor (Figure 6). 3D-MJ is also about as potent ($EC_{50}=1\times10^{-9}$ M) in its ability (efficacy or potency) to promote HL60 differentiation as compared to 1 α ,25-dihydroxyvitamin D₃ ($EC_{50}=2\times10^{-9}$ M) (See Figure 7). Also, compound 3D-MJ ($EC_{50}=3\times10^{-10}$ M) has about the same transcriptional activity in bone cells as 1 α ,25-dihydroxyvitamin D₃ ($EC_{50}=1\times10^{-10}$ M) (See Figure 8). These data also indicate that 3D-MJ will have significant activity as an anti-cancer agent, especially for preventing or treating osteosarcoma, leukemia, colon cancer, breast cancer, skin cancer and prostate cancer because it has direct cellular activity in causing cell differentiation and in suppressing cell growth.

[0097] 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 3D-MJ and 1,25(OH)₂D₃ in intestine and bone were tested. As expected, the native hormone (1,25(OH)₂D₃) increased serum calcium levels at the dosages tested (Figure 9). Figure 9 also shows that 3D-MJ has significant activity in mobilizing calcium from bone. Administration of 3D-MJ at 87 pmol/day for 4 consecutive days resulted in only slightly less mobilization of bone calcium than the native hormone at the same 87 pmol/day dose in releasing bone calcium stores.

[0098] Intestinal calcium transport was evaluated in the same groups of animals using the everted gut sac method (Figure 10). These results show that the compound 3D-MJ is about as potent in promoting intestinal calcium transport activity when administered at the recommended lower dosages, as compared to 1,25(OH)₂D₃. Thus, it may be concluded that 3D-MJ has relatively high intestinal calcium transport activity at the tested doses.

[0099] These results further illustrate that 3D-MJ is an excellent candidate for numerous human therapies as described herein. 3D-MJ is an excellent candidate for treating a cancer because: (1) it has significant VDR binding, transcription activity and cellular differentiation activity; and (2) it is easily synthesized. Because of its selective activity in the intestine and bone and increased potency on cellular differentiation, 3D-MJ might also be useful in treatment of bone diseases, such as senile osteoporosis, postmenopausal osteoporosis, steroid-induced osteoporosis, low bone turnover osteoporosis, osteomalacia, and renal osteodystrophy.

[00100] For prevention and/or treatment purposes, the compounds of this invention defined by formula **I**, **Ia**, and **Ib** 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.

[00101] The compounds of formula **I** and particularly 3-desoxy-2MD of formula **Ia** and 3D-MJ of formula **Ib**, 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 μ g to 1000 μ g per day of the compounds **I**, particularly 3-desoxy-2MD and 3D-MJ, preferably from about 0.1 μ g to

about 500 μ g 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. 1 α -hydroxyvitamin D₂ or D₃, or 1 α ,25-dihydroxyvitamin D₃ -- in situations where different degrees of bone mineral mobilization and calcium transport stimulation is found to be advantageous.

[00102] Compositions for use in the above-mentioned treatments comprise an effective amount of the compounds I, particularly 3-desoxy-2MD and 3D-MJ, as defined by the above formula **I**, **Ia**, and **Ib**, 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 μ g to about 1000 μ g per gm of composition, preferably from about 0.1 μ g to about 500 μ g per gram of composition, and may be administered topically, transdermally, orally, rectally, nasally, sublingually or parenterally in dosages of from about 0.01 μ g/day to about 1000 μ g /day, and preferably from about 0.1 μ g/day to about 500 μ g/day.

[00103] The compounds I, particularly 3-desoxy-2MD and 3D-MJ, 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.

[00104] The compounds I, particularly 3-desoxy-2MD and 3D-MJ, 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.

[00105] 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.

[00106] 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.

[00107] 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.

[00108] 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.

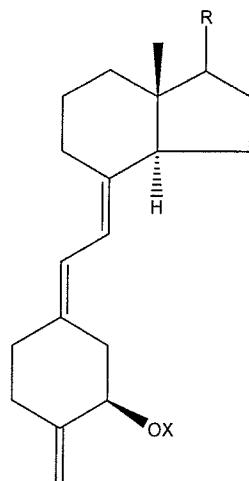
[00109] Formulations suitable for topical administration include liquid or semi-liquid preparations such as liniments, lotions, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops; or as sprays.

[00110] 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 100 μ .

