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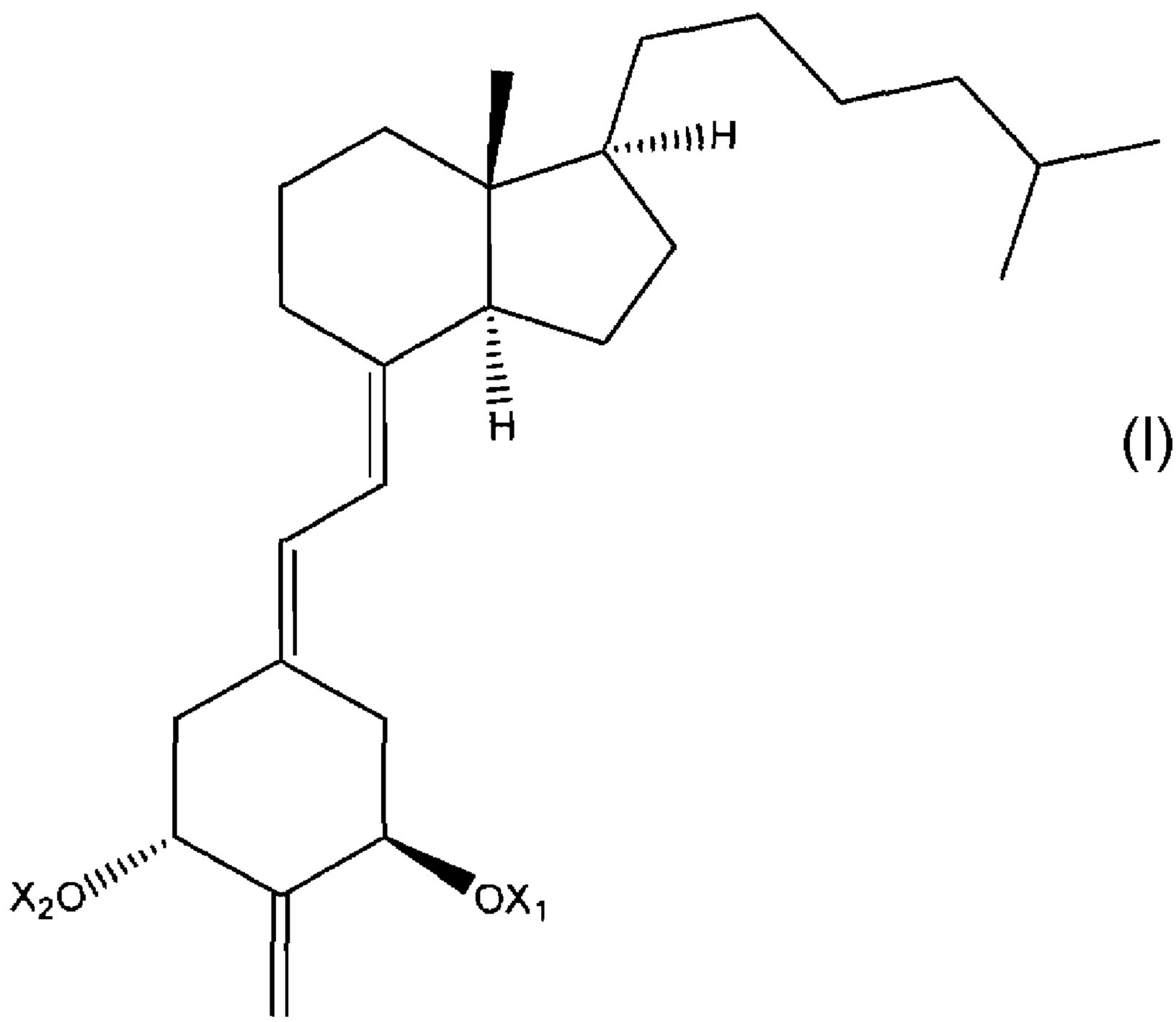
(71) Demandeur/Applicant:
WISCONSIN ALUMNI RESEARCH FOUNDATION, US

(72) Inventeurs/Inventors:
DELUCA, HECTOR F., US;
PLUM, LORI A., US;
CLAGETT-DAME, MARGARET, US;
BARYCKI, RAFAL, US

(74) Agent: BORDEN LADNER GERVAIS LLP

(54) Titre : COMPOSES ANALOGUES A LA 2-METHYLENE-1ALPHA-HYDROXY-19,21-DINORVITAMINE D3 ET LEURS UTILISATIONS

(54) Title: 2-METHYLENE-1ALPHA-HYDROXY-19,21-DINORVITAMIN D3 ANALOGS AND USES THEREOF



(I)

(57) Abrégé/Abstract:
Compounds of formula I are provided where X_1 and X_2 are independently selected from H or hydroxy protecting groups. Such compounds are used in preparing pharmaceutical compositions and are useful in treating a variety of biological conditions.

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(71) Applicant *(for all designated States except US)*: **WISCONSIN ALUMNI RESEARCH FOUNDATION** [US/US]; 614 Walnut Street, 13th Floor, Madison, WI 53705 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DELUCA, Hector, F.** [US/US]; 1809 Highway BB, Deerfield, WI 53531 (US). **PLUM, Lori, A.** [US/US]; 6139 Highway H., Arena, WI 53503 (US). **CLAGETT-DAME, Margaret** [US/US]; 1809 Highway BB, Deerfield, WI 53531 (US). **BARYCKI, Rafal** [PL/US]; 708 Eagle Heights, Apartment H, Madison, WI 53705 (US).

(74) Agents: **WOZNY, Thomas, M.** et al.; Andrus, Sceales, Starke & Sawall, LLP, 100 East Wisconsin Avenue, Suite 1100, Milwaukee, WI 53202-4178 (US).

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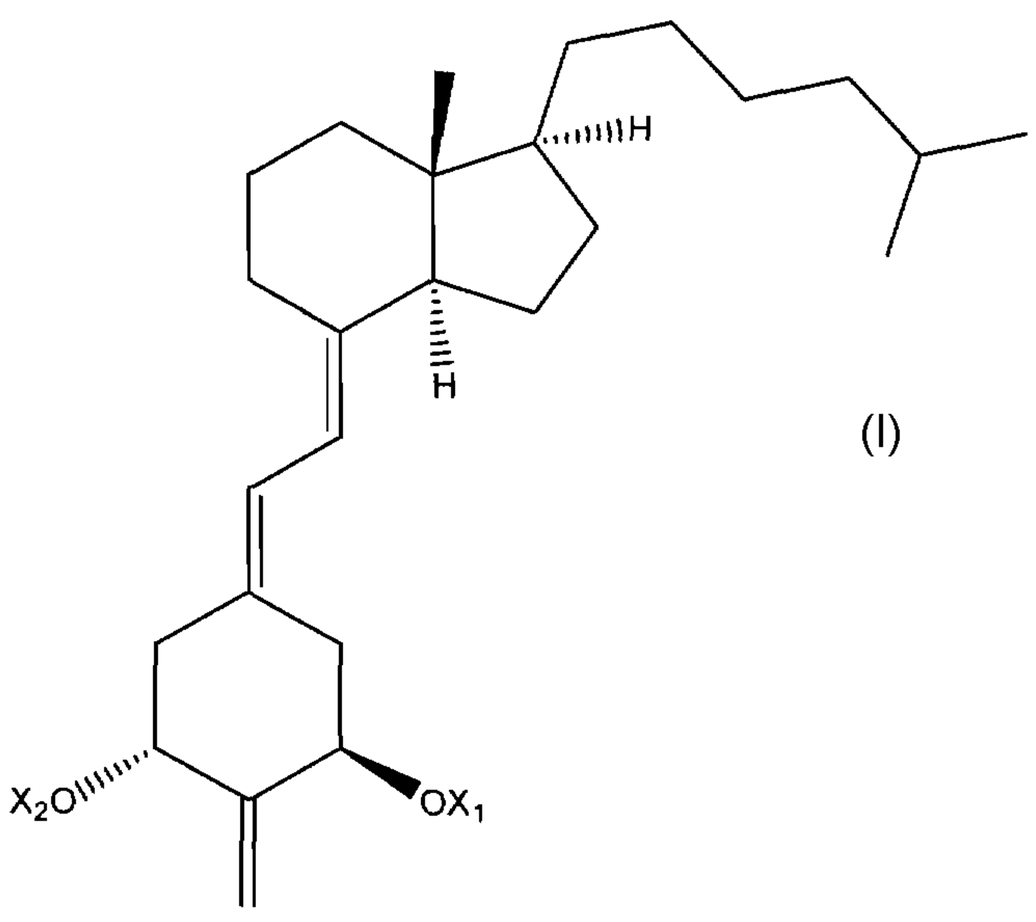

(I)

(57) Abstract: Compounds of formula I are provided where X_1 and X_2 are independently selected from H or hydroxy protecting groups. Such compounds are used in preparing pharmaceutical compositions and are useful in treating a variety of biological conditions.

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2-METHYLENE-1α-HYDROXY-19,21-DINORVITAMIN D_3 ANALOGS AND USES THEREOF

FIELD OF THE INVENTION

[0001] This invention relates to vitamin D compounds, and more particularly to 2-methylene-1α-hydroxy-19,21-dinorvitamin D_3 (SY-44) and to pharmaceutical formulations that include this compound. The invention also relates to the use of 2-methylene-1α-hydroxy-19,21-dinorvitamin D_3 or salts thereof in the preparation of medicaments for use in treating various diseases.

BACKGROUND OF THE INVENTION

[0002] The natural hormone, 1α,25-dihydroxyvitamin D_3 (also referred to as 1α,25-dihydroxycholecalciferol and calcitriol) 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 is useful in the treatment of a variety of diseases as established in the art, such as renal osteodystrophy, vitamin D-resistant rickets, osteoporosis, psoriasis, and certain malignancies (see for example, Zemplar, Calcipotriol, MC-903, Dovonex, 22-oxa-1α, 25-$(OH)_2D_3$) Slatopolsky, E., Finch, J., Ritter, C., Denda, M., Morrissey, J., Brown, A. & DeLuca, H. (1995) Am. J. Kidney Dis. 26, 852-860; Kubodera, N., Sato, K. & Nishii, Y. (1997) in Vitamin D, eds. Feldman, D., Glorieux, F.H. & Pike, J.W. (Academic, New York), Vol. 63, pp. 1071-1086; Calverley, M.J. (1987) Tetrahedron Lett. 43, 4609-4619; Uskokovic, M.R., Studzinski, G.P. & Reddy, S.G. (1997) in Vitamin D, eds. Feldman, D., Glorieux, F.H. & Pike, J.W. (Academic, New York), Vol. 62, pp. 1045-1070; Kensler, T.W., Dolan, P.M., Gange, S.J., Lee, J.-K., Wang, Q. & Posner, G.H. (2000) Carcinogenesis 21, 1341-1345; Binderup, L., Binderup, E. & Godfredsen, W.O. (1997) in Vitamin D, eds. Feldman, D., Glorieux, F.H. & Pike, J.W. (Academic, New York), Vol. 61, pp. 1027-1043; Jones, G. (1997) in Vitamin D, eds. Feldman, D., Glorieux, F.H. & Pike, J.W. (Academic, New York), Vol. 58, pp.

973-994; Brown, A.J. & Slatopolsky, E. (1997) in Vitamin D, eds. Feldman, D., Glorieux, F.H. & Pike, J.W. (Academic, New York), Vol. 59, pp. 995-1009; Shankar, V.N., Propp, A.E., Schroeder, N.S., Surber, B.W., Makin, H.L.J. & Jones, G. (2001) Arch. Biochem. Biophys. 387, 297-306. All these references are incorporated herein by reference for all purposes.

[0003] As discussed above, renal osteodystrophy is a bone disease that occurs when the kidneys fail to maintain the proper levels of calcium and phosphorus in the blood. Renal osteodystrophy is a common problem in people with kidney disease and affects 90 percent of dialysis patients.

[0004] Renal osteodystrophy is most serious in children because their bones are still growing. The condition slows bone growth and causes deformities. One such deformity occurs when the legs bend inward toward each other or outward away from each other; this deformity is referred to as "renal rickets." Another important consequence is short stature. Symptoms can be seen in growing children with renal disease even before they start dialysis.

[0005] The bone changes from renal osteodystrophy can begin many years before symptoms appear in adults with kidney disease. The symptoms of renal osteodystrophy are not usually seen in adults until they have been on dialysis for several years. Older patients and women who have gone through menopause are at greater risk for this disease because they're already vulnerable to osteoporosis, even without kidney disease. If left untreated, the bones gradually become thin and weak, and a person with renal osteodystrophy begins to experience bone and joint pain and an increased risk of bone fractures.

[0006] In healthy adults, bone tissue is continually being remodeled and rebuilt. The kidneys play an important role in maintaining healthy bone mass and structure because it balances calcium and phosphorus levels in the blood. If calcium levels in the blood become too low, the parathyroid glands release parathyroid hormone (PTH). This hormone draws calcium from the bones to raise blood calcium levels. Too much PTH in the blood causes disturbances in calcium and phosphorus homeostasis. This in turn removes too much calcium from the bones; over time, the constant removal of calcium weakens the bones.

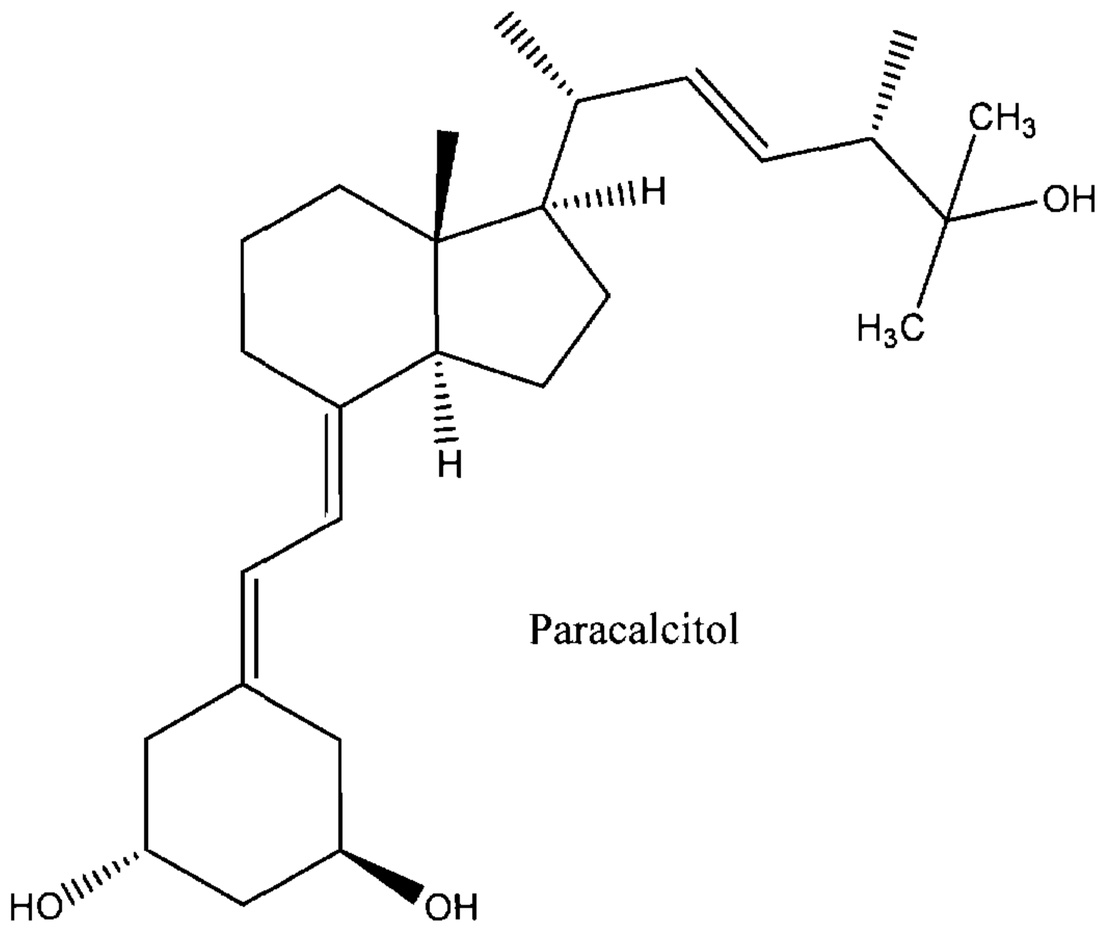
[0007] In this context, secondary hyperparathyroidism is characterized by an elevation of PTH associated with inadequate levels of active vitamin D hormone. Typically, Vitamin D requires two sequential hydroxylations in the liver and the kidney to bind to activate the Vitamin D receptor (VDR). The endogenous VDR activator, calcitriol [1,25$(OH)_2$ D_3] is a hormone that binds to VDRs that are present in the parathyroid gland, intestine, kidney, and bone to maintain parathyroid function and calcium and phosphorus homeostasis, and to VDRs found in many other tissues, including prostate, endothelium and immune cells. Phosphorus also helps regulate calcium levels in the bones. Healthy kidneys remove excess phosphorus from the blood. When the kidneys stop working normally, phosphorus levels in the blood can become too high, leading to lower levels of calcium in the blood and resulting in the loss of calcium from the bones.

[0008] Healthy kidneys produce calcitriol to help the body absorb dietary calcium into the blood and the bones. If calcitriol levels drop too low, PTH levels increase, and calcium is removed from the bones. Calcitriol and PTH work together to keep calcium balance normal and bones healthy. In a patient with kidney failure, the kidneys stop making calcitriol, dietary calcium is not absorbed and calcium is removed from the bones.

[0009] Controlling PTH levels prevents calcium from being withdrawn from the bones. Usually, overactive parathyroid glands are controllable with a change in diet, dialysis treatment, or medication. The drug cinacalcet hydrochloride (Sensipar), approved by the Food and Drug Administration in 2004, lowers PTH levels by binding to the calcium receptor that controls PTH release. If PTH levels cannot be controlled, the parathyroid glands may need to be removed surgically. Other treatments for the condition include taking synthetic calcitriol as a pill or in an injectable form.

