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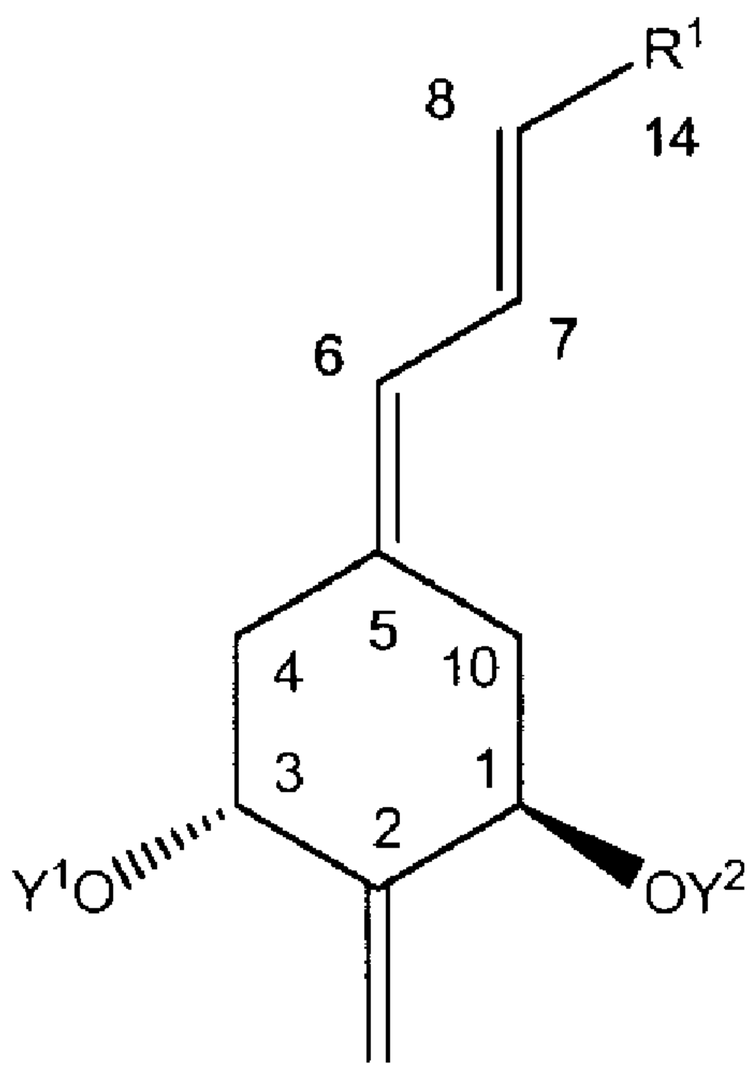
(54) Titre : ANALOGUES DES-C,D D'1α,25-DIHYDROXY-19-NORVITAMINE D3
(54) Title: DES-C,D ANALOGS OF 1α,25-DIHYDROXY-19-NORVITAMIN D3



(57) Abrégé/Abstract:
Des-C,D 2-methylene-19-norvitamin D_3 analogs are provided including compounds of formula 1, in which R^1 is a straight or branched chain alkyl or alkylene group having from 8 to 27 carbons and bearing an OY^3 group; and Y^1, Y^2 and Y^3 are independently selected from H or hydroxy-protecting groups. Such compounds may be used in preparing pharmaceutical compositions and are useful in treating a variety of biological conditions. Formula(I)

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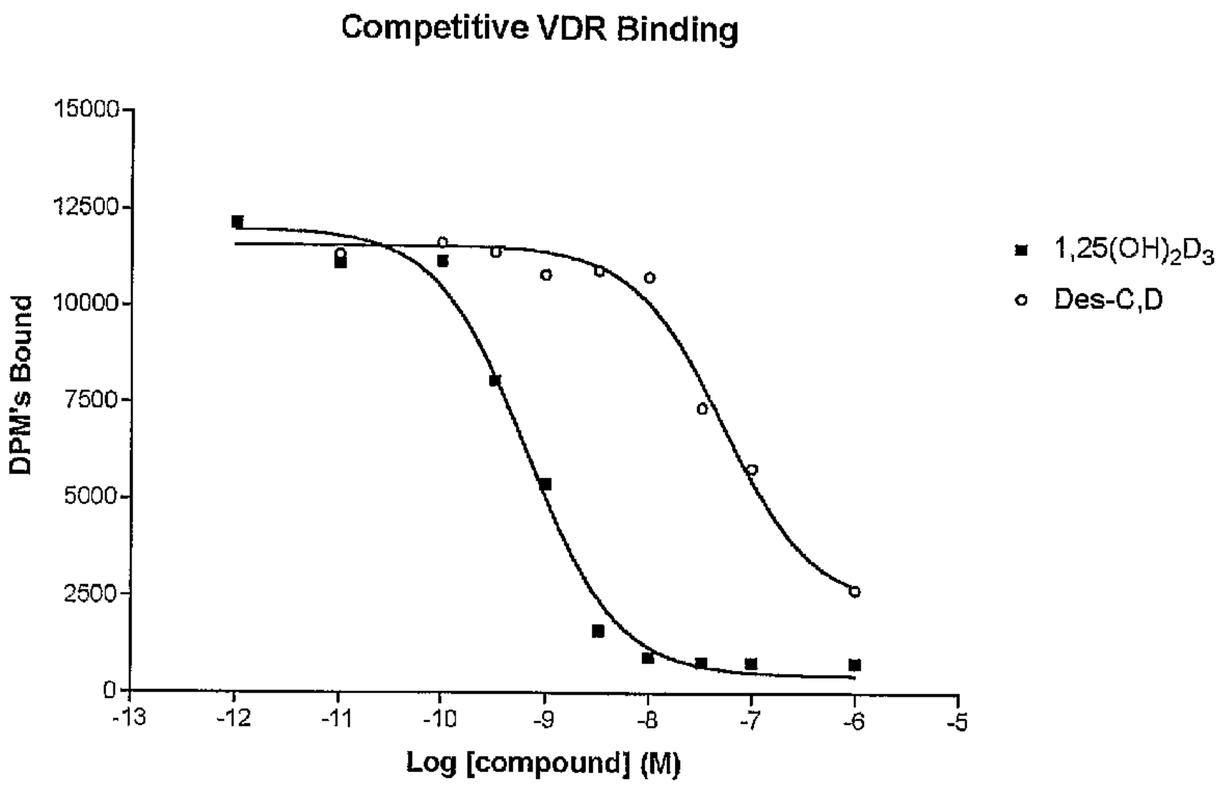
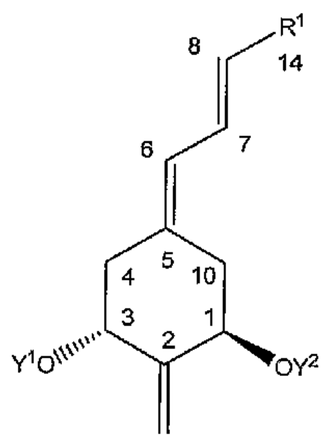
(54) Title: DES-C,D ANALOGS OF 1ALPHA,25-DIHYDROXY-19-NORVITAMIN D3