[00111] 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.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

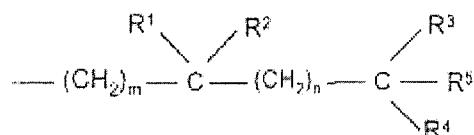
1. A compound having the formula:



where X is selected from the group consisting of hydrogen and a hydroxy-protecting group, and where R may be hydrogen, an alkyl, hydroxyalkyl or fluoroalkyl group, or R may represent a side chain of the formula:



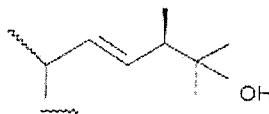
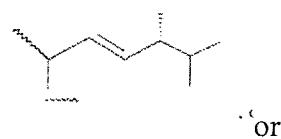
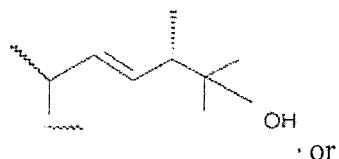
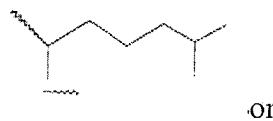
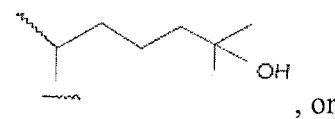
where the stereochemical center at carbon 20 may have the R or S configuration, and where Z in the above side chain structure is selected from Y, -OY, -CH₂OY, -C≡CY and -CH=CHY, where the double bond in the side chain may have the cis or trans geometry, and where Y is selected from hydrogen, methyl, -COR⁵ and a radical of the structure:



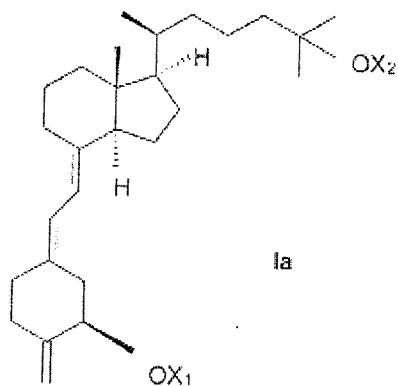
where m and n, independently, represent the integers from 0 to 5, where R¹ is selected from hydrogen, deuterium, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C₁₋₅-alkyl, which may be straight chain or branched and optionally bear a hydroxy or protected-hydroxy substituent, and where each of R², R³, and R⁴, independently, is selected from deuterium, deuteroalkyl, hydrogen, fluoro, trifluoromethyl and C₁₋₅ alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R¹ and R², taken together, represent an oxo group, or an alkylidene group having a general formula C_kH_{2k}, where k is an integer, the group =CR²R³, or the group -(CH₂)_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 of $-CH(CH_3)-$, $-(CH_2)_m-$ or $-(CH_2)_n-$ 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 $-(CH_2)_n-$ of the side chain may be replaced by an oxygen or sulfur atom.

2. The compound of claim 1, wherein R is selected from:

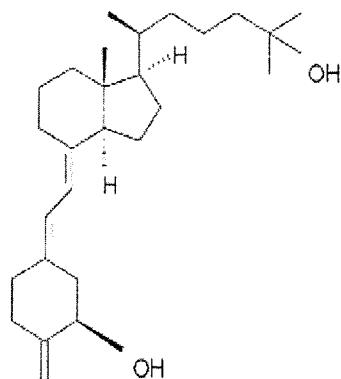


3. A compound having the formula:



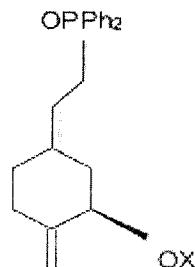
where X_1 and X_2 , which may be the same or different, are each selected from hydrogen or a hydroxy-protecting group.

4. A compound having the formula:



and named (20S)-3-desoxy-2-methylene-1 α ,25-dihydroxy-19-nor-vitamin D₃.

5. A compound having the formula:

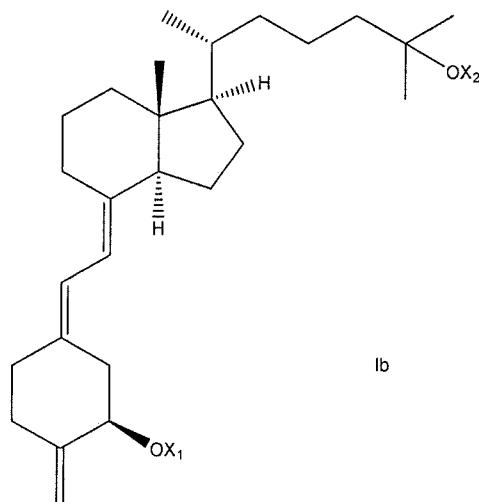


where X is selected from the group consisting of hydrogen and a hydroxy-protecting group.

6. A compound according to any one of claims 1, 2 and 5, wherein X is hydrogen.

7. A compound according to claim 5, wherein X is t-butyldimethylsilyl.

8. A compound having the formula:



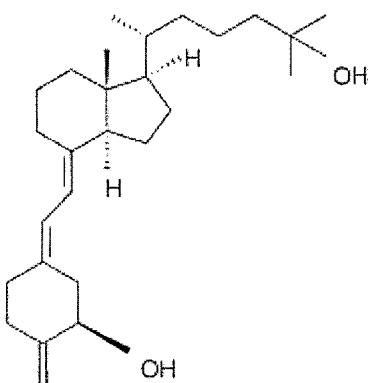
where X_1 and X_2 , which may be the same or different, are each selected from hydrogen or a hydroxy-protecting group.