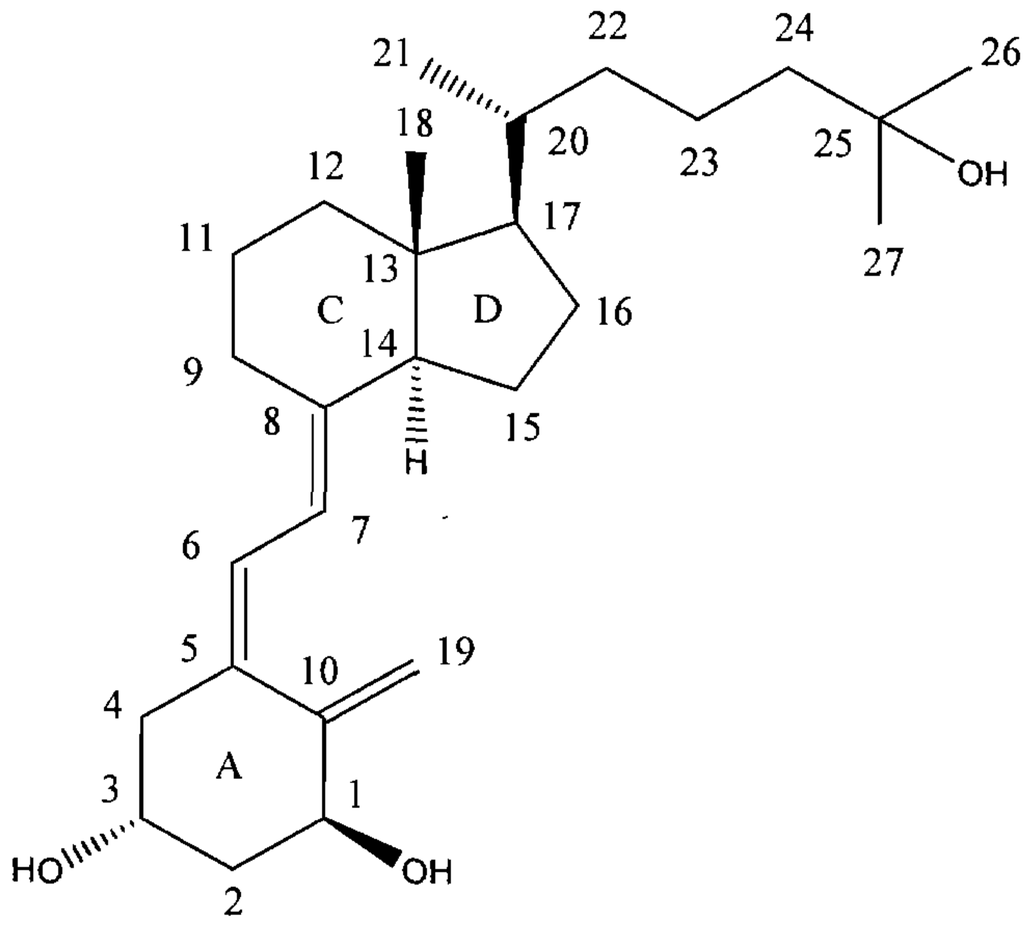
[0010] Renal osteodystrophy can also be treated with changes in diet. Reducing dietary intake of phosphorus is one of the most important steps in preventing bone disease. Often, medications such as calcium carbonate (Tums), calcium acetate (PhosLo), sevelamer hydrochloride (Renagel), or lanthanum carbonate (Fosrenol) are prescribed with meals and snacks to bind phosphorus in the bowel, which decreases the absorption of phosphorus into the blood.

[0011] Other treatment choices for renal osteodystrophy include Paricalcitol, the active ingredient of Zemplar (paracalcitol injection, USP), which is a synthetic, biologically active vitamin D analog of calcitriol with modifications to the side chain and the A (19-nor) ring. Preclinical and in vitro studies have demonstrated that paricalcitol's actions are mediated through binding to the VDR, resulting in the selective activation of Vitamin D response pathways. Calcitriol and paricalcitol have been shown to reduce parathyroid hormone levels by inhibiting PTH synthesis and secretion.



Paracalcitol

[0012] The structure of 1α,25-dihydroxyvitamin D_3 and the numbering system used to denote the carbon atoms in this compound are shown below.



1α,25-Dihydroxyvitamin D_3 = 1α,25-Dihydroxycholecalciferol = Calcitriol

[0013] Typically, the class of vitamin D analogs such as 19-nor-vitamin D compounds is characterized by the absence of carbon 19 from the A-ring exocyclic methylene group, typical of the vitamin D system. 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).

[0014] In U.S. Application Serial Nos. 11/669,029 and 11/669,053 filed on January 30, 2007, (20R, 25S)-2-methylene-19,26-dinor-1α,25-dihydroxyvitamin D3 (NEL) and (20S, 25S)-2-methylene-19,26-dinor-1α,25-dihydroxyvitamin D3 (RAK) have been described and examined by DeLuca et al. as potential drugs for treatment of renal osteodystrophy. 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 the 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)).

[0015] Various 2-substituted analogs of 1α,25-dihydroxy-19-nor-vitamin D_3 have also been synthesized, i.e. compounds substituted at the 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.

[0016] In a continuing effort to explore the 19-nor class of pharmacologically important vitamin D compounds, analogs that are characterized by the presence of a

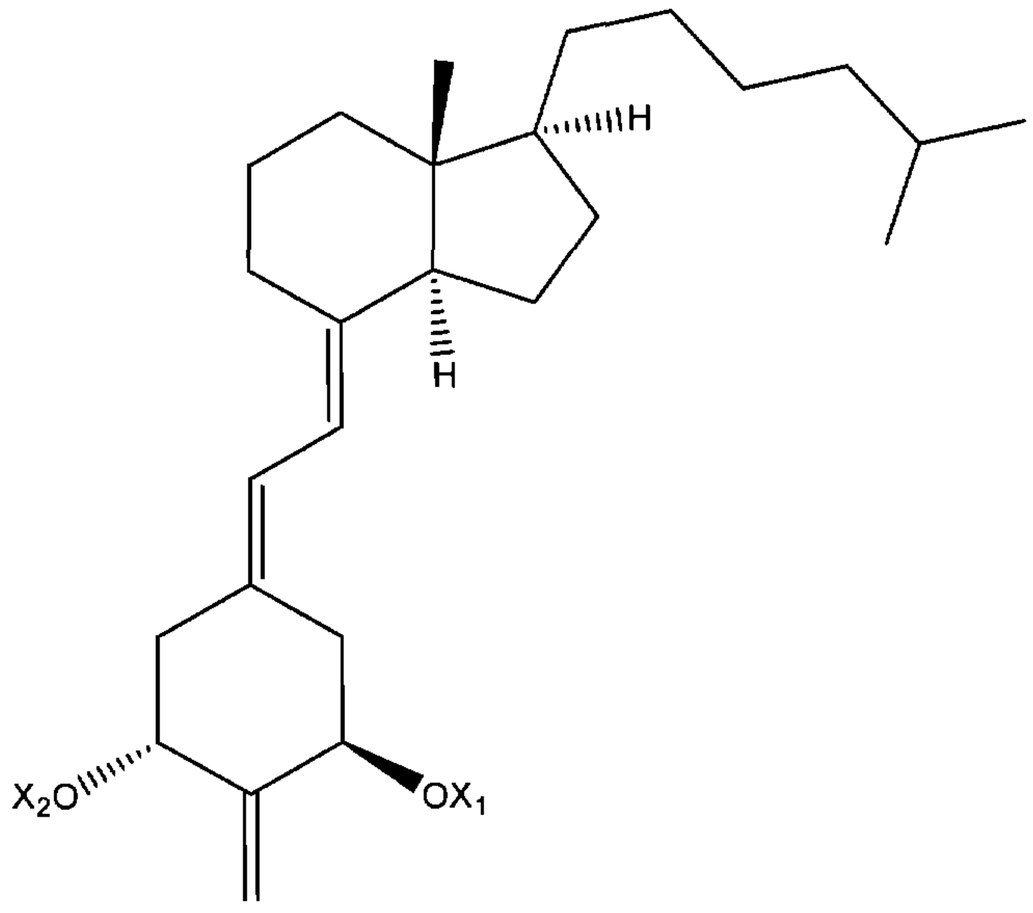
methylene substituent at carbon 2 (C-2), a hydroxyl group at carbon 1 (C-1), and a shortened side chain attached to carbon 20 (C-20) have also been synthesized and tested. 1α-hydroxy-2-methylene-19-nor-pregnacalciferol is described in U.S. Patent No. 6,566,352 while 1α-hydroxy-2-methylene-19-nor-(20S)-homopregnacalciferol is described in U.S. Patent No. 6,579,861 and 1α-hydroxy-2-methylene-19-nor-bishomopregnacalciferol is described in U.S. Patent No. 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. Other 19-nor compounds are disclosed in US Patent Application Nos. 10/996,642 and 10/997,698. All these patents and patent applications are incorporated herein by reference for all purposes.

[0017] Since the currently available treatments, including compounds and formulations described above have various limitations to a greater or lesser extent, new compounds and pharmaceutical formulations are desirable that cure various diseases.

SUMMARY OF THE INVENTION

[0018] The invention generally provides 2-methylene-1α-hydroxy-19,21-dinorvitamin D_3 (SY-44) and related compounds, pharmaceutical formulations that include SY-44 and the use of this compound in the preparation of medicaments for use in treating various disease states.

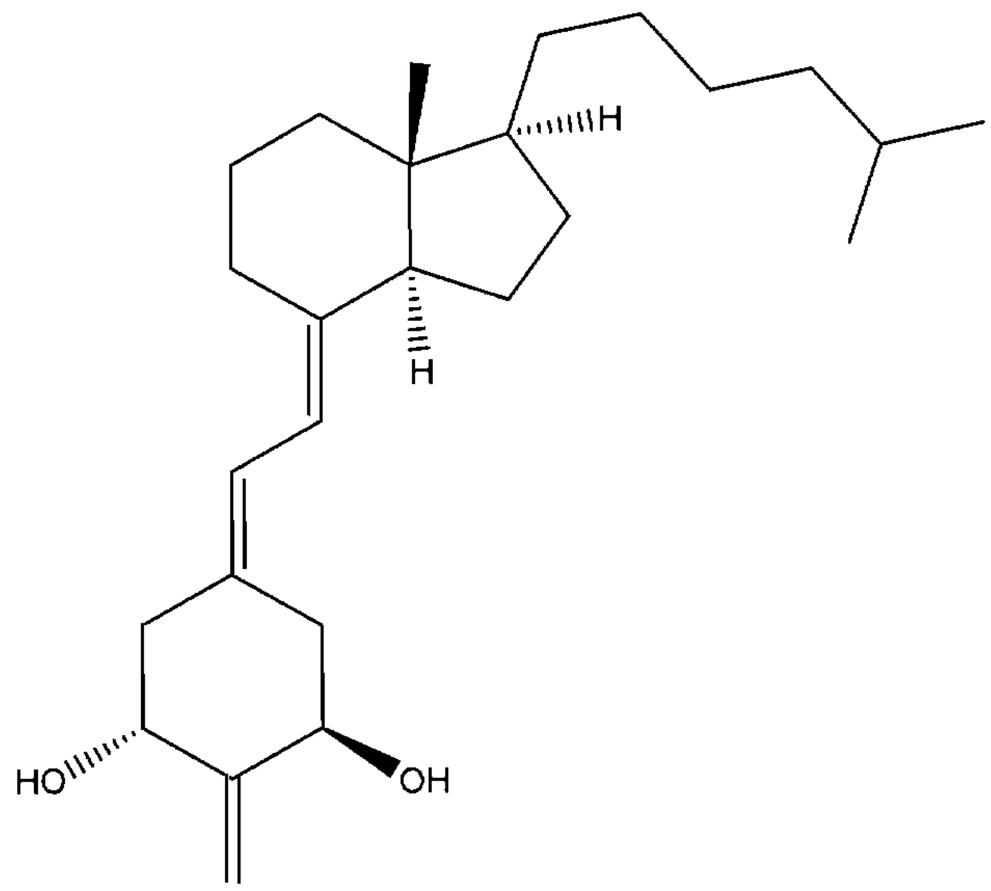
[0019] Therefore, in one aspect, the invention provides a compound having the formula I as shown below:



I

[0020] where $X_1$and X_2 are the same or different and are independently selected from H or hydroxy-protecting groups. In some embodiments, X_1 and X_2 are hydroxy protecting groups such as silyl ether groups, alkyl ether groups, alkoxyalkyl ether group, acetal groups and ester groups. In some such embodiments, X_1 and X_2 are t-butyldimethylsilyl ether group (TBDMS), trimethylsilyl ether group (TMS), triethylsilyl ether group (TES), Triisopropylsilyl ether group (TIPS), t-butyldiphenylsilyl ether group (TBDPS), tetrahydropyran group (THP), methoxyethoxymethyl group (MEM), methoxymethyl group (MOM), benzyl ether group, t-butyl ether group, N-phthalimido acetal group (Nphth), isopropylidene, trimethoxy butane, 2,4-dimethylpentan-3-yloxycarbonyl group (Doc). Various other hydroxy protecting groups are known to one of ordinary skill in the art, for example see Jarowicki et al, J. Chem. Soc., Perkin Trans. 1, 1998, 4005-4037, which is incorporated herein by reference for all purposes.

[0021] In other embodiments, X_1 and X_2 are H such that the compound is 2-methylene-1α-hydroxy-19,21-dinorvitamin D_3 (SY-44) having the formula II as shown below:



II

[0022] Another embodiment of the present invention provides a pharmaceutical composition, comprising an effective amount of the compound of formula I or II and a pharmaceutically acceptable carrier. In this pharmaceutical composition the effective amount comprises from about 0.01 μg to about 1 mg of the compound per gram of the composition. More preferably, the effective amount comprises from about 0.1 μg to about 500 μg of the compound per gram of the composition.

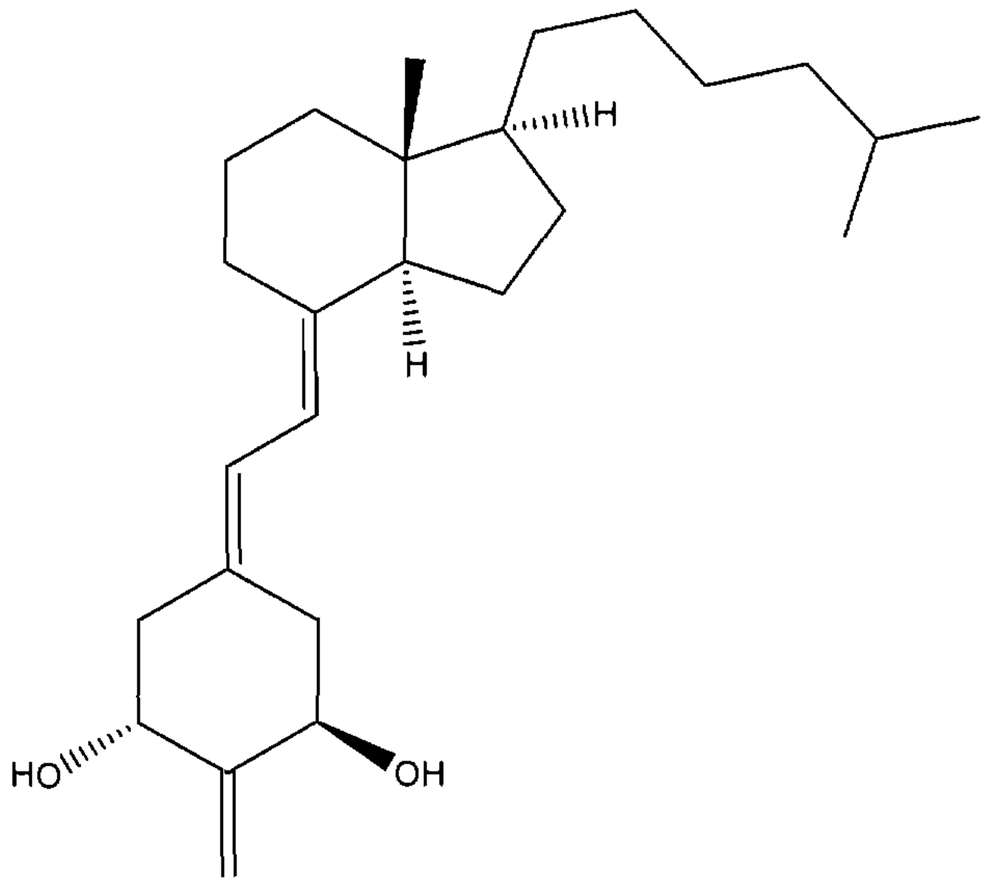
[0023] In certain embodiments, the present invention provides a method of treating a subject suffering from a biological condition, comprising administering an effective amount of the compound of formula I or II to the subject, wherein the biological condition is selected from metabolic bone diseases, such as osteomalacia and vitamin D resistant rickets; psoriasis; leukemia; colon cancer; breast cancer; prostate cancer; skin cancer; lung cancer; multiple sclerosis; lupus; diabetes mellitus; host versus graft reaction; rejection of organ transplants; an inflammatory disease selected from rheumatoid arthritis, asthma, or inflammatory bowel diseases selected from celiac disease, ulcerative colitis and Crohn's disease; a skin condition selected from wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration, or insufficient sebum secretion; renal osteodystrophy; osteopenia; or osteoporosis particularly senile osteoporosis, postmenopausal osteoporosis, steroid-induced

osteoporosis and low bone turnover osteoporosis. In an exemplary embodiment, the biological condition is renal osteodystrophy, vitamin D-resistant rickets, osteoporosis or psoriatic arthritis. In another exemplary embodiment, the biological condition is metabolic bone disease. In another exemplary embodiment, the biological condition is selected from leukemia, colon cancer, breast cancer, skin cancer, lung cancer, or prostate cancer. In yet another exemplary embodiment, the biological condition is selected from multiple sclerosis, lupus, diabetes mellitus, host versus graft reaction, or rejection of organ transplants. In still other exemplary embodiment, the biological condition is selected from rheumatoid arthritis, asthma, or inflammatory bowel diseases selected from celiac disease, ulcerative colitis and Crohn's disease. In yet other exemplary embodiment, the biological condition is selected from wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration, or insufficient sebum secretion.