9. A compound according to claim 3 or claim 8, wherein X_2 is hydrogen.

10. A compound according to any one of claims 3, 8 and 9, wherein X_1 is hydrogen.

11. A compound according to claim 3 or claim 8, wherein X_1 and X_2 are both t-butyldimethylsilyl.

12. A compound having the formula:



and named (20R)-3-desoxy-2-methylene-1 α ,25-dihydroxy-19-nor-vitamin D₃.

13. A pharmaceutical composition containing an effective amount of at least one compound according to any one of claims 1 to 4 and 8 to 12, together with a pharmaceutically acceptable excipient.

14. The pharmaceutical composition of claim 13, wherein said effective amount comprises from about 0.01 μ g to about 1000 μ g per gram of composition.

15. The pharmaceutical composition of claim 13 or claim 14, wherein said effective amount comprises from about 0.1 μ g to about 500 μ g per gram of composition.

16. A method of treating a disease selected from the group consisting of osteosarcoma, leukemia, colon cancer, breast cancer, skin cancer and prostate cancer comprising administering to a subject with said disease an effective amount of a compound according to any one of claims 1 to 4 and 8 to 12, or a composition according to any one of claims 13 to 15.

17. A method of treating metabolic bone disease where it is desired to maintain or increase bone mass comprising administering to a patient with said disease an effective amount of a compound according to any one of claims 1 to 12, or a composition according to any one of claims 13 to 15.

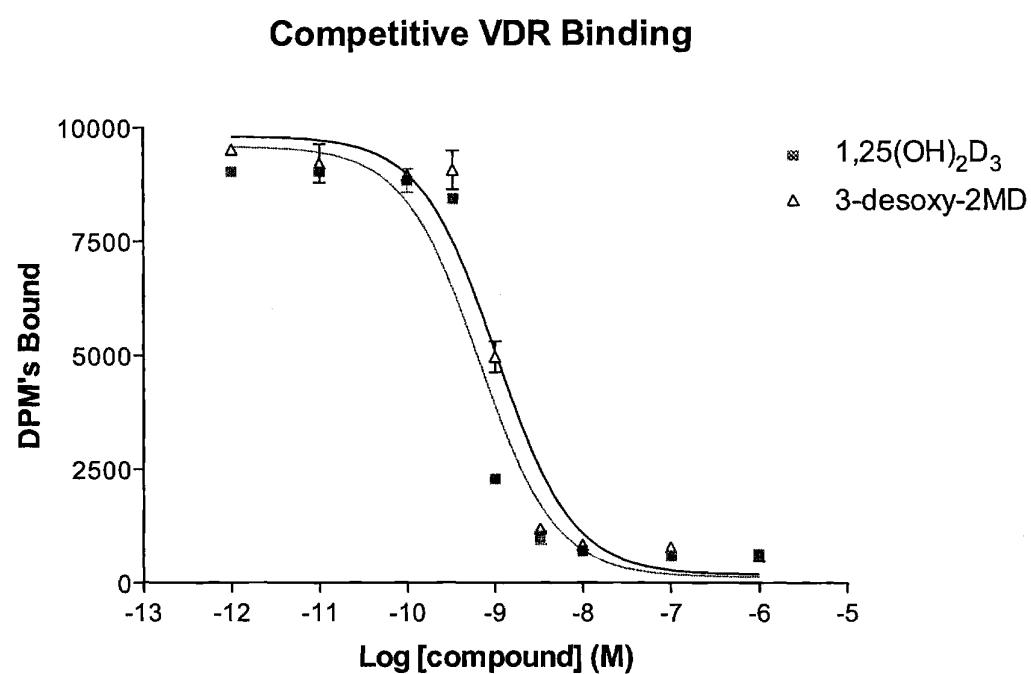
18. The method of claim 17, where the disease is senile osteoporosis, postmenopausal osteoporosis, steroid-induced osteoporosis, low bone turnover osteoporosis, osteomalacia, or renal osteodystrophy.

19. The method of any one of claims 16 to 18, wherein the compound is administered orally, parenterally, transdermally, rectally, nasally or sublingually.

20. The method of any one of claims 16 to 19, wherein the compound is administered in a dosage of from about 0.01ug/day to about 1000 μ g/day.

21. Use of a compound according to any one of claims 1 to 4 and 8 to 12, or a composition according to any one of claims 13 to 15, in the preparation of a medicament for the treatment of a disease selected from the group consisting of osteosarcoma, leukemia, colon cancer, breast cancer, skin cancer and prostate cancer.