[0024] Also preferably, in this embodiment, the effective amount of the compound is administered orally, parenterally, transdermally, nasally, rectally, sublingually or topically to the subject. Yet more preferably, the effective amount of the compound is administered intraperitoneally. In this embodiment, the compound is administered in a dosage of from 0.01 μg per day to 1 mg per day.

[0025] Another aspect of the invention provides the use of the compound of formula I in the preparation of a medicament for the treatment of a biological condition selected from metabolic bone diseases such as osteomalacia and vitamin D resistant rickets; psoriasis; leukemia; colon cancer; breast cancer; prostate cancer; skin cancer; lung cancer; multiple sclerosis; lupus; diabetes mellitus; host versus graft reaction; rejection of organ transplants; an inflammatory disease selected from rheumatoid arthritis, asthma, or inflammatory bowel diseases selected from celiac disease, ulcerative colitis and Crohn's disease; a skin condition selected from wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration, or insufficient sebum secretion; renal osteodystrophy; osteopenia, or osteoporosis, particularly senile osteoporosis, postmenopausal osteoporosis, steroid-induced osteoporosis and low bone turnover osteoporosis..

[0026] Yet another preferred embodiment of the present invention provides the compound having the formula II



II

[0027] The invention also teaches a pharmaceutical composition having an effective amount of the compound of formula II and a pharmaceutically acceptable carrier.

[0028] Another aspect of the invention provides the use of the compound of formula II in the preparation of a medicament for the treatment of a biological condition selected from metabolic bone diseases such as osteomalacia and vitamin D resistant rickets; psoriasis; leukemia; colon cancer; breast cancer; prostate cancer; skin cancer; lung cancer; multiple sclerosis; lupus; diabetes mellitus; host versus graft reaction; rejection of organ transplants; an inflammatory disease selected from rheumatoid arthritis, asthma, or inflammatory bowel diseases selected from celiac disease, ulcerative colitis and Crohn's disease; a skin condition selected from wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration, or insufficient sebum secretion; renal osteodystrophy; osteopenia; or osteoporosis, particularly senile osteoporosis, postmenopausal osteoporosis, steroid-induced osteoporosis and low bone turnover osteoporosis.

[0029] Further objects, features and advantages of the invention will be apparent from the following detailed description, drawings and appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] Figures 1-5 illustrate various biological activities of 2-methylene-1α-hydroxy-19,21-dinorvitamin D_3 (referred to as "SY-44" in the Figures) compared with those of the native hormone 1α, 25-dihydroxyvitamin D_3 (referred to as "1, $25(OH)_2D_3$" in the Figures).

[0031] Figure 1 is a graph comparing the relative activity of SY-44 and $1,25(OH)_2D_3$ to compete for binding with [^{3}H]-1,25-$(OH)_2$-D_3 to the full-length recombinant rat vitamin D receptor.

[0032] Figure 2 is a bar graph comparing the bone calcium mobilization activity of SY-44 with that of $1,25(OH)_2D_3$.

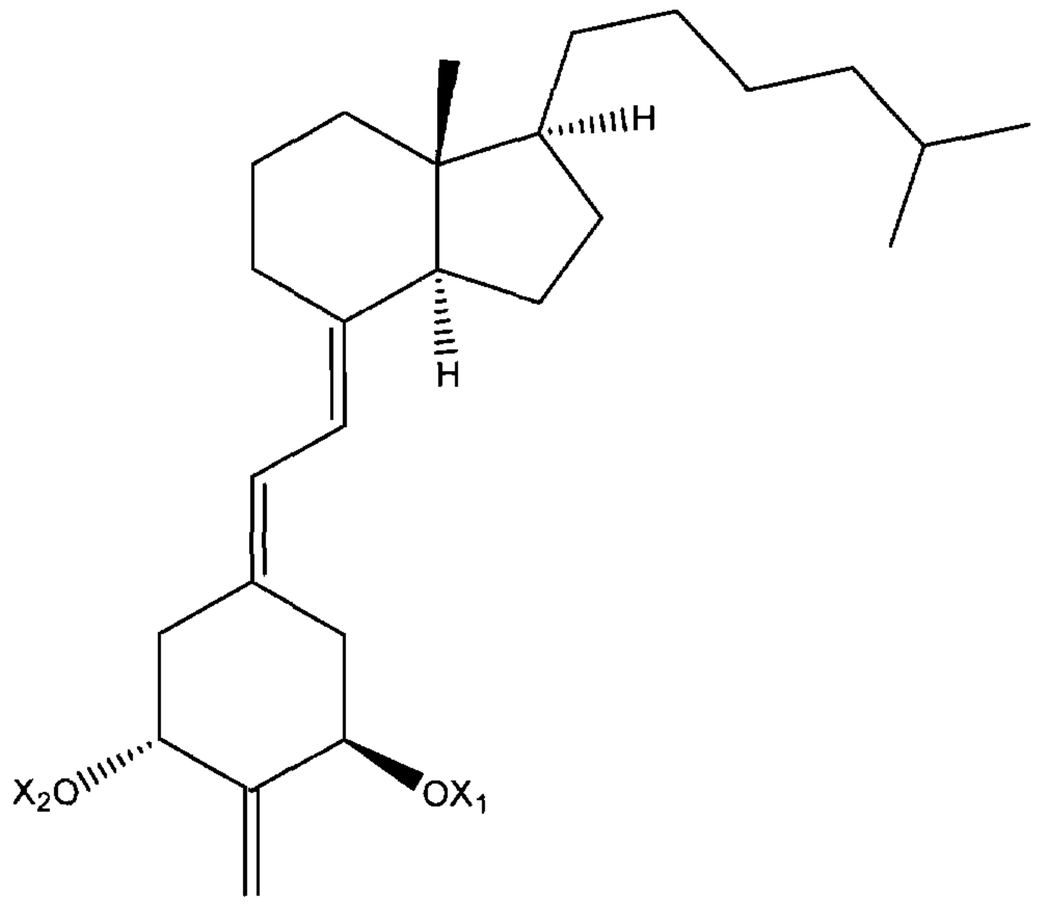
[0033] Figure 3 is a bar graph comparing the intestinal calcium transport activity of SY-44 with that of $1,25(OH)_2D_3$.

[0034] Figure 4 is a graph comparing the percent HL-60 cell differentiation as a function of the concentration of SY-44 with that of $1,25(OH)_2D_3$.

[0035] Figure 5 is a graph comparing the in vitro transcription activity of SY-44 with that of $1,25(OH)_2D_3$.

DETAILED DESCRIPTION OF THE INVENTION

[0036] Generally, the invention provides a compound having the formula I as shown below:



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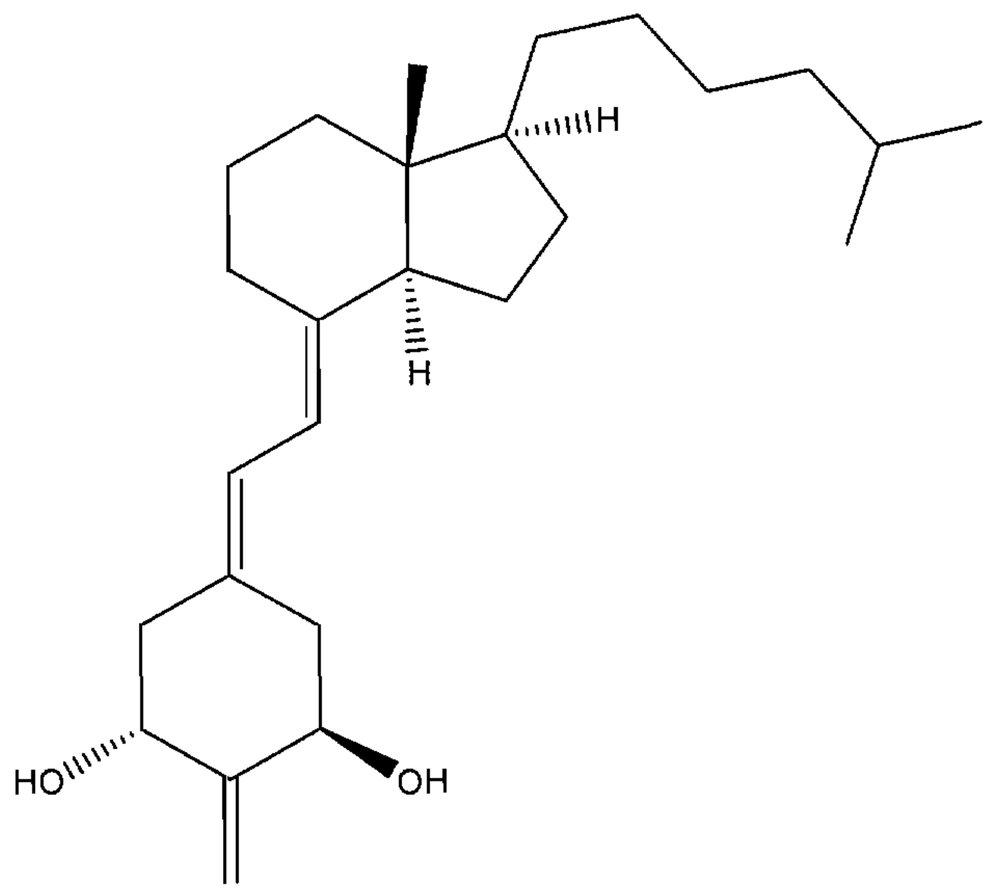
[0037] where X_1 and X_2 are the same or different and are independently selected from H or hydroxy-protecting groups. In some embodiments, X_1 and X_2 are

hydroxy protecting groups such as silyl ether groups, alkyl ether groups, alkoxyalyl ether group, acetal groups and ester groups. In some such embodiments, X_1 and X_2 are t-butyldimethylsilyl ether group (TBDMS), trimethylsilyl ether group (TMS), triethylsilyl ether group (TES), Triisopropylsilyl ether group (TIPS), t-butyldiphenylsilyl ether group (TBDPS), tetrahydropyran group (THP), methoxyethoxymethyl group (MEM), methoxymethyl group (MOM), benzyl ether group, t-butyl ether group, N-phthalimido acetal group (Nphth), isopropylidene, trimethoxybutane, 2,4-dimethylpentan-3-yloxycarbonyl group (Doc). Various other hydroxy protecting groups are known to one of ordinary skill in the art, for example see Jarowicki et al, J. Chem. Soc., Perkin Trans. 1, 1998, 4005-4037, which is incorporated herein by reference for all purposes.

[0038] Also as used herein, the term "hydroxy-protecting group" signifies any group commonly used for the temporary protection of the hydroxy (-OH) functional group, such as, but not limited to, alkoxycarbonyl, acyl, alkylsilyl or alkylarylsilyl groups (hereinafter referred to simply as "silyl" groups), and alkoxyalkyl groups. Alkoxycarbonyl protecting groups are alkyl-O-CO- groups 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. 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. An extensive list of protecting groups for the hydroxy functionality is found in Protective Groups in Organic Synthesis, Greene, T.W.; Wuts, P. G. M., John Wiley & Sons, New York, NY, (3rd Edition, 1999) which can be added or removed using the procedures set forth therein and which is hereby incorporated by reference in its entirety and for all purposes as if fully set forth herein.

[0039] A "protected hydroxy" group is a hydroxy group derivatized or protected by any of the above groups commonly used for the temporary or permanent protection of hydroxy functional groups, e.g., the silyl, alkoxyalkyl, acyl or alkoxycarbonyl groups, as previously defined.

[0040] In other embodiments, X_1 and X_2 are H such that the compound is 2-methylene-1α-hydroxy-19,21-dinorvitamin D_3 (SY-44) having the formula II as shown below:



II

[0041] The compound of formula II (SY-44) exhibits a desired, and highly advantageous, pattern of biological activity. This compound is characterized by high binding to vitamin D receptors, capability to stimulate transcription of reporter gene stably transfected in Ros17/2.8 (bone) cells and capability to induce differentiation of HL-60 cells. Further, it has high intestinal calcium transport activity, as compared to that of 1α,25-dihydroxyvitamin D_3, and has low ability to mobilize calcium from bone, as compared to 1,25-dihydroxyvitamin D_3. Thus, it is useful as a therapy for metabolic bone diseases. It may also be useful as a therapy for osteopenia as well as suppression of secondary hyperparathyroidism or renal osteodystrophy.

[0042] The compound of the invention is also 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 reaction, and rejection of organ transplants; and additionally for the treatment of inflammatory diseases, such as rheumatoid arthritis,

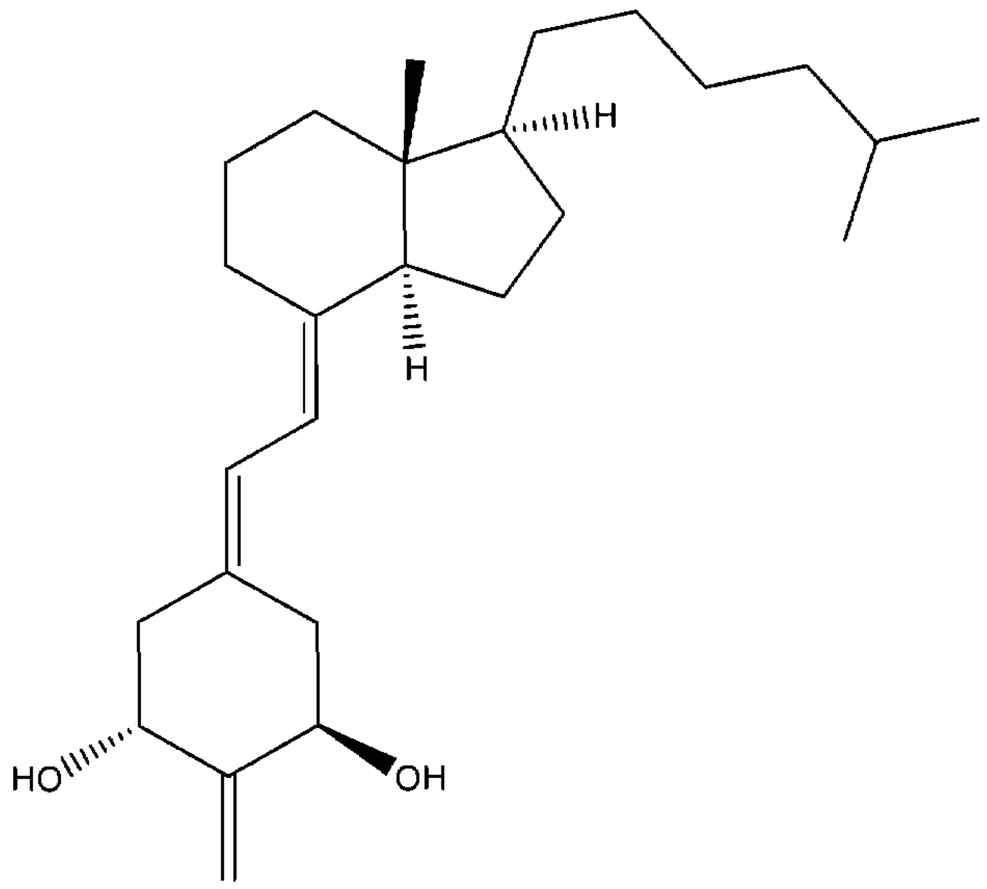
asthma, and inflammatory bowel diseases such as celiac disease, ulcerative colitis and Crohn's disease. Acne, alopecia and hypertension are other conditions which are treated with the compound of the invention.

[0043] The above compound is also characterized by relatively high cell differentiation activity. Thus, this compound also provides a therapeutic agent for the treatment of psoriasis, or as an anti-cancer agent, especially against leukemia, colon cancer, breast cancer, skin cancer, lung 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.

[0044] The compounds of the invention are used to prepare pharmaceutical formulations or medicaments that include a compound of the invention in combination with a pharmaceutically acceptable carrier. Such pharmaceutical formulations and medicaments are used to treat various biological disorders such as those described herein. Methods for treating such disorders typically include administering an effective amount of the compound or an appropriate amount of a pharmaceutical formulation or a medicament that includes the compound to a subject suffering from the biological disorder. In some embodiments, the subject is a mammal. In some such embodiments, the mammal is selected from a rodent, a primate, a bovine, an equine, a canine, a feline, an ursine, a porcine, a rabbit, or a guinea pig. In some such embodiments, the mammal is a rat or is a mouse. In some embodiments, the subject is a primate such as, in some embodiments, a human.

[0045] The compounds is present in a composition to treat the above-noted diseases and disorders in an amount from about 0.01μg/gm to about 1 mg/gm of the composition, preferably from about 0.1μg/gm to about 500μg/gm of the composition, and is administered topically, transdermally, orally, or parenterally in dosages of from about 0.01μg/day to about 1 mg/day, preferably from about 0.1μg/day to about 500μg/day.

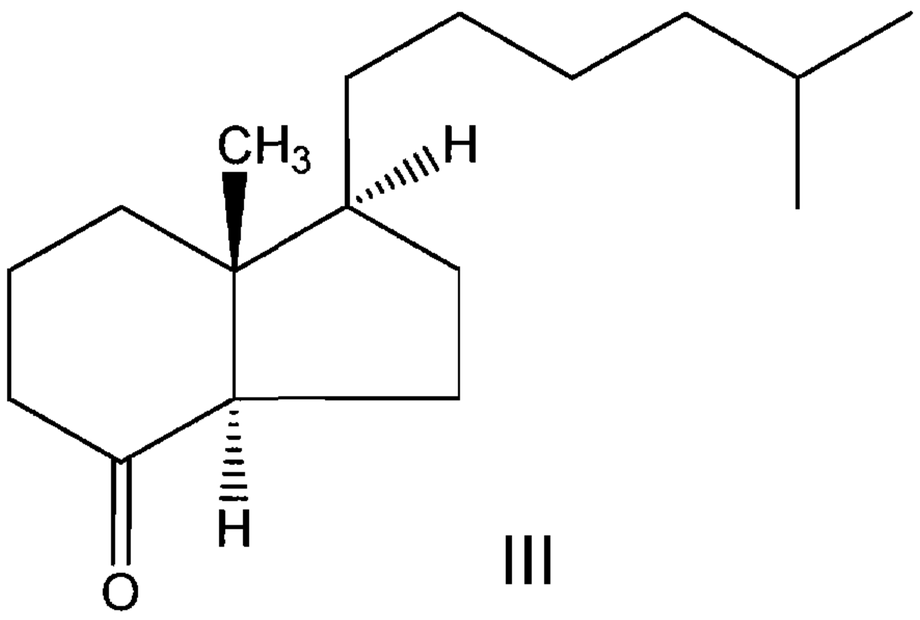
[0046] In one embodiment, the invention provides compounds II as shown below:



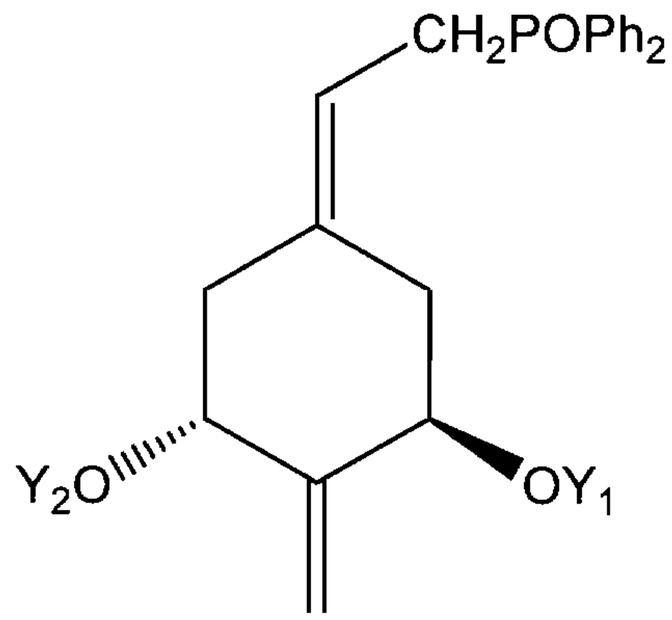
II

[0047] In a preferred embodiment, 2-methylene-1α-hydroxy-19,21-dinorvitamin D_3 (SY-44) was synthesized, and tested, and is useful in treating a variety of biological conditions as described herein.

[0048] Preparation of 2-methylene-1α-hydroxy-19,21-dinorvitamin D_3 (SY-44) can be accomplished by condensing an appropriate bicyclic Windaus-Grundmann type ketone (III) with the allylic phosphine oxide IV followed by deprotection (removal of the Y_1 and Y_2 groups). Other compounds of the present invention are similarly synthesized.



III



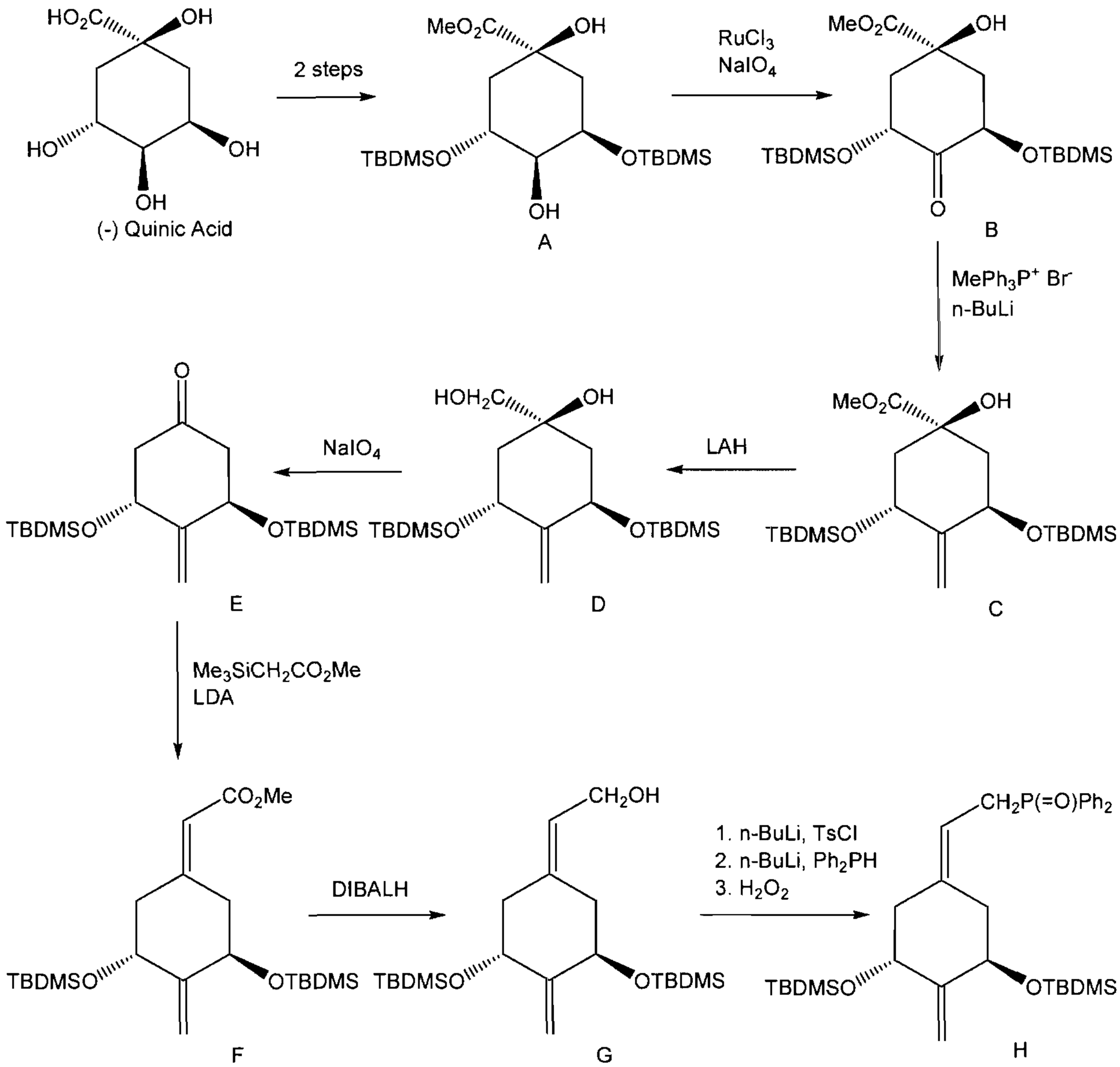
IV

[0049] In phosphine oxide IV, Y_1 and Y_2 are preferably hydroxy-protecting groups such as silyl protecting groups. In a preferred embodiment, the triethylsilyl group (TES) and t-butyldimethylsilyl (TBDMS) group are examples of a particularly useful hydroxy-protecting groups. The process described above represents an

application of the convergent synthesis concept, which has been applied effectively to the preparation of numerous vitamin D compounds (see 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. Patent No. 5,086,191; DeLuca et al., U.S. Patent No. 5,536,713; and DeLuca et al., U.S. Patent No. 5,843,928 all of which are hereby incorporated by reference in their entirety and for all purposes as if fully set forth herein).

[0050] Phosphine oxide IV is a convenient reagent that can be used to prepare a large number of 19-nor vitamin D compounds and is prepared according to the procedures described by Sicinski et al., J. Med. Chem., 41, 4662 (1998), DeLuca et al., U.S. Patent No. 5,843,928; Perlman et al., Tetrahedron Lett. 32, 7663 (1991); and DeLuca et al., U.S. Patent No. 5,086,191. Scheme I shows the general procedure for synthesizing phosphine oxide IV as outlined in U.S. Patent No. 5,843,928 which is hereby incorporated by reference in its entirety as if fully set forth herein. Modification of the method shown in Scheme I is used to produce a large number of vitamin D analogs as will be apparent to those skilled in the art. For example, a wide variety of phosphonium compounds is used in place of the $MePh_3P^+ Br^-$ used to convert ketone B to alkene C. Examples of such compounds include $EtPh_3P^+ Br^-$, $PrPh_3P^+ Br^-$, and compounds generally prepared by reaction of triphenylphosphine with an alkyl halide, an alkenyl halide, a protected-hydroxyalkyl halide, and a protected hydroxyalkenyl halide. Alkenes prepared using this procedure may then be carried through to prepare a phosphine oxide in an analogous manner to that used to prepare phosphine oxide H in Scheme I. Alternatively, an alkene analogous to compound C of Scheme I is reduced with $(Ph_3P)_3RhCl$ and H_2 to provide other vitamin D analogs. See U.S. Patent No. 5,945,410 and Sicinski, R. R. et al., J. Med. Chem., 41, 4662-4674 (1998) both of which are hereby incorporated by reference in their entireties and for all purposes. Therefore, the procedure for forming the phosphine oxide shown in Scheme I is used to prepare a wide variety of vitamin D analogs in addition to the compound of the present invention.

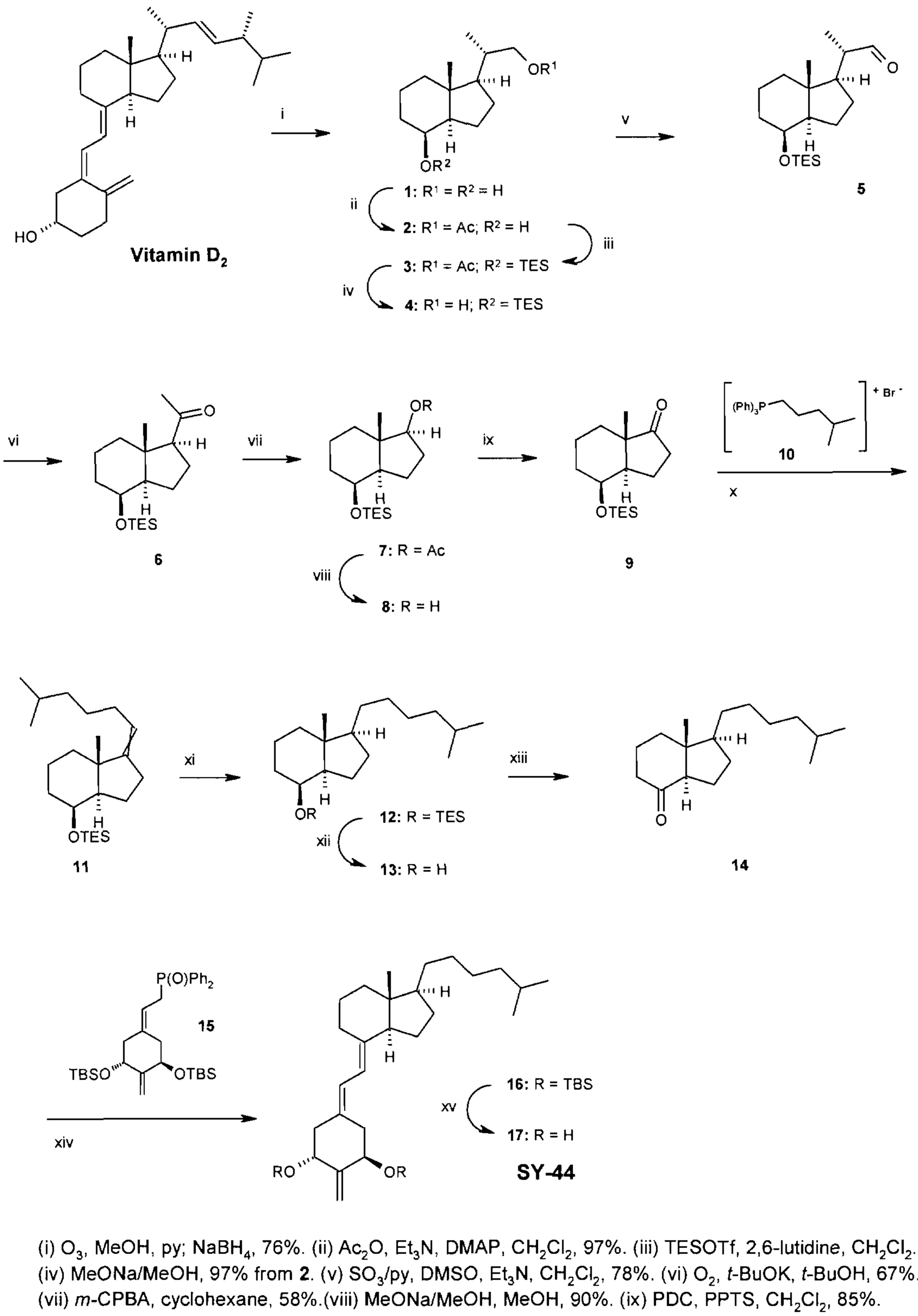
[0051] Scheme I



[0052] Hydraindanones of structure III can prepared by known methods or adapted methods as will be readily apparent to one of skill in the art and described herein. Specific examples of some important bicyclic ketones used to synthesize vitamin D analogs are those described in Mincione et al., Synth. Commun 19, 723, (1989); and Peterson et al., J. Org. Chem. 51, 1948, (1986).

[0053] In one preferred embodiment, ketone III (14) and compound of Formula II (SY-44) (17) were prepared by the following Scheme II, as shown below:

[0054] Scheme II



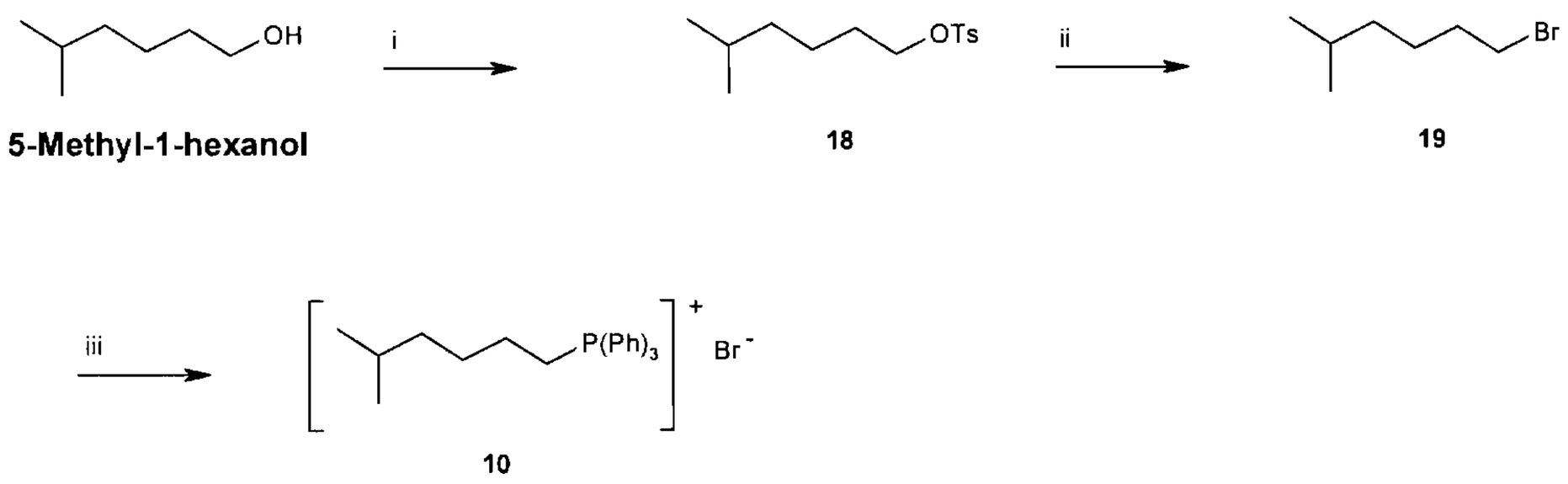
(i) O_3, MeOH, py; $NaBH_4$, 76%. (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 97%. (iii) TESOTf, 2,6-lutidine, CH_2Cl_2. (iv) MeONa/MeOH, 97% from **2**. (v) SO_3/py, DMSO, Et_3N, CH_2Cl_2, 78%. (vi) O_2, *t*-BuOK, *t*-BuOH, 67%. (vii) *m*-CPBA, cyclohexane, 58%.(viii) MeONa/MeOH, MeOH, 90%. (ix) PDC, PPTS, CH_2Cl_2, 85%. (x) **10**, *t*-BuOK, THF, 63%. (xi) 5% Pd/C, EtOAc, 93%. (xii) CSA, *n*-BuOH, 98%. (xiii) PDC, PPTS, CH_2Cl_2, 80%. (xiv) **15**, PhLi, THF, 90%. (xv) CSA, *n*-BuOH, 11% from **14**.

[0055] An overall process for synthesizing 2-alkylidene-19-nor-vitamin D compounds is illustrated and described in U.S. Patent No. 5,843,928, U.S. Patent No. 6,627,622, U.S. Patent No. 6,579,861, U.S. Patent No. 5,086,191, U.S. Patent No.

5,585,369, and U.S. Patent No. 6,537,981, which are hereby incorporated by reference in its entirety and for all purposes as if fully set forth herein.

[0056] Compounds of formula I and formula II can be prepared using the methods shown in Schemes I, and II. For the compound of formula II, the starting material, compound 10, was prepared using known procedures, as shown below in Scheme III. See also, Andrzej R. Daniewski and Wen Liu, J. Org. Chem. 66, 626-628 (2001), which is hereby incorporated by reference in its entirety and for all purposes as if fully set forth herein.

[0057] Scheme III:



(i) TsCl, Et_3N, DMAP, CH_2Cl_2, 96%. (ii) LiBr, DMF, 55%. (iii) Ph_3P, PhMe, 81%.

[0058] Following examples illustrate synthesis and biological activity of the compounds provided in the present invention. These Examples are for illustration purposes only and should not be deemed to limit the scope of the invention.

[0059] Example I: SY-44 SYNTHESIS

[0060] Des-A,B-23,24-dinorcholane-8β,22-diol (1).