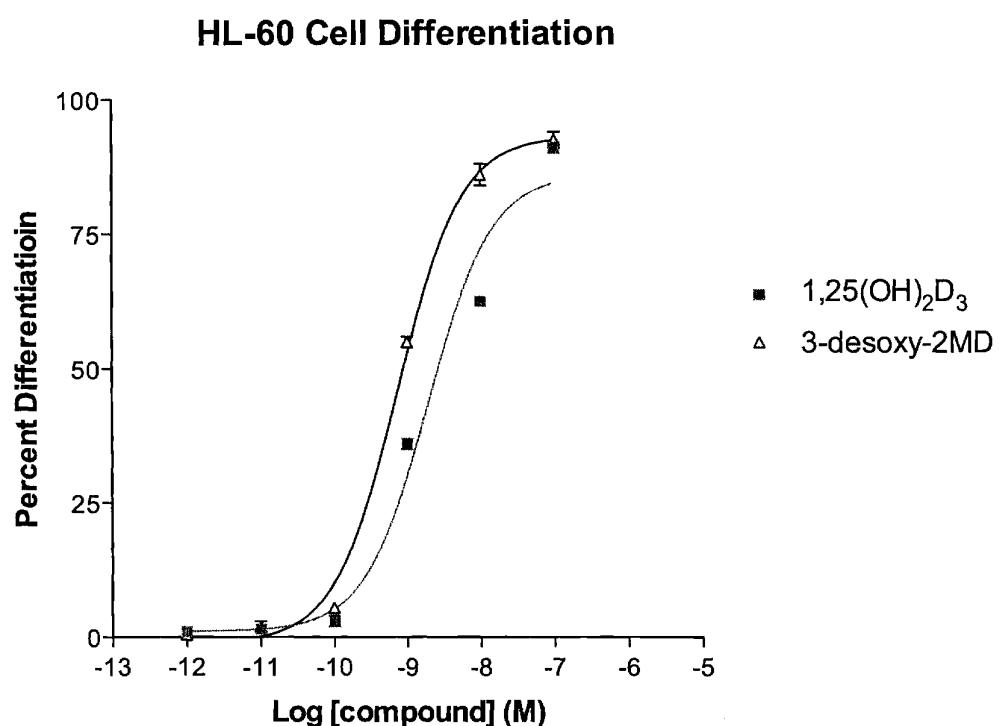
22. Use of a compound according to any one of claims 1 to 4 and 8 to 12, or a composition according to any one of claims 13 to 15, in the preparation of a medicament for the treatment of a metabolic bone disease where it is desired to maintain or increase bone mass.



K_i : $1,25(\text{OH})_2\text{D}_3 = 1 \times 10^{-10} \text{ M}$
 $3\text{-desoxy-2MD} = 2 \times 10^{-10} \text{ M}$

Figure 1

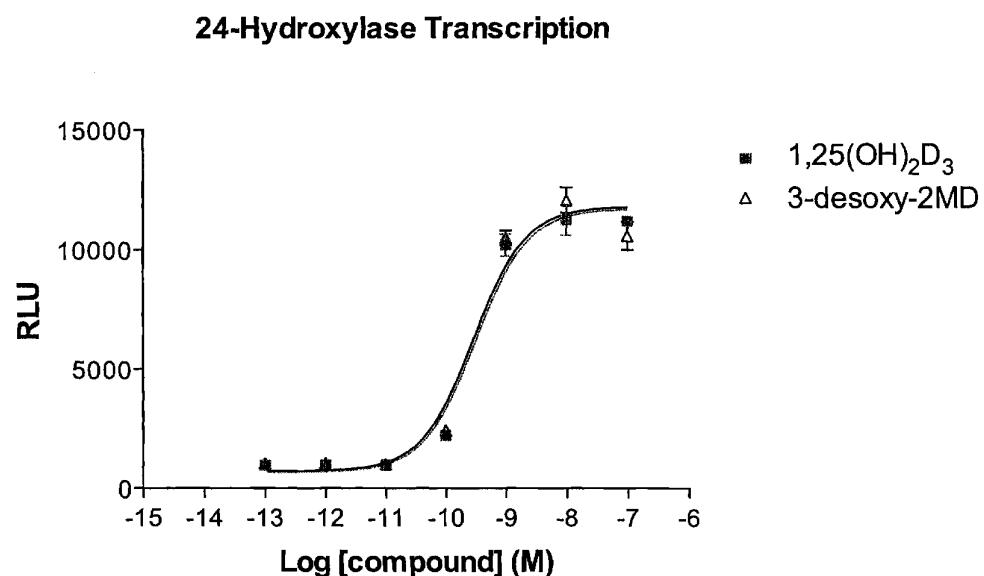
2/12



EC₅₀: 1,25(OH)₂D₃ = 2 x 10⁻⁹ M
3-desoxy-2MD = 7 x 10⁻¹⁰ M

Figure 2

3/12



EC₅₀: 1,25(OH)₂D₃ = 3 x 10⁻¹⁰ M
3-desoxy-2MD = 3 x 10⁻¹⁰ M

Figure 3

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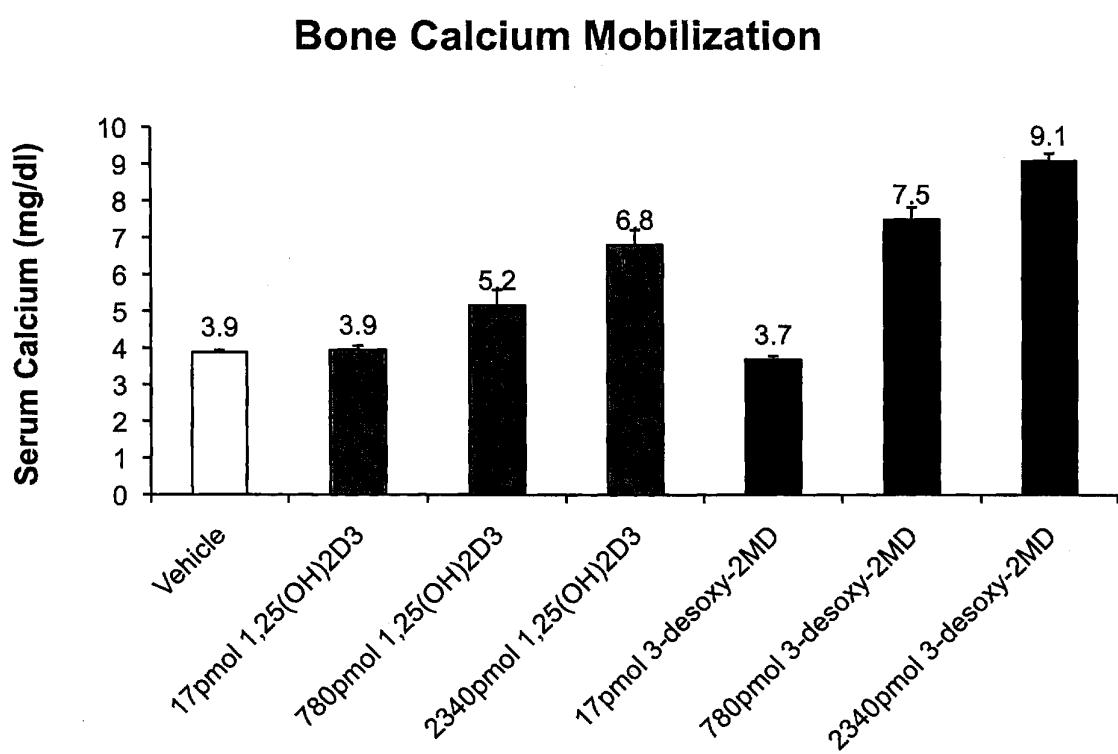


Figure 4A

5/12

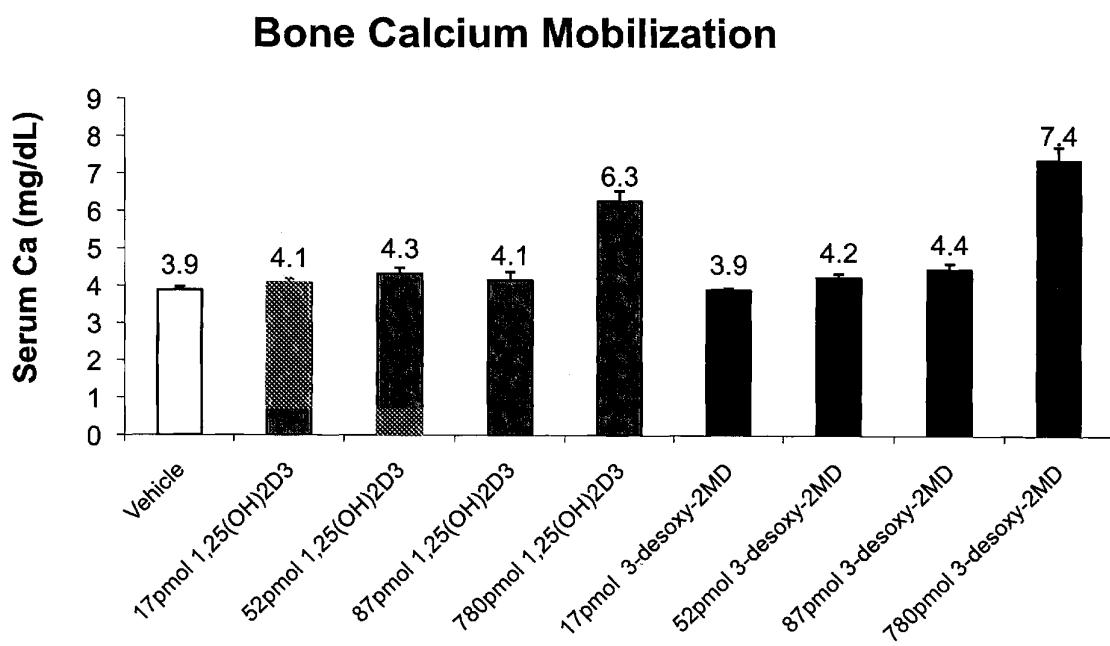


Figure 4B

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Intestinal Calcium Transport