[0061] A solution of vitamin D_2 (5 g; 12.7 mmol) in methanol (400 mL) and pyridine (5 mL) was cooled to -78 °C while purging with argon. The argon stream was stopped and stream of ozone was passed until blue color appeared. The solution was purged with oxygen until blue color disappeared and treated with $NaBH_4$ (1.2 g; 32 mmol). After 20 min. the second portion of $NaBH_4$ (1.2 g; 32 mmol) was added and reaction was allowed to warm to room temperature. The third portion of $NaBH_4$ (1.2 g; 32 mmol) was added and reaction mixture was stirred at room temperature overnight. The reaction was quenched with 70 mL of water and concentrated under vacuum. The residue was extracted with methylene chloride (3 x 100 mL). The organic phase was washed with 1M aqueous solution of HCl (2 x 100 mL), saturated

aqueous solution of $NaHCO_3$ (100 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography (25% ethyl acetate/hexane) to yield 2.05 g (9.69 mmol; 76% yield) of diol 1 as white crystals. $[\alpha]_D$ = + 56.0 (c 0.95, $CHCl_3$); m.p. 110 ÷ 111 °C; ^{1}H 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 Hz, J = 6.8 Hz), 3.64 (1H, dd, J = 10.5 Hz, J = 3.2 Hz), 4.09 (1H, d, J = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 16.6, 17.4, 22.6, 26.6, 33.5, 38.2, 40.2, 41.3, 52.3, 52.9, 67.8, 69.2; MS (EI) m/z 212 (M^+, 2), 194 (17), 179 (18), 163 (10), 135 (19), 125 (34), 111 (100); exact mass calculated for $C_{13}H_{22}O$ ($[M - H_2O]^+$) 194.1671, found 194.1665.

[0062] Des-A,B-22-(acetoxy)-23,24-dinorcholane-8β-ol (2).

[0063] To a stirred solution of 1 (3.50 g, 16.5 mmol) and DMAP (100 mg) in triethylamine (3.00 mL, 1.67 g, 21.6 mmol) and methylene chloride (300 mL) acetic anhydride (1.54 mL, 2.18 g, 16.5 mmol) was added dropwise at 0 °C. The reaction mixture was kept at 4 °C overnight. Solvents were removed under reduced pressure and the residue was redissolved in methylene chloride (200 mL), washed with 10% aqueous solution of HCl (50 mL), saturated aqueous solution of $NaHCO_3$ (50 mL) and water (50 mL). Organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 4.06 g (16.0 mmol; 97% yield) of 2 as white crystals. $[\alpha]_D$ = +33.7 (c 0.90), $CHCl_3$); m.p. 78 ÷ 80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) □δ0.96 (3H, s), 1.00 (3H, d, J = 6.6 Hz), 2.05 (3H, s), 3.77 (1H, dd, J = 10.6 Hz, J = 7.7 Hz), 4.06 (1H, dd, J = 10.6 Hz, J = 3.3 Hz), 4.11 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 17.0, 17.4, 21.0, 22.5, 26.6, 33.5, 35.3, 40.2, 41.9, 52.3, 53.2, 69.1, 69.4, 171.4; MS (EI) m/z 254 (M^+, 2), 236 (5), 205 (2), 194 (12), 176 (22), 161 (14), 135 (16), 125 (34), 111 (100); exact mass (ESI) calculated for $C_{15}H_{23}O_3Na$ ($[M + Na]^+$) 277.1780, found 277.1791.

[0064] Des-A,B-22-(acetoxy)-8β-[(triethylsilyl)oxy]-23,24-dinorcholane (3).

[0065] To a stirred solution of 2 (4.00 g, 16.6 mmol) in methylene chloride (40 mL) and 2,6-lutidine (2.67 mL, 2.46 g, 23.0 mmol) triethylsilyl trifluoromethanesulfonate (4.52 mL, 5.28 g, 20.0 mmol) was added dropwise under argon at -50 °C. After 30 min, wet methylene chloride (5 mL) and water (80 mL) were added. The reaction mixture was extracted with methylene chloride (3 x 120 mL) and organic phase was washed with saturated aqueous solution of $CuSO_4$ (50 mL), dried

over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude 3 as oil. $[\alpha]_D$ = +42.2 (c 1.25, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.55 (6H, q, J = 7.9 Hz), 0.93 (3H, s), 0.95 (9H, t, J = 8.0 Hz), 0.98 (3H, d, J = 6.6 Hz), 2.05 (3H, s), 3.77 (1H, dd, J = 10.6 Hz, J = 7.5 Hz), 4.04-4.07 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.9, 6.9, 13.5, 17.1, 17.6, 21.0, 23.0, 26.8, 34.6, 35.4, 40.6, 42.2, 52.8, 53.4, 69.2, 69.6, 171.4; MS (EI) m/z 368 (M^+, 4), 339 (30), 325 (15), 177 (89), 145 (100); exact mass calculated for $C_{21}H_{40}O_3Si$ 368.2747, found 368.2748.

[0066] Des-A,B-8β-[(triethylsilyl)oxy]-23,24-dinorcholane-22-ol (4).

[0067] To a stirred solution of crude 3 in methanol (100 mL) 10% solution of sodium methanolate in methanol (20 mL) was added dropwise. After 2 h saturated aqueous solution of NH_4Cl (20 mL) and water (60 mL) were added and the mixture was extracted with CH_2Cl_2 (5 x 100 mL). Organic phase was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the residue was purified on silica gel column (10 ÷ 20% ethyl acetate/hexane) to give 5.25 g (16.1 mmol; 97 % yield from 2) of 4. $[\alpha]_D$ = +40.3 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (6H, q, J = 7.9 Hz), 0.93-0.97 (12H, m), 1.02 (3H, d, J = 6.6 Hz), 3.37 (1H, dd, J = 10.4 Hz, J = 6.8 Hz), 3.63 (1H, dd, J = 10 Hz, J = 3.0 Hz), 4.04 (1H, d, J = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9, 6.9, 13.6, 16.6, 17.6, 23.0, 26.8, 34.6, 38.3, 40.6, 42.1, 52.8, 53.1, 68.0, 69.3; MS (EI) m/z 326 (M^+, 10), 311 (2), 297 (93), 283 (36), 225 (16), 193 (21), 177 (100); exact mass calculated for $C_{19}H_{38}O_2Si$ 326.2641, found 326.2639.

[0068] Des-A,B-8β-[(triethylsilyl)oxy]-23,24-dinorcholane-22-al (5).

[0069] Sulfur trioxide pyridine complex (7.42 g, 46.5 mmol) was added to the stirred solution of 4 (2.32 g, 7.02 mmol) in triethylamine (5.46 mL, 3.94 g, 39.0 mmol), anhydrous DMSO (8.0 mL) and anhydrous CH_2Cl_2 (40 mL) at 0 °C under argon. After 20 min. methylene chloride (150 mL) was added and reaction mixture was washed with saturated aqueous solution of $CuSO_4$ (40 mL) and water (40 mL). Organic phase was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and residue was purified on silica gel (0.5 ÷ 2% ethyl acetate/hexane) to give 1.80 mg (5.56 mmol; 78% yield) of 5. $[\alpha]_D$ = +42.6 (c 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.57 (6H, q, J = 7.9 Hz), 0.94 - 0.98 (12H, m), 1.10 (3H, d, J = 6.8 Hz), 2.35 (1H, m), 4.07 (1H, d, J = 2.5 Hz), 9.58 (1H, d, J = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0, 6.9, 13.4, 13.9, 17.6, 23.3, 26.2, 34.6, 40.6, 42.7, 49.1, 51.8, 52.5,

53.2, 69.1, 205.3; MS (EI) m/z 324 (M^+, 4), 311 (12), 295 (100); exact mass calculated for $C_{17}H_{31}O_2Si$ ($[M - C_2H_5]^+$) 295.2093, found 295.2086.

[0070] Des-A,B-8β-[(triethylsilyl)oxy]-pregnane-20-one (6).

[0071] Through a solution of potassium tert-butanolate (3.7 g; 33 mmol) in tert-butanol (90 mL) oxygen was passed for 15 min. Then a solution of 5 in tert-butanol (45 mL) was added dropwise while purging with oxygen. Saturated aqueous solution of NH_4Cl (80 mL) and water (50 mL) were added and the reaction products were extracted with Et_2O (5 x 150 mL). Organic phase was dried over anhydrous $MgSO_4$, concentrated under reduced pressure and the residue was purified by column chromatography (3 ÷ 6% ethyl acetate/hexane) to give 1.14 g (3.68 mmol; 67 % yield) of 6. $[\alpha]_D$ = +107.1 (c 0.80, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (6H, q, J = 7.9 Hz), 0.85 (3H, s), 0.94 (9H, t, J = 7.9 Hz), 2.09 (3H, s), 2.47 (1H, t, J = 9.0 Hz), 4.07 (1H, d, J = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9, 6.9, 15.3, 17.6, 21.8, 23.1, 31.5, 34.4, 39.9, 43.7, 53.3, 64.5, 68.9, 209.5; MS (EI) m/z 310 (M^+, 50), 281 (84), 211 (73), 173 (94), 87 (100); exact mass calculated for $C_{18}H_{34}O_2Si$ 310.2328, found 310.2332.

[0072] Des-A,B-8β-[(triethylsilyl)oxy]-testosterone acetate (7).

[0073] To a stirred solution of 6 in cyclohexane (50 mL) meta-chloroperbenzoic acid (77% max.; 1.5 g) was added at 0 °C. Then the reaction mixture was warmed up to room temperature and stirred for 5 days. Next portions of meta-chloroperbenzoic acid (1.0 g, 0.8 g and 0.6 g) were added after 1 day, 2 days and 4 days, respectively. The suspension was filtered off and the filtrate was washed with saturated aqueous solution of $NaHCO_3$ (20 mL). Organic phase was dried over anhydrous $MgSO_4$, concentrated under reduced pressure and the residue was purified by column chromatography (1 ÷ 3% ethyl acetate/hexane) to give 0.89 g (2.73 mmol; 58% yield) of 7. $[\alpha]_D$ = +18.7 (c 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.56 (6H, q, J = 7.9 Hz), 0.95 (9H, t, J = 7.9 Hz), 1.11 (3H, s), 2.03 (3H, s), 4.05 (1H, d, J = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9, 6.9, 13.6, 17.2, 21.2, 22.2, 26.7, 34.5, 37.8, 42.0, 47.8, 69.0, 82.9, 171.3; MS (EI) m/z 326 (M^+, 3), 297 (18), 283 (8), 145 (70), 135 (100); exact mass calculated for $C_{18}H_{34}O_3Si$ 326.2277, found 326.2269.

[0074] Des-A,B-8β-[(triethylsilyl)oxy]-testosterone (8).

[0075] 7 (972 mg; 2.98 mmol) was dissolved in methanol (25 mL) and treated with 10% solution of sodium metoxide in methanol (5 mL) for 2.5 h. Saturated aqueous solution of NH_4Cl (10 mL) and water (15 mL) were added and product was extracted wit methylene dichloride (5 x 75 mL). Organic phase was dried over anhydrous $MgSO_4$, concentrated under reduced pressure and the residue was purified by column chromatography (5 ÷ 15% ethyl acetate/hexane) to give 764 mg (2.69 mmol; 90% yield) of 8. $[\alpha]_D$ = +39.6 (c 0.95, $CHCl_3$); m.p. 95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.56 (6H, q, J = 7.9 Hz), 0.95 (9H, t, J = 7.9 Hz), 0.96 (3H, s), 3.56 (1H, m), 4.02 (1H, d, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0, 6.9, 12.4, 17.3, 22.2, 29.9, 34.6, 37.5, 42.2, 48.1, 69.1, 82.2; MS (EI) m/z 284 (M^+, 9), 255 (100), 237 (40), 135 (42), 103 (66); exact mass calculated for $C_{14}H_{27}O_2Si$ ($[M - C_2H_5]^+$) 255.1780, found 255.1770.

[0076] Des-A,B-8β-[(triethylsilyl)oxy]-androstane-17-one (9).

[0077] To a stirred solution of 8 (760 mg; 2.68 mmol) and PPTS (30 mg; 0.12 mmol) in methylene dichloride (90 mL) PDC (2.25 g; 5.98 mmol) was added at 0 °C. Cooling bath was removed and the reaction mixture was stirred for 9 h. Then solvent was removed under reduced pressure and the residue was purified by column chromatography (5 ÷ 10% ethyl acetate/hexane) to give 642 mg (2.28 mmol; 85% yield) of 9. $[\alpha]_D$ = +82.9 (c 0.90, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.60 (6H, q, J = 7.9 Hz), 0.97 (9H, t, J = 7.9 Hz), 1.11 (3H, s), 2.43-2.47 (1H, m), 4.19 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.9, 6.9, 16.3, 17.0, 21.3, 32.3, 34.5, 35.3, 47.5, 48.8, 69.9, 221.2; MS (EI) m/z 282 (M^+, 10), 252 (100), 133 (17), 103 (39); exact mass calculated for $C_{16}H_{30}O_2Si$ 282.2015, found 282.2013.

[0078] (17Z)-Des-A,B-8β-[(triethylsilyl)oxy]-21-norcholest-17-ene (11).

[0079] To a stirred suspension of 10 (4.10 g; 9.35 mmol) in THF (13.5 mL) 1M solution of potassium tert-butoxide in THF (8.90 mL; 8.90 mmol) was added dropwise at -10 °C. The suspension was stirred and warmed up to 0 °C over 30 min. Then a solution of 9 (716 mg; 2.53 mmol) in THF (3.0 mL) was added via cannula and the resulting mixture was stirred at 45 °C for 4 days. Then saturated aqueous solution of NH_4Cl (20 mL) and water (30 mL) were added and the mixture was extracted with diethyl ether (3 x 100 mL). Organic phase was dried over anhydrous $MgSO_4$, concentrated under reduced pressure and the residue was purified by column

chromatography (hexane ÷ 5% ethyl acetate/hexane) to give 572 mg (1.60 mmol; 63% yield) of 11 (Z/E ratio 5:1). $[\alpha]_D$ = +4.1 (c 0.95, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 0.56 (6H, q, J = 7.9 Hz), 0.86 (6H, d, J = 6.7 Hz), 0.95 (9H, t, J = 7.9 Hz), 1.10 (3H, s), 4.11 (1H, s), 4.94 (0.83H, t, J = 7.3 Hz), 5.36 (0.17H, t, J = 4.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0, 7.0, 18.0, 19.9, 22.6, 22.7, 23.8, 27.5, 27.6, 27.7, 28.0, 28.7, 30.6, 34.6, 38.3, 38.7, 38.9, 44.2, 52.8, 69.7, 119.3, 130.0, 149.9; MS (EI) m/z 364 (M^+, 6), 335, (23), 321 (10), 279 (37), 232 (54), 205 (43), 171 (51), 147 (100); exact mass calculated for $C_{23}H_{44}OSi$ 364.3161, found 364.3175.

[0080] Des-A,B-8β-[(triethylsilyl)oxy]-21-norcholestane (12).

[0081] A stirred mixture of 11 (552 mg; 1.52 mmol) and 5% Pd/C (160 mg) in ethyl acetate (20 mL) was treated with hydrogen overnight. Then the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified on silica gel Sep-Pack cartridge (hexane) to give 515 mg (1.41 mmol; 93% yield) of 12. $[\alpha]_D$ = +41.8 (c 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (6H, q, J = 7.9 Hz), 0.81 (3H, s), 0.86 (6H, d, J = 6.6 Hz), 0.95 (9H, t, J = 7.9 Hz), 4.05 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0, 7.0, 14.1, 17.6, 22.7, 22.7, 23.4, 27.8, 28.0, 29.1, 30.0, 35.0, 38.9, 39.1, 41.5, 51.7, 52.8, 69.2; MS (EI) m/z 337 (100), 323 (59), 271 (67), 233 (77); exact mass calculated for $C_{21}H_{41}OSi$ ($[M - C_2H_5]^+$) 337.2927, found 337.2911.

[0082] Des-A,B-21-norcholestane-8β-ol (13).

[0083] To a stirred solution of 12 (485 mg; 1.33 mmol) in n-butanol (25 mL) (1S)-(+)-10-camphorsulfonic acid (330 mg; 1.42 mmol). After 1 day solvent was removed under reduced pressure and the residue was purified by column chromatography (5 ÷ 15% ethyl acetate/hexane) to give 328 mg (1.30 mmol; 98% yield) of 13. $[\alpha]_D$ = +34.1 (c 1.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (3H, s), 0.86 (6H, d, J = 6.6 Hz), 4.10 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 17.4, 22.7, 22.7, 22.9, 27.6, 28.0, 28.0, 29.0, 29.9, 33.9, 38.5, 39.1, 41.3, 51.5, 52.3, 69.3; MS (EI) m/z 252 (M^+, 43), 237 (44), 219 (22), 209 (19), 125 (49), 111 (100); exact mass calculated for $C_{17}H_{32}O$ 252.2453, found 252.2446.

[0084] Des-A,B-21-norcholestane-8-one (14).

[0085] To a stirred solution of 13 (10 mg; 35 μmol) and PPTS (2 crystals) in methylene dichloride (3 mL) PDC (55 mg; 145 μmol) was added at 0°C. Cooling bath

was removed and the mixture was stirred for 3 h. Then solvent was removed under reduced pressure and the residue was purified on silica gel Sep-Pack cartridge (2 - 5% ethyl acetate/hexane) to give 8 mg (32 μmol; 80% yield) of 14. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (3H, s), 0.87 (6H, d, J = 6.6 Hz), 2.42 (1H, dd, J = 11.2 Hz, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 19.6, 22.6, 22.7, 24.0, 27.8, 27.8, 28.0, 28.9, 30.2, 37.2, 39.1, 41.1, 49.7, 51.6, 61.5, 211.9; MS (EI) m/z 250 (M^+, 94), 235 (94), 207 (92), 159 (84), 152 (100); exact mass calculated for $C_{17}H_{30}O$ 250.2297, found 250.2292.

[0086] 2-methylene-1α-hydroxy-19,21-dinorvitamin D_3 (SY-44) (17).

[0087] To a stirred solution of 15 (20 mg; 35 μmol) in THF (300 μ) 10 □L of 1.2 M solution of PhLi in cyclohexane/ether (7/3) was added at -20 °C until the solution became deep orange. Then 27 μL (32 μmol) of the solution of PhLi was added drop wise. After 20 min. the reaction mixture was cooled down to -78 °C and the solution of 14 (7 mg; 28 μmol) in THF (150 μL) was added via cannula. After 3 h cooling bath was removed and the reaction mixture was stirred at 4 °C overnight. Then ethyl acetate (10 mL) was added and organic phase was washed with brine (2 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified on silica gel Sep-Pack cartridge (hexane ÷ 2% ethyl acetate/hexane) to give 5 mg (8 μmol) of crude 16.