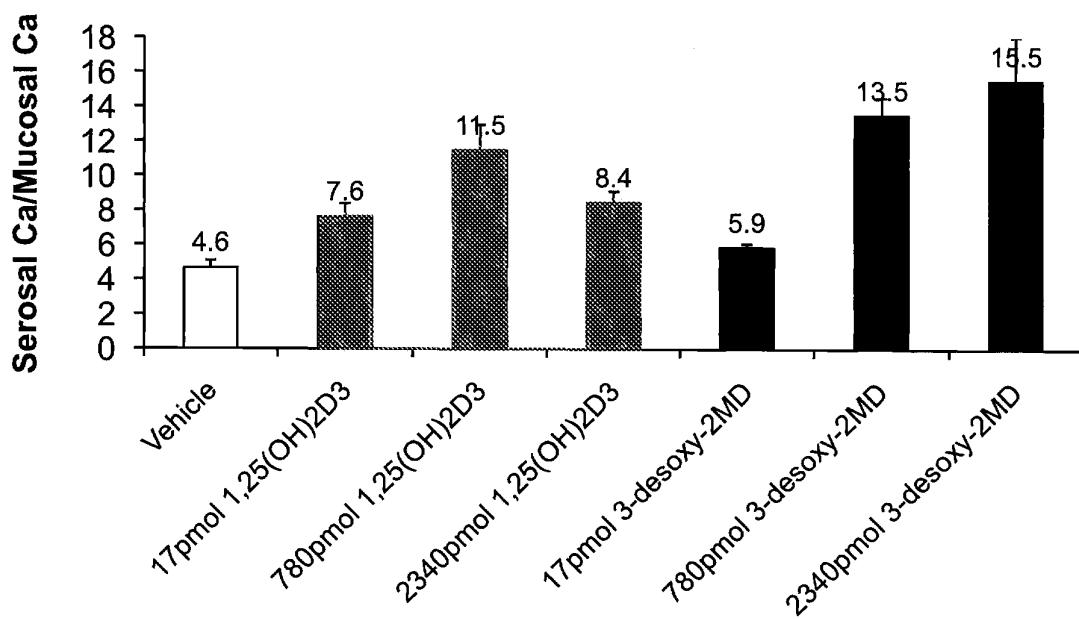


Figure 5A

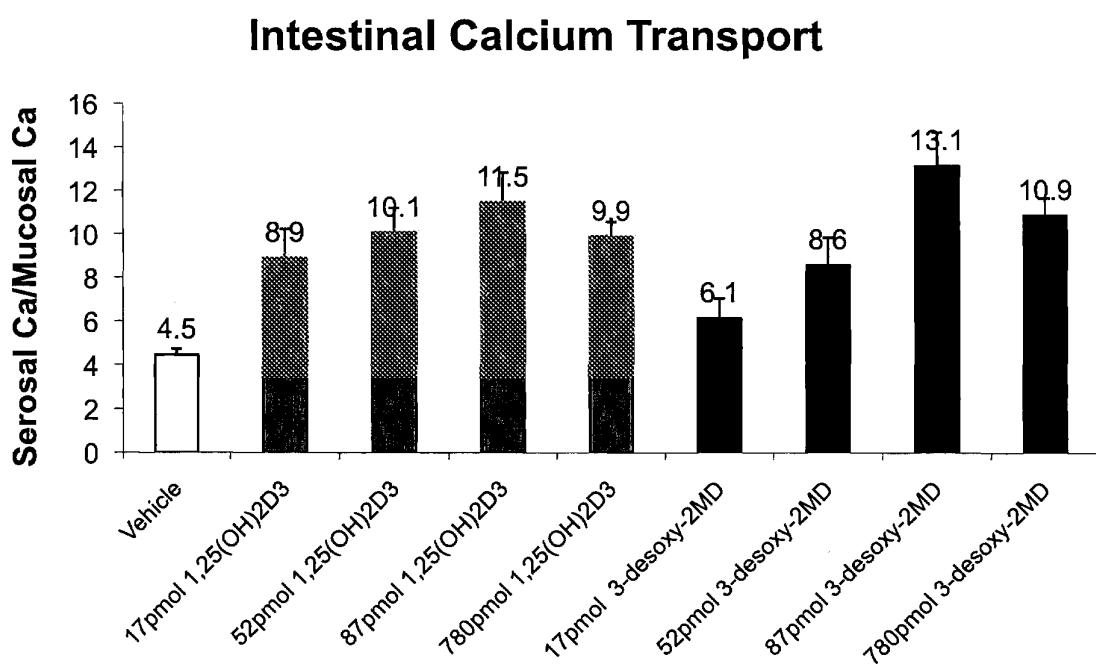
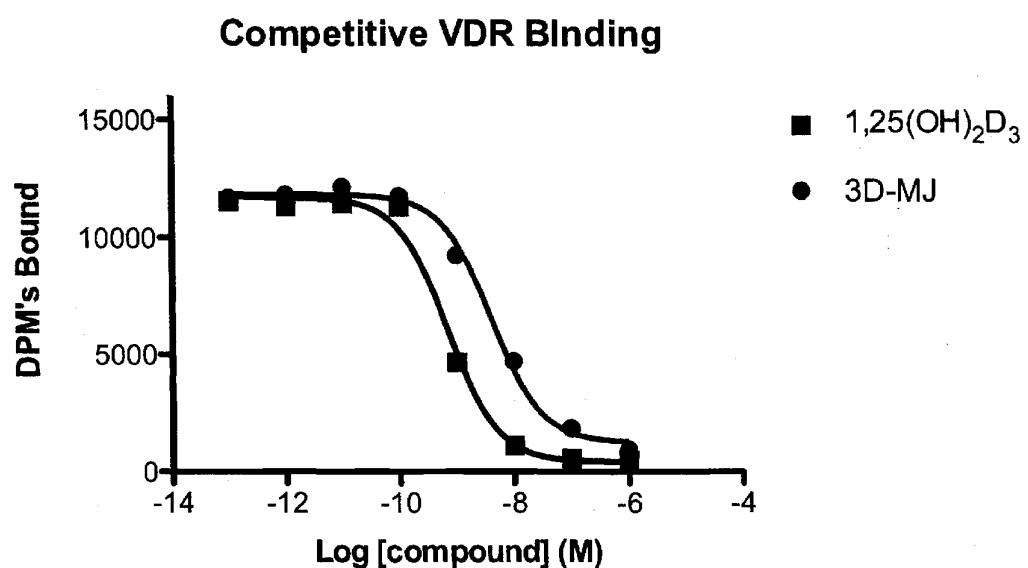