[0088] To a stirred solution of 16 (5 mg; 8 μmol) in n-butanol (700 μL) (1S)-(+)-10-camphorsulfonic acid (5 mg; 22 μmol) was added at 0 °C. Then cooling bath was removed and the reaction mixture was stirred for 1 week. A few drops of saturated aqueous solution of $NaHCO_3$ and water (2 mL) were added and the mixture was extracted with ethyl acetate (3 x 5 mL). Combined organic phases were dried over anhydrous $MgSO_4$, concentrated under reduced pressure and the residue was purified on silica gel Sep-Pack cartridge (20 - 30% ethyl acetate/hexane) to give 1 mg (3 μmol; 11% yield from 14) of 17. UV (EtOH) λ_{max} = 243, 251, 261 nm; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.45 (3H, s), 0.87 (6H, d, J = 6.6 Hz), 2.28 - 2.36 (2H, m), 2.58 (1H, m), 2.82 – 2.87 (2H, m), 4.45 – 4.51 (2H, m), 5.09 (1H, s), 5.11 (1H, s), 5.88 (1H, d, J = 11.3 Hz), 6.36 (1H, d, J = 11.3 Hz).

[0089] Toluene-4-sulfonic acid 5-methyl-hexyl ester (18).

[0090] To a stirred solution of 5-methyl-1-hexanol (3.65 mL; 3.00 g; 25.7 mmol), triethylamine (5.00 mL; 3.64 g; 36.0 mmol) and DMAP (200 mg; 1.64 mmol) in methylene dichloride (120 mL) tosyl chloride (5.72 g; 30.0 mmol) was added at 0 °C. Then cooling bath was removed and the mixture was allowed to stand overnight. Saturated aqueous solution of NH_4Cl (30 mL) and water (30 mL) were added and the mixture was extracted with methylene dichloride (3 x 150 mL). Combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (5 - 10% ethyl acetate/hexane) to give 6.66 g (24.7 mmol; 96% yield) of 22. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (6H, d, J = 6.6 Hz), 1.09 (2H, m), 1.28 (2H, m), 1.47 (1H, m), 1.62 (2H, m), 2.45 (3H, s), 4.02 (2H, t, J = 6.5 Hz), 7.34 (2H, d, J = 8.1 Hz), 7.79 (2H, d, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 22.5, 23.2, 27.8, 29.1, 38.2, 70.2, 127.9, 129.8, 133.2, 144.6; MS (EI) m/z 255 (2), 226 (2), 205 (3), 190 (5), 173 (67), 155 (57), 98 (59), 91 (100); exact mass calculated for $C_{13}H_{19}O_3S$ ($[M - CH_3]^+$) 255.1055, found 255.1062.

[0091] 1-Bromo-5-methyl-hexane (19).

[0092] To a stirred solution of LiBr (6.26 g; 72.0 mmol) in DMF (40 mL) a solution of 18 (6.60 g; 24.4 mmol) in DMF (6 mL) was added. The resulting mixture was stirred at 45 °C for 3 h. Then water (100 mL) was added and the reaction product was extracted with diethyl ether (5 x 250 mL). Removal of solvent yielded in 2.40 g (13.4 mmol; 55%) of 19. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (6H, d, J = 6.6 Hz), 1.19 (2H, m), 1.42 (2H, m), 1.54 (1H, m), 1.83 (2H, m), 3.41 (2H, t, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 26.0, 27.8, 33.1, 34.1, 38.0; MS (EI) m/z 179 (M^+, 80), 163 (14), 155 (9), 137 (100); exact mass calculated for $C_6H_{12}Br$ ($[M - CH_3]^+$) 163.0122, found 163.0121.

[0100] (5-methylhexyl)triphenylphosphonium bromide (10).

[0101] A solution of 19 (2.30 g; 12.8 mmol) and triphenylphosphine (3.70 g; 14.1 mmol) was refluxed in toluene (12 mL) for 20 h. Then solvent was removed and the resulting crystal was washed with toluene (3 mL) and diethyl ether (3 mL) to give 4.57 g (10.4 mmol; 81% yield) of 10. m.p. 227 - 228 °C; ^{1}H NMR (500 MHz, CD_3CN) δ 0.82 (6H, d, J = 6.6 Hz), 1.16 (2H, m), 1.42 - 1.52 (3H, m), 1.59 (2H, m), 3.30 (2H, m), 7.72 (12H, m), 7.85 (3H, m); ^{13}C NMR (125 MHz, CD_3CN) δ 22.7, 23.2, 28.4, 28.8, 28.9, 38.6, 131.2, 131.3, 134.7, 134.7, 136.0.

[0102] Example II: BIOLOGICAL ACTIVITY

[0103] (A) Vitamin D Receptor Binding

[0104] Test Material

[0105] Protein Source

[0106] 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.

[0107] Study Drugs

[0108] 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; Analogs: molar extinction coefficient = 42,000 and λ_{max} = 252 nm). Radiolabeled ligand (^{3}H-$1,25(OH)_2D_3$, ~159 Ci/mmole) was added in ethanol at a final concentration of 1 nM.

[0109] Assay Conditions

[0110] 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.

[0111] (B) HL-60 Differentiation

[0112] Test Material

[0113] Study Drugs

[0114] 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.

[0115] Cells

[0116] 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.

[0117] Assay Conditions

[0118] HL60 cells were plated at 1.2 x 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).

[0119] (C) In vitro Transcription Assay

[0120] Transcription activity was measured in ROS 17/2.8 (bone) cells that were stably transfected with a 24-hydyroxylase (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)

[0121] (D) Intestinal Calcium Transport and Bone Calcium Mobilization

[0122] Male, weanling Sprague-Dawley rats were placed on Diet 11 (Suda et al., Purified Rodent Diet-Diet 11, containing 0.47% and 0.3% phosphorus and fat soluble vitamins A, D, E and K are provided ad libitum) (0.47% Ca) diet +AEK for one week followed by Diet 11 (0.02% Ca) +AEK for 3 weeks. The rats were then switched to a diet containing 0.47% Ca for one week followed by two weeks on a 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 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. The everted gut sac assay was carried out as previously described by Martin and Deluca, Am. J. Physiol. 216, 1351 (1969); (DeLuca et al., U.S. Patent 4,188,345), which are incorporated by reference as if fully set forth herein.

[0123] Dose Preparation

[0124] Control Material

[0125] A. Negative Control Material

[0126] The negative control material is prepared by volumetrically measuring ethanol (< 5%) and propylene glycol, mixing, and then placing in storage at 2 to 8˚C.

[0127] B. Positive Control Material

[0128] $1,25(OH)_2D_3$ is prepared by determining the concentration of an ethanol stock solution using UV spectrophotometry (extinction coefficient = 18,200; λ_{max} = 265 nm). The required amount of $1,25(OH)_2D_3$ is volumetrically measured into propylene glycol so that there was less than 5% ethanol in the final solution. The solution is mixed and then stored at 2 to 8˚C.

[0129] Test Material

[0130] The analogs are prepared by first determining the concentration of an ethanol stock solution using UV spectrophotometry (extinction coefficient = 42,000; λ_{max} = 252 nm). The analog solutions are then volumetrically added to propylene glycol so that there was less than 5% ethanol in the final solution. The solution is mixed and stored at 2 to 8˚C.

[0131] Serum Calcium Analysis

[0132] Twenty-four hours after the final dose, approximately 1 ml of blood is collected from the tail artery of each experimental animal. The blood is allowed to coagulate at room temperature and then centrifuged at 3000 x g for 15 minutes. The serum is transferred to a polypropylene tube and stored frozen at -20˚C. The level of calcium is determined by diluting the serum into 0.1% lanthum chloride and measuring the absorbance on an atomic absorption spectrophotometer (Perkin Elmer Model 3110, Shelton, CT).

[0133] 2-methylene-1α-hydroxy-19,21-dinorvitamin D_3 (SY-44) binds to the recombinant vitamin D receptor, and is 10 times less active when compared to 1α,25-dihydroxyvitamin D_3 in this respect (see Figure 1). Additionally, it is also 10 times less active in stimulating transcription of a reporter gene stably transfected in Ros17/2.8 (bone) cells (see Figure 5). It is also slightly less active as 1α,25-dihydroxyvitamin D_3 in inducing differentiation of HL-60 cells (see Figure 4). It has less bone calcium mobilization activity than does 1α,25-dihydroxyvitamin D_3 (see Figure 2). It has higher intestinal calcium transport activity than does 1α,25-dihydroxyvitamin D_3 (see Figure 3). Accordingly, SY-44 is expected to possess significant activity in suppressing parathyroid hormone levels in normal rats.

[0134] Similarly, other similar compounds of the present invention as shown in formula I or II, are expected to bind to the vitamin D receptor, stimulate transcription of a reporter gene stably transfected in Ros17/2.8 (bone) cells, induce differentiation of HL-60 cells, have limited calcemic activity when measured either by intestinal calcium transport or bone calcium mobilization than 1α,25-dihydroxyvitamin D_3 and possess significant activity in suppressing parathyroid hormone levels.

[0135] Accordingly, this compound SY-44 and other compounds described in the invention should find its uses in the treatment of autoimmune diseases such as multiple sclerosis, type I diabetes, rheumatoid arthritis, lupus, and other similar degenerative diseases. It should also have significant activity in treating malignant growth such as colorectal, breast, skin, lung and prostate cancers. This compound should also be useful in treating secondary hyperparathyroidism found in patients who have lost kidney function such as those on hemodialysis or peritoneal dialysis. It may also be useful in treating osteopenia as well as metabolic bone diseases such as osteomalacia, vitamin D resistant rickets and osteoporosis particularly senile osteoporosis, postmenopausal osteoporosis, steroid-induced osteoporosis and low bone turnover osteoporosis because of its significant activity in intestinal absorption of calcium.

[0136] In one embodiment, the compounds of formula I are used in a pharmaceutical composition. For example, each ml of the pharmaceutical composition may comprise 5μg of the compound, 30% (v/v) propylene glycol and 20% (v/v) alcohol.

[0137] The compounds of the invention are also useful in preventing or treating obesity, inhibiting adipocyte differentiation, 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 differentiation, inhibiting SCD-1 gene transcription, and or reducing body fat in animal subject includes administering to the animal subject, an effective amount of the compound or a pharmaceutical composition that includes the compound. Administration of the compound or the pharmaceutical composition to the subject inhibits adipocyte differentiation, inhibits gene transcription, and/or reduces body fat in the animal subject.

[0138] For treatment purposes, the compounds defined by formula I and formula II are 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. Pharmaceutically acceptable excipients and carriers are generally known to those skilled in the art and are thus included in the instant invention. Such excipients and carriers are described, for example, in "Remingtons Pharmaceutical Sciences" Mack Pub. Co., New Jersey (1991), which is hereby incorporated by reference in its entirety and for all purposes as if fully set forth herein.

[0139] The compounds are administered orally, topically, parenterally, nasally, rectally, sublingually or transdermally. The compounds are 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. In some embodiments, doses of from 0.001 μg to about 1 mg per day of the compound are appropriate for treatment purposes. In some such embodiments an appropriate and effective dose may range from 0.01 μg to 1 mg per day of the compound. In other such embodiments an appropriate and effective dose may range from 0.1 μg to 500 μg per day of the compound. Such doses will be adjusted according to the type of disease

or condition to be treated, the severity of the disease or condition, and the response of the subject as is well understood in the art. The compound is suitably administered alone, or together with another active vitamin D compound.

[0140] In one embodiment, the compound of formula II is used in a pharmaceutical composition. For example, each ml of the pharmaceutical composition may comprise 5μg of the compound, 30% (v/v) propylene glycol and 20% (v/v) alcohol.

[0141] Compositions for use in the invention include an effective amount of (2-methylene-1α-hydroxy-19,21-dinorvitamin D_3 (SY-44) as the active ingredient, and a suitable carrier. An effective amount of the compound for use in accordance with some embodiments of the invention will generally be a dosage amount such as those described herein, and is administered topically, transdermally, orally, nasally, rectally, sublingually or parenterally. In one embodiment, the dosage is administered intraperitoneally.

[0142] The compounds of formula I or II are 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.

[0143] The compound is formulated as creams, lotions, ointments, aerosols, suppositories, topical patches, pills, capsules or tablets, 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.

[0144] 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.

[0145] Formulations of the present invention suitable for oral administration is 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.

[0146] Formulations for rectal administration is in the form of a suppository incorporating the active ingredient and carrier such as cocoa butter, or in the form of an enema.

[0147] 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.

[0148] 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.

[0149] 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 microns.

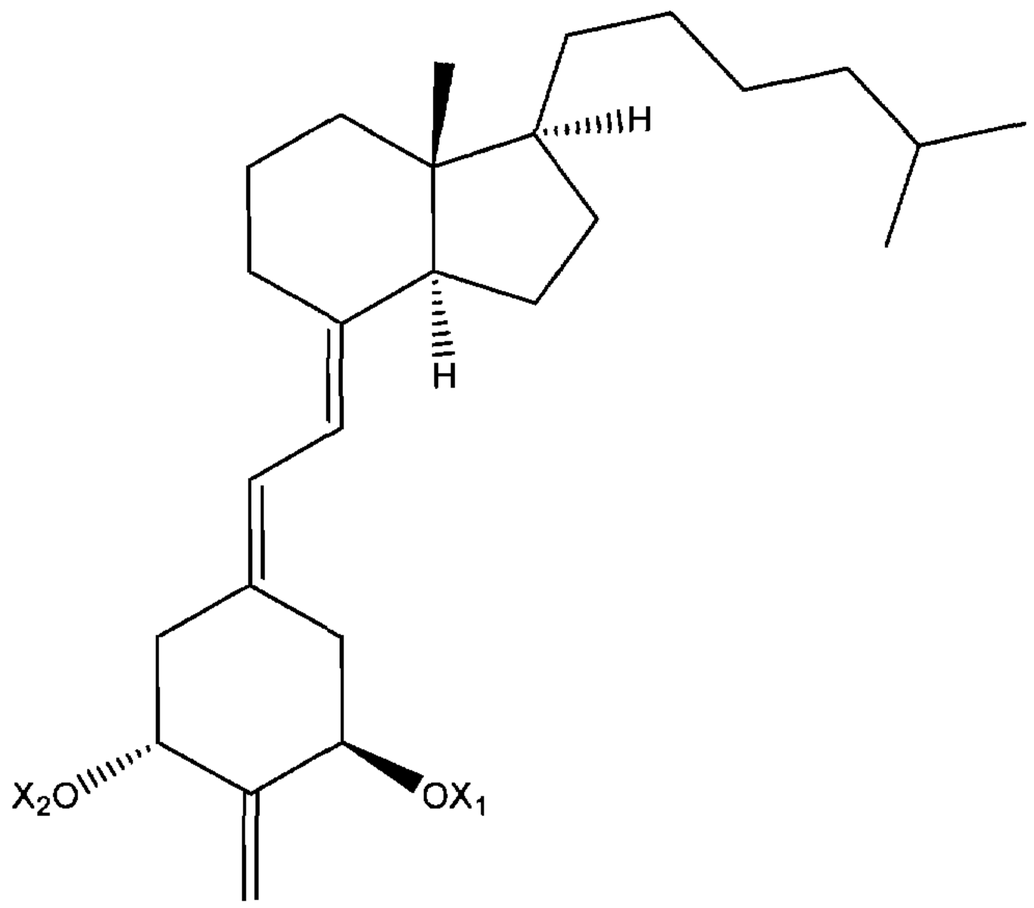
[0150] The formulations may conveniently be presented in dosage unit form and is prepared by any of the methods well known in the art of pharmacy. By the term "dosage unit" is meant a unitary, i.e., a single dose which is capable of being administered to a patient as a physically and chemically stable unit dose comprising either the active ingredient as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

[0151] All references cited herein are specifically incorporated by reference in their entireties and for all purposes as if fully set forth herein.

[0152] It is understood that the invention is not limited to the embodiments set forth herein for illustration, but embraces all such forms thereof as come within the scope of the following claims.

WHAT IS CLAIMED IS

1. A compound having the formula I



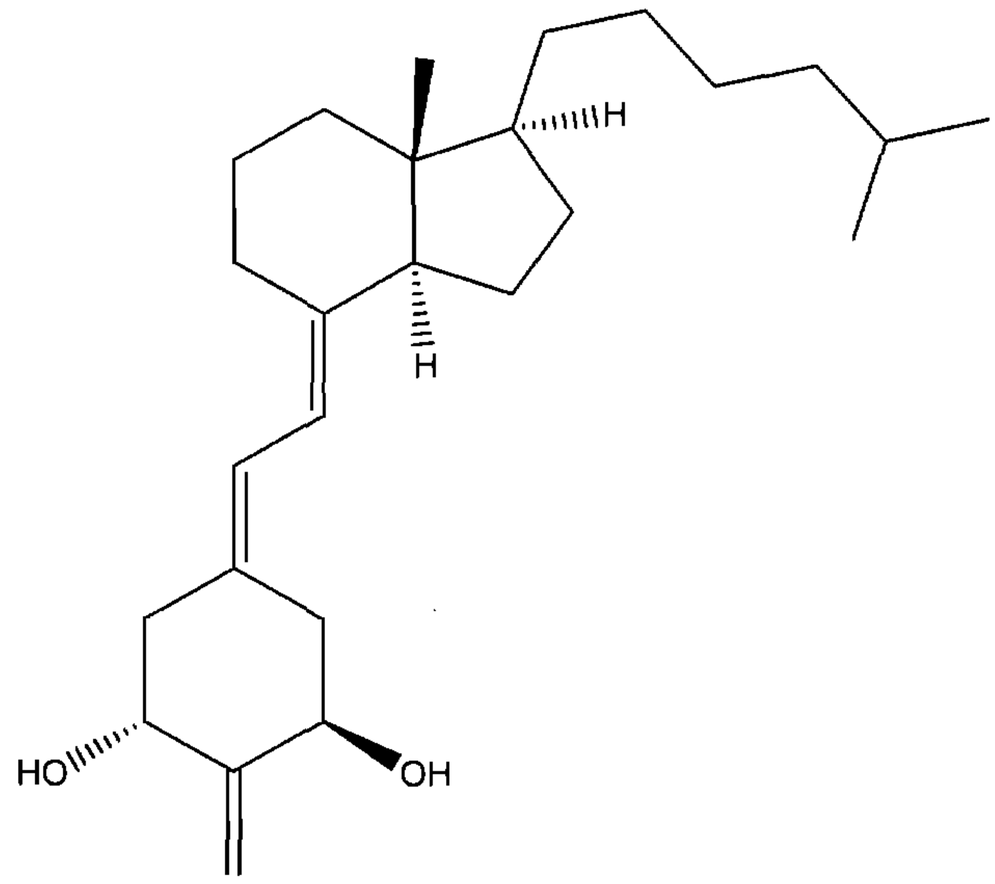
I

wherein X_1 and X_2 are independently selected from H and hydroxy protecting groups.