Figure 5B

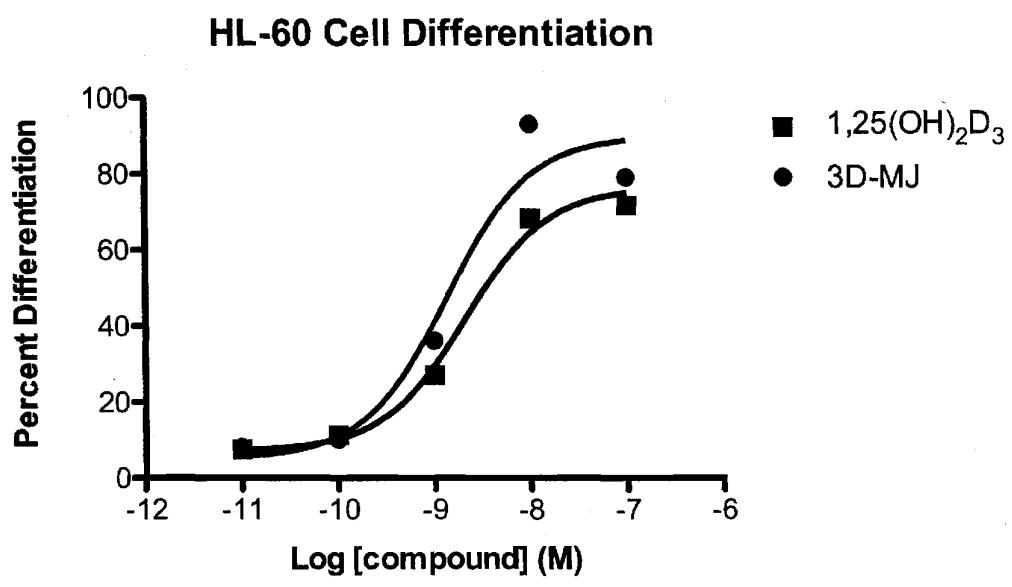
8/12



$$K_i: 1,25(\text{OH})_2\text{D}_3 = 1 \times 10^{-10} \text{ M}$$
$$3\text{D-MJ} = 7 \times 10^{-10} \text{ M}$$