2. The compound of claim 1, wherein X_1 and X_2 are hydroxy protecting groups.

3. The compound of claim 2, wherein X_1 and X_2 are triethylsilyl or t-butyldimethylsilyl groups.

4. The compound of claim 1, wherein X_1 and X_2 is H and the compound has the formula II



II

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5. A pharmaceutical composition, comprising an effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

6. The pharmaceutical composition of claim 5 wherein the effective amount comprises from about 0.01 μg to about 1 mg of the compound per gram of the composition.

7. The pharmaceutical composition of claim 5 wherein the effective amount comprises from about 0.1 μg to about 500 μg of the compound per gram of the composition.

8. A method of treating a subject suffering from a biological condition, comprising administering an effective amount of the compound of claim 1 to the subject, wherein the biological condition is selected from a metabolic bone disease; psoriasis; leukemia; colon cancer; breast cancer; prostate cancer; skin cancer; lung cancer; multiple sclerosis; lupus; diabetes mellitus; host versus graft reaction; rejection of organ transplants; an inflammatory disease selected from rheumatoid arthritis, asthma, or inflammatory bowel diseases; a skin condition selected from wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration, or insufficient sebum secretion; renal osteodystrophy; osteopenia; or osteoporosis.

9. The method of claim 8, wherein the biological condition is renal osteodystrophy, vitamin D-resistant rickets, osteoporosis or psoriatic arthritis.

10. The method of claim 8, wherein the biological condition is selected from leukemia, colon cancer, breast cancer, skin cancer, lung cancer or prostate cancer.

11. The method of claim 8, wherein the biological condition is selected from multiple sclerosis, lupus, diabetes mellitus, host versus graft reaction, or rejection of organ transplants.

12. The method of claim 8, wherein the biological condition is selected from rheumatoid arthritis, asthma, or inflammatory bowel diseases selected from celiac disease, ulcerative colitis and Crohn's disease.

13. The method of claim 8, wherein the biological condition is selected from wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration, or insufficient sebum secretion.

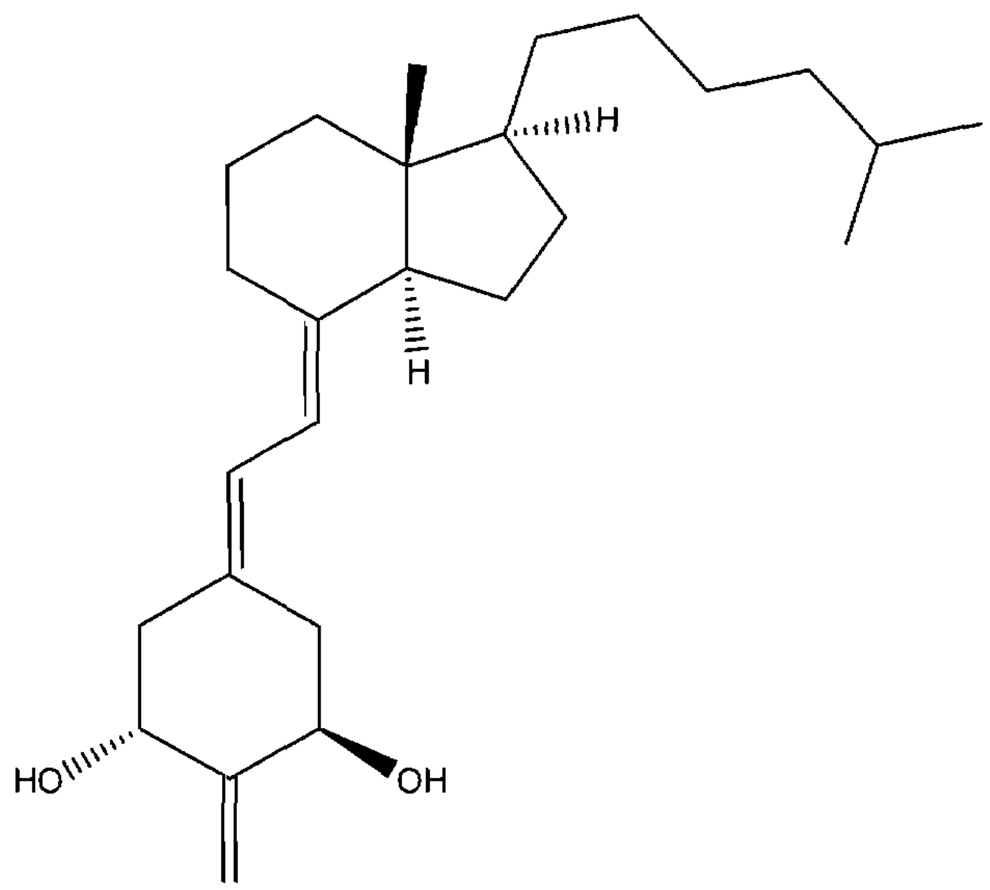
14. The method of claim 8 wherein the biological condition is metabolic bone disease.

15. The method of claim 8, wherein the compound is administered orally, parenterally, nasally, rectally, sublingually, transdermally or topically to the subject.

16. The method of claim 8, wherein the compound is administered intraperitoneally.

17. The method of claim 8, wherein the compound is administered in a dosage of from 0.01 μg per day to 1 mg per day.

18. A compound having the formula II



II

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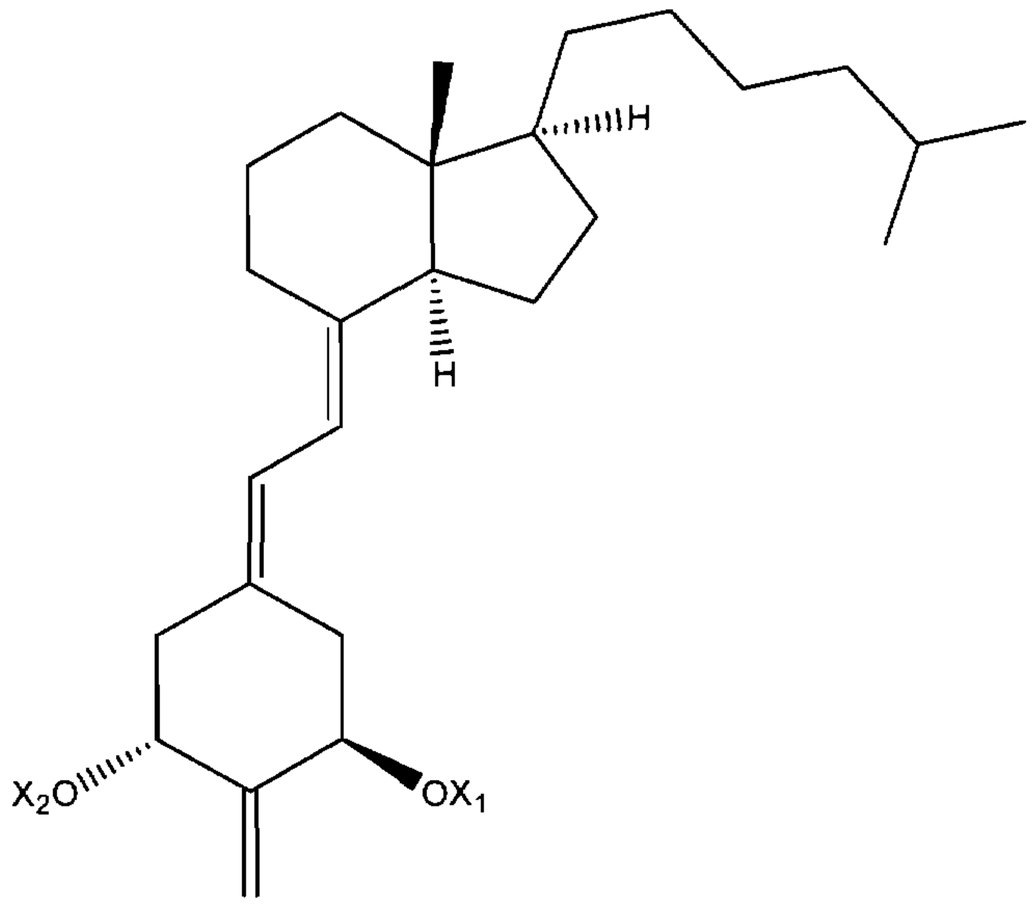
19. A pharmaceutical composition, comprising an effective amount of the compound of claim 18 and a pharmaceutically acceptable carrier.

20. The pharmaceutical composition of claim 19 wherein the effective amount comprises from about 0.01 μg to about 1 mg of the compound per gram of the composition.

21. The pharmaceutical composition of claim 19 wherein the effective amount comprises from about 0.1 μg to about 500 μg of the compound per gram of the composition.

22. A method of treating or preventing obesity of an animal, inhibiting adipocyte differentiation, inhibiting SCD-1 gene transcription, and/or reducing body fat in an animal comprising administering to an animal in need thereof an effective amount fo a compound having the formula:



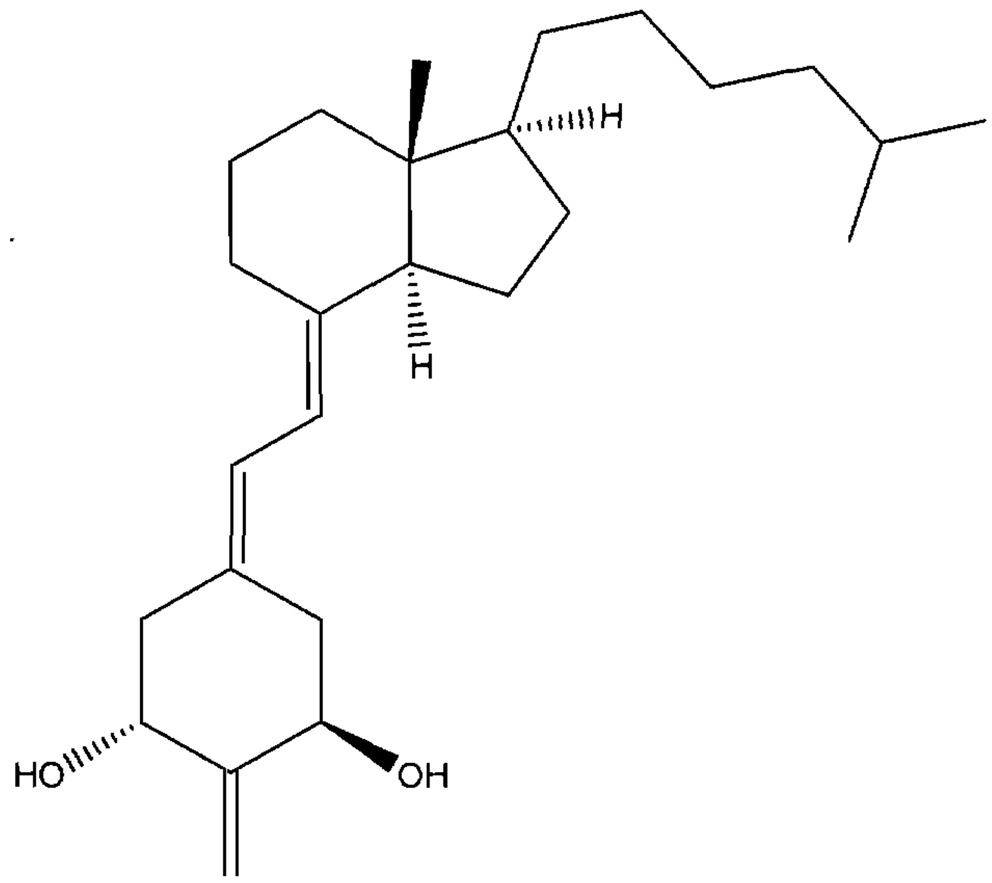
I

wherein X_1 and X_2 are independently selected from H and hydroxy protecting groups.

23. The method of claim 22, wherein the compound is administered orally, parenterally, nasally, rectally, sublingually, transdermally or topically to the animal.