Figure 6

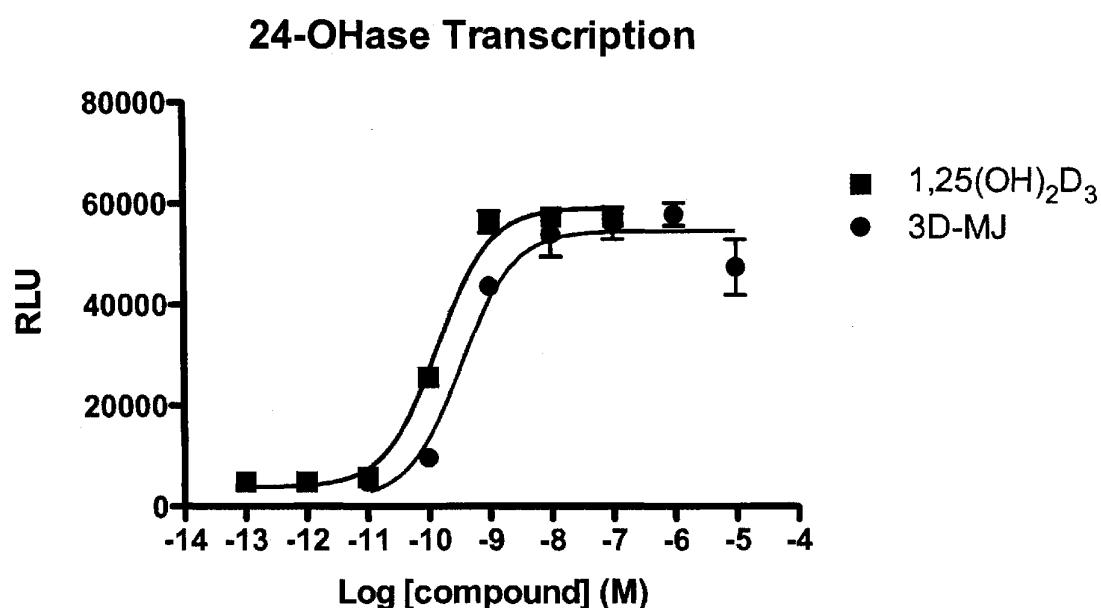
9/12



EC₅₀: 1,25(OH)₂D₃ = 2 x 10⁻⁹ M
3D-MJ = 1 x 10⁻⁹ M

Figure 7

10/12



EC₅₀: 1,25(OH)₂D₃ = 1 × 10⁻¹⁰ M
3D-MJ = 3 × 10⁻¹⁰ M

Figure 8

11/12

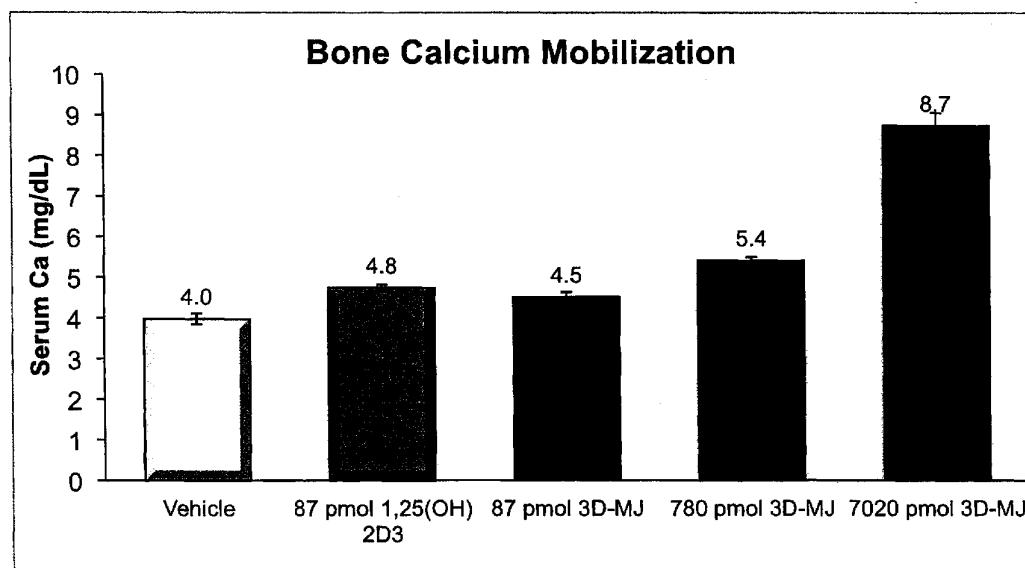


Figure 9

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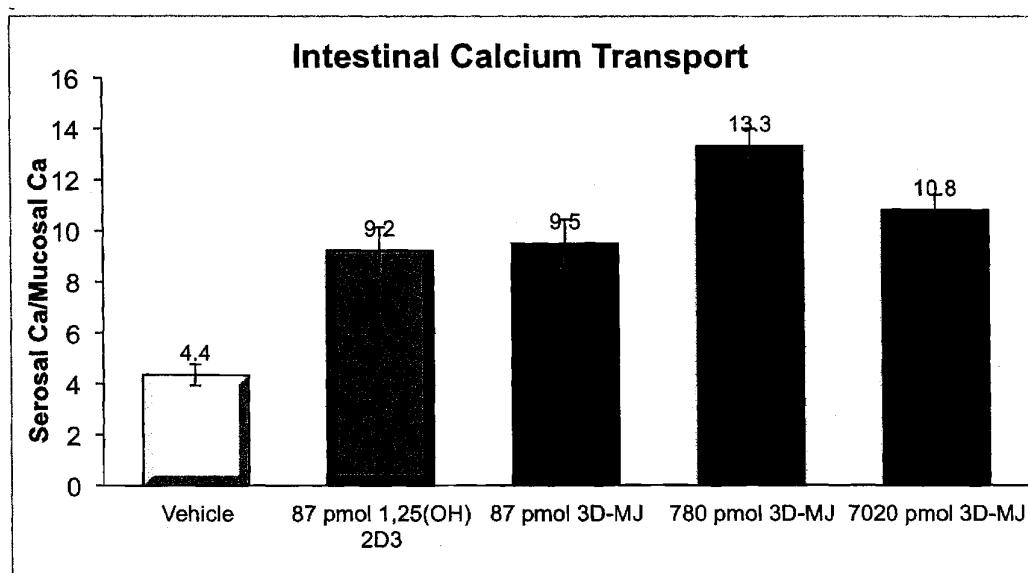


Figure 10