24. The method of claim 22, wherein the compound is administered in a dosage of from 0.01 μg per day to 1 mg per day.

25. The method of claim 22, wherein the compound is 2-methylene-1α-hydroxy-19,21-dinorvitamin D_3 having the formula:

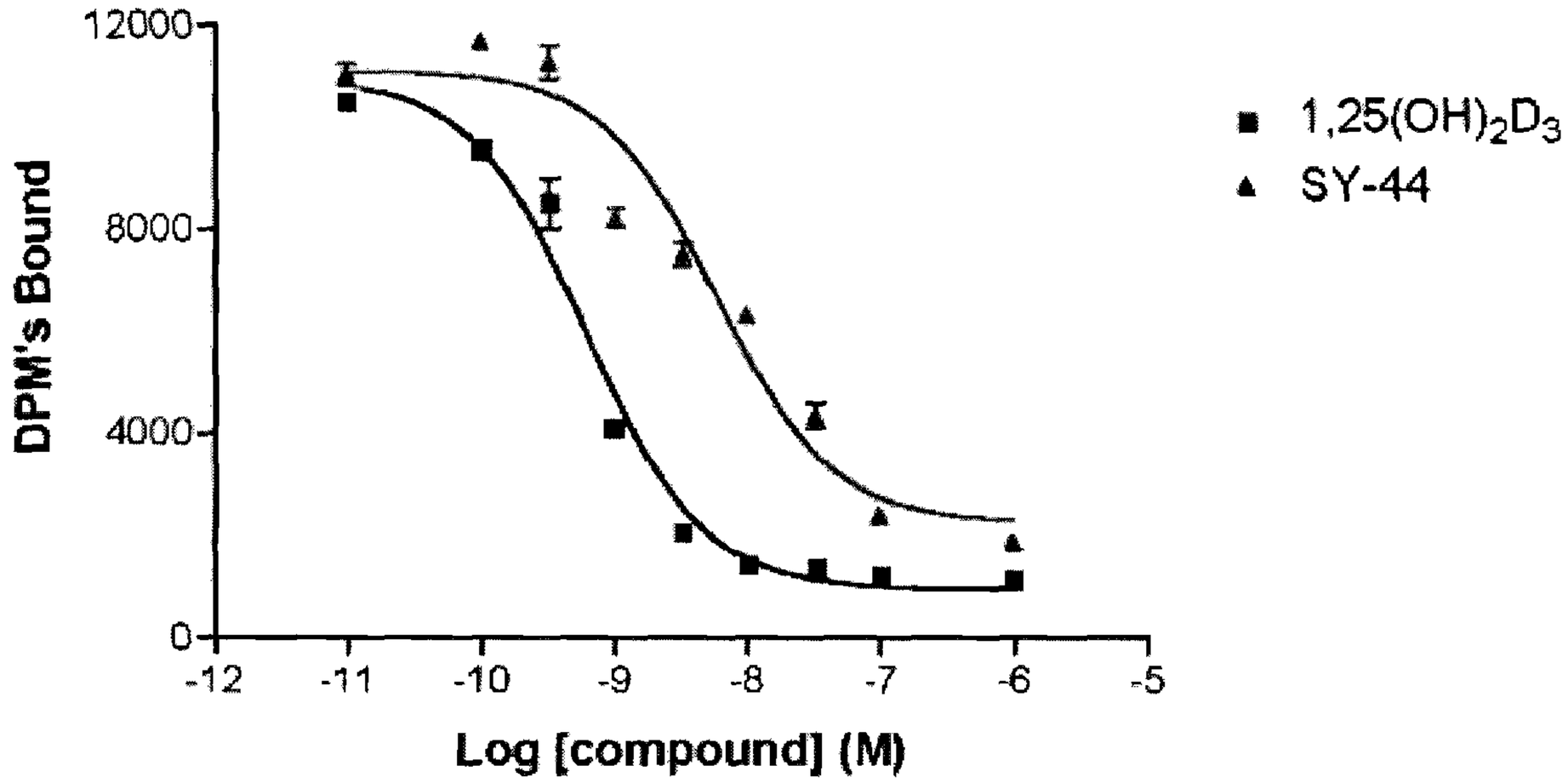


II

26. The method of claim 22, wherein the animal is a human.

27. The method of claim 22, wherein the animal is a domestic animal.

28. The method of claim 22, wherein the animal is an agricultural animal.



K_i: $1,25(OH)_2D_3 = 1.1 \times 10^{-10}$ M

SY-44 = 1.0×10^{-9} M

Fig. 1

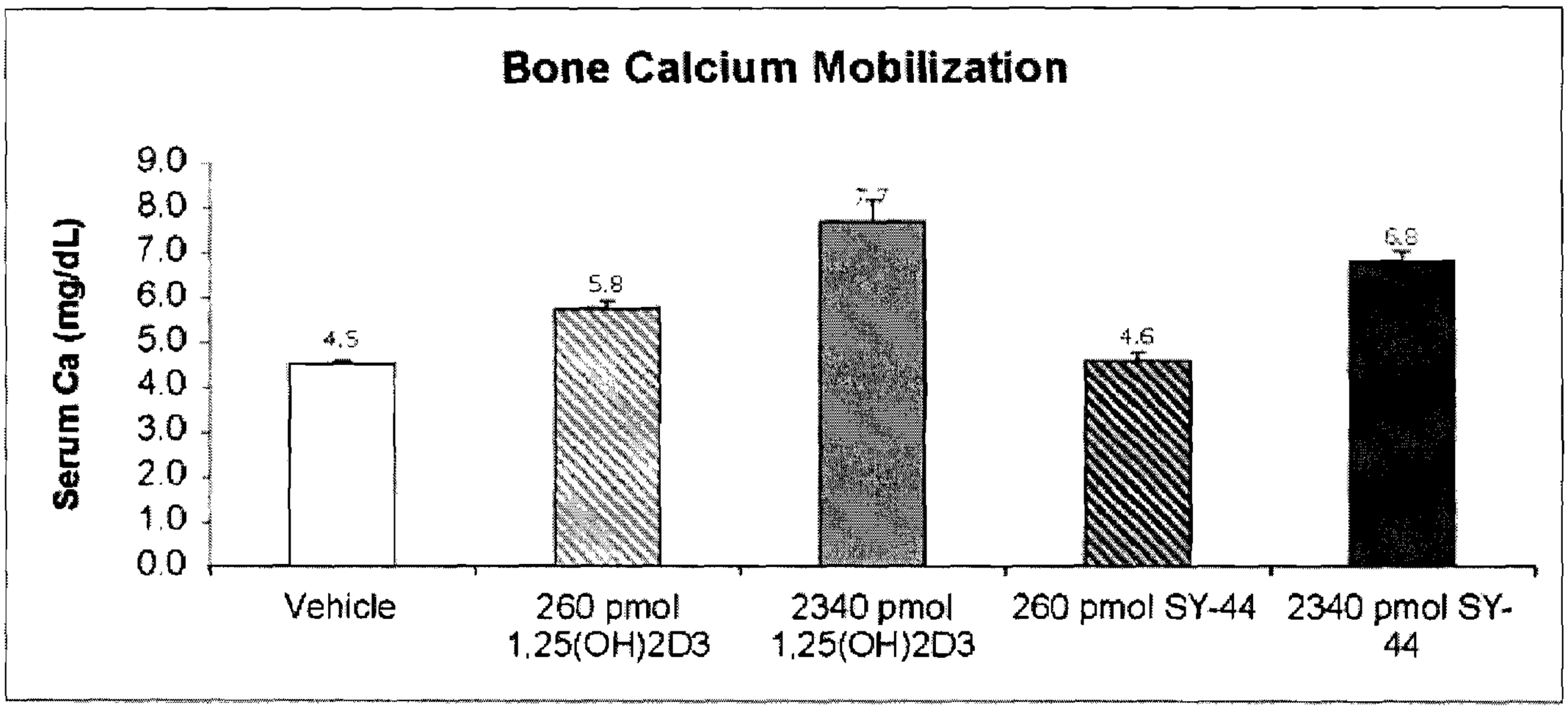

Bone Calcium Mobilization
Serum Ca (mg/dL)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
4.5
5.8
7.7
4.6
6.8
Vehicle
260 pmol 1,25(OH)2D3
2340 pmol 1,25(OH)2D3
260 pmol SY-44
2340 pmol SY-44

Fig. 2

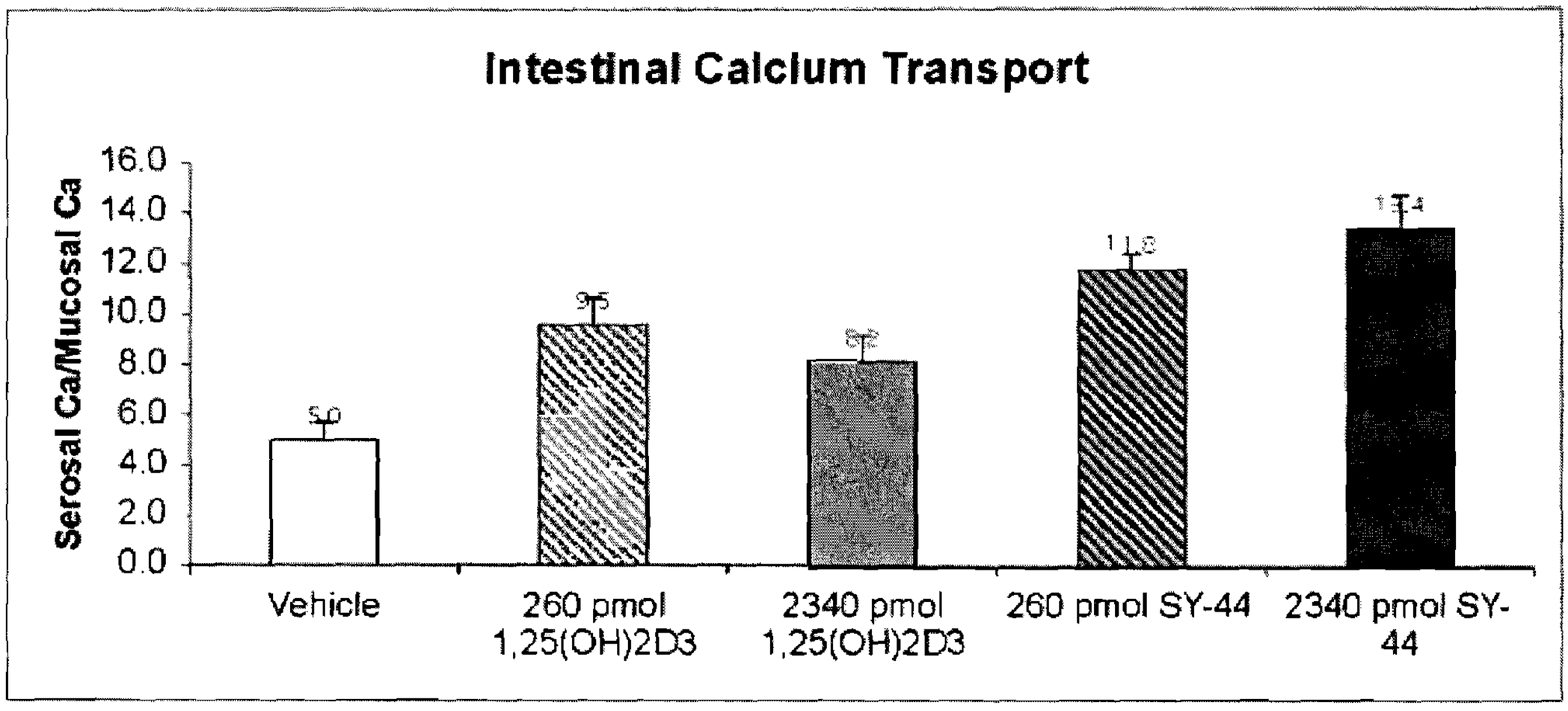
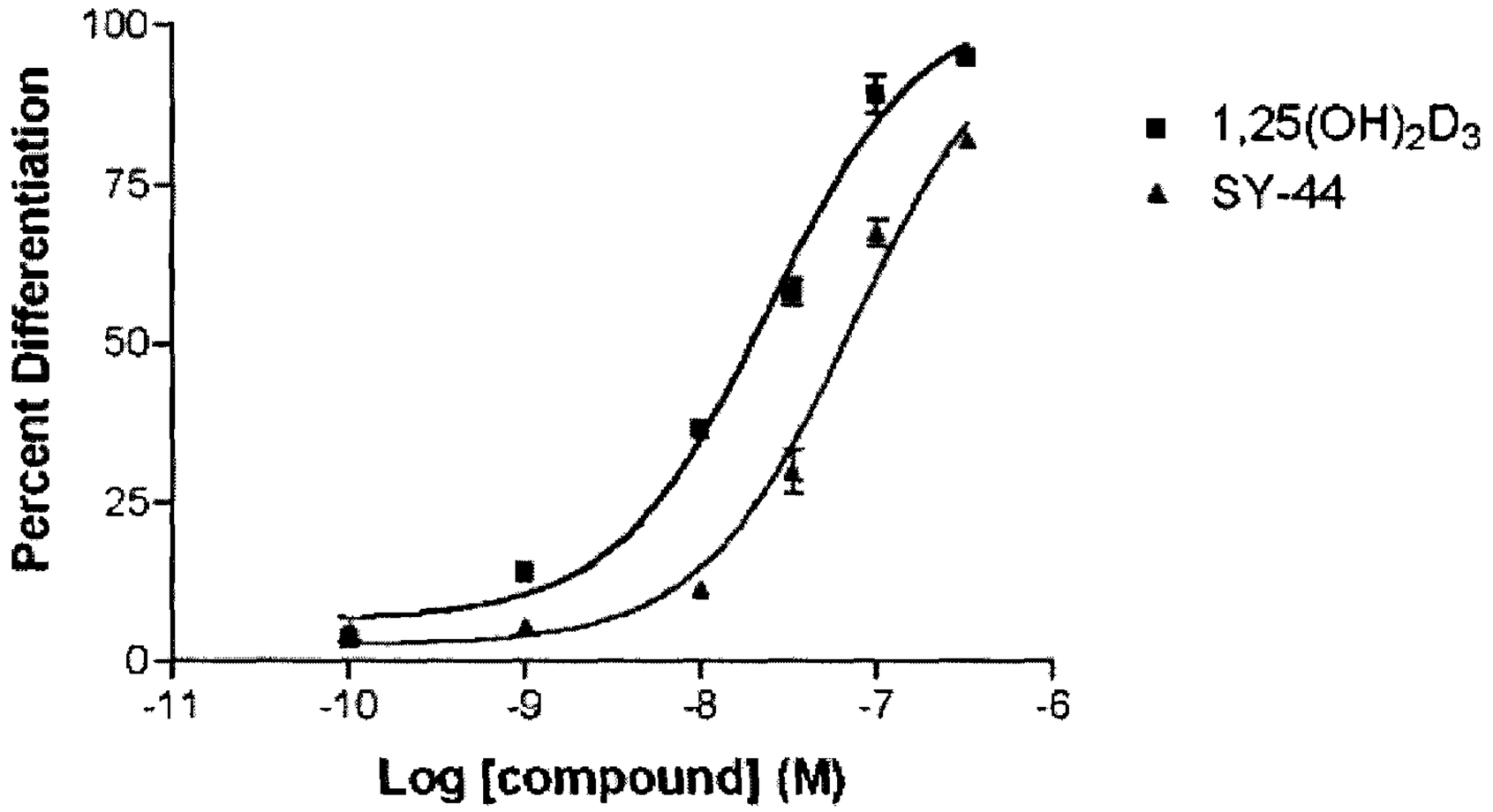

Intestinal Calcium Transport
Serosal Ca/Mucosal Ca
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
Vehicle
260 pmol 1,25(OH)2D3
2340 pmol 1,25(OH)2D3
260 pmol SY-44
2340 pmol SY-44

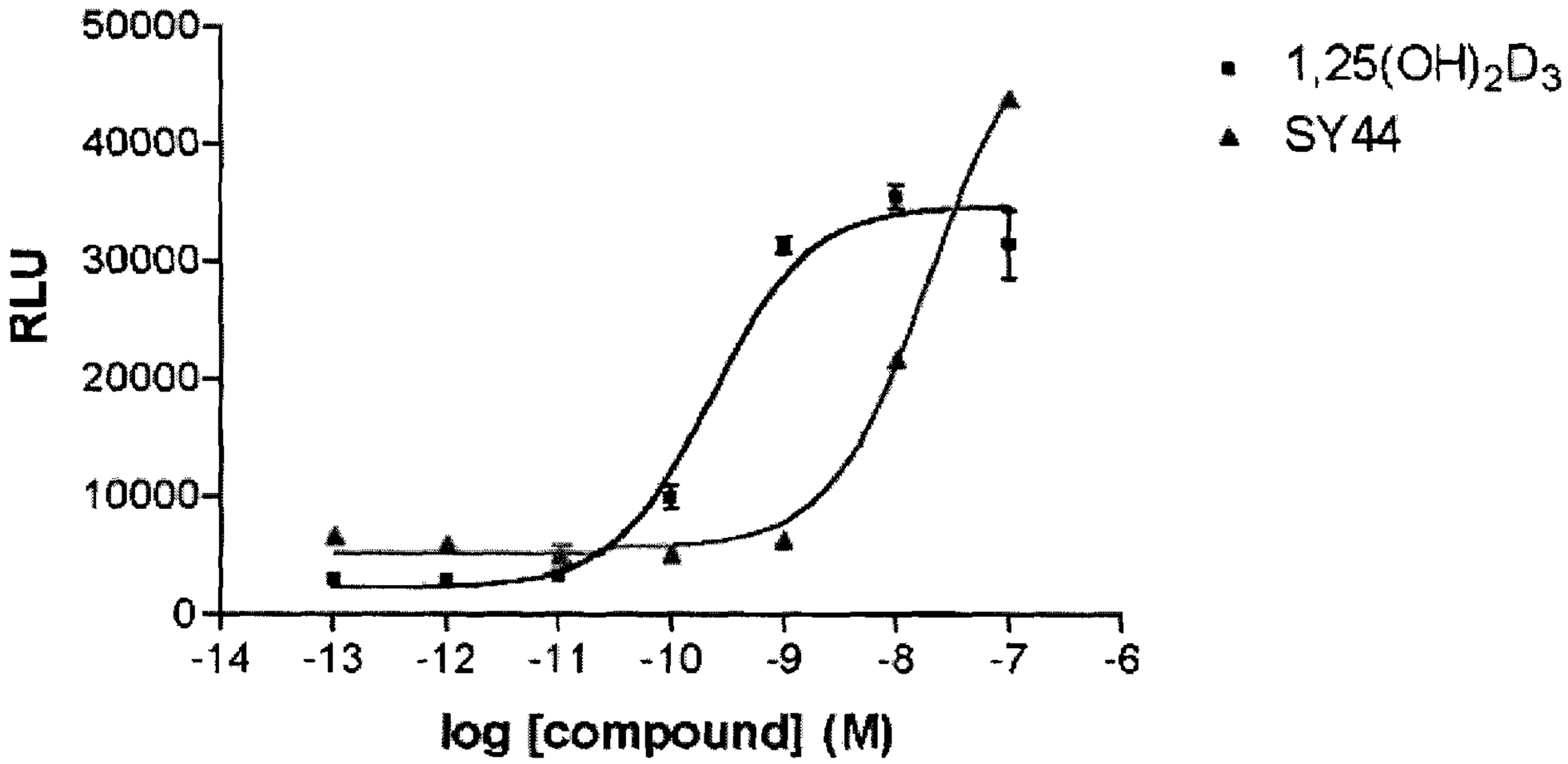
Fig. 3



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

SY-44 = 7.3×10^{-8} M

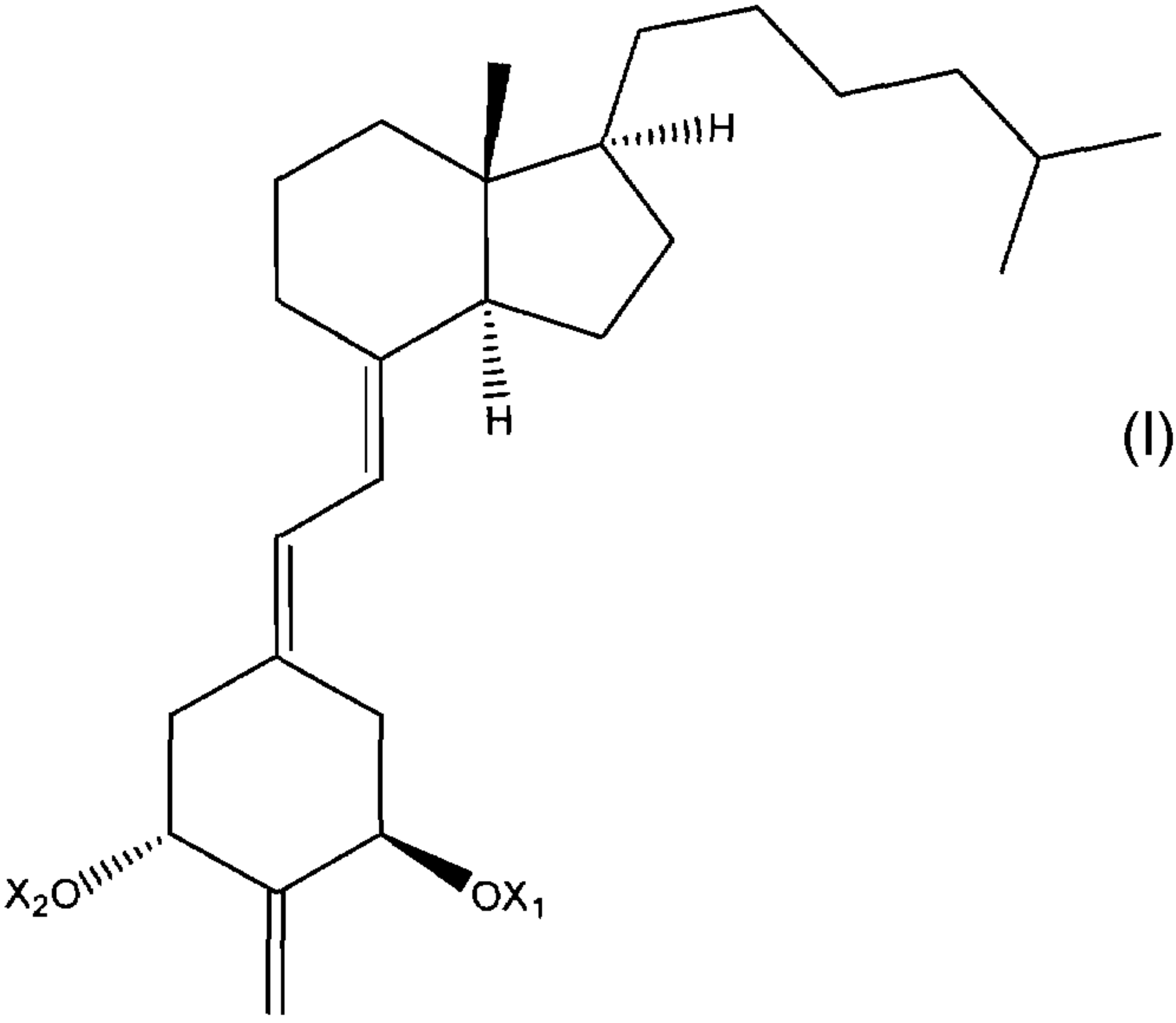
Fig. 4



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

SY-44 = 1.9×10^{-8} M

Fig. 5



(I)