(57) Abstract: *Des*-C,D 2-methylene-19-norvitamin D_3 analogs are provided including compounds of formula 1, in which R^1 is a straight or branched chain alkyl or alkylene group having from 8 to 27 carbons and bearing an OY^3 group; and Y^1, Y^2 and Y^3 are independently selected from H or hydroxy-protecting groups. Such compounds may be used in preparing pharmaceutical compositions and are useful in treating a variety of biological conditions. Formula(I)

K_i: $1,25(OH)_2D_3 = 9.6 \times 10^{-11}$ M
Des-C,D = ~7.5×10^{-9} M



(I)

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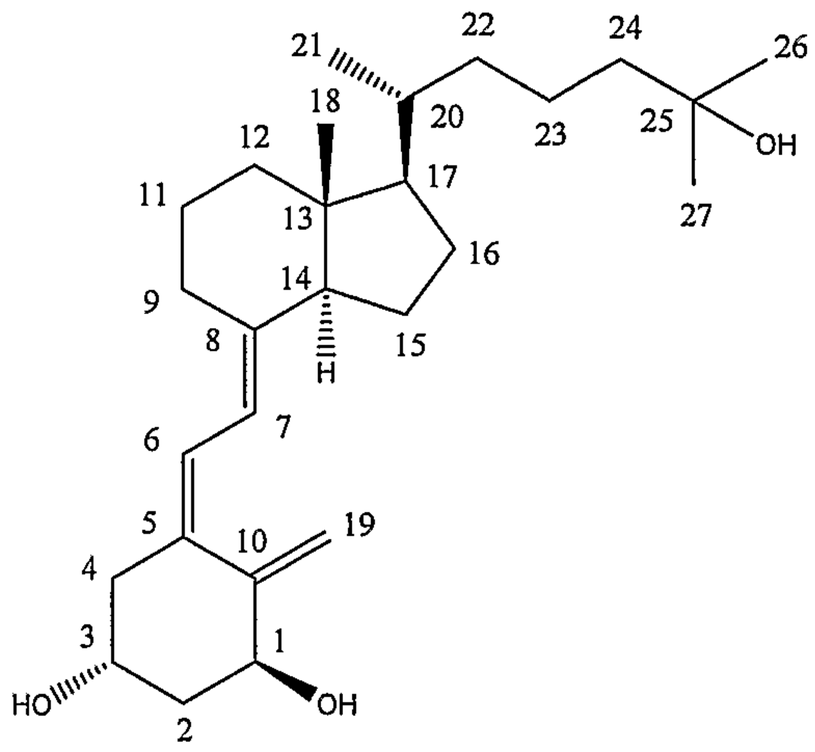
Des-C,D Analogs of 1α,25-Dihydroxy-19-Norvitamin D_3

FIELD OF THE INVENTION

[0001] This invention relates to analogs of vitamin D compounds that do not include the C and D rings, more particularly to *des*-C,D analogs of 1α,25-dihydroxy-19-norvitamin D_3, and still more particularly to *des*-C, D analogs of 2-methylene-1α,25-dihydroxy-19-norvitamin D_3 and to pharmaceutical formulations that include these compounds or mixtures thereof. The invention also relates to the use of the compounds, and mixtures 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 may be useful in the treatment of a variety of diseases as renal osteodystrophy, vitamin D-resistant rickets, osteoporosis, psoriasis, and certain malignancies. 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

[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 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. Patent No. 5,086,191).

[0004] 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. Patent 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.

[0005] U.S. Patent No. 4,666,634 discloses 2β-hydroxy and alkoxy (e.g.,

ED-71) analogs of 1α,25-dihydroxyvitamin D_3 as potential drugs for use in treating osteoporosis and for use 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 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)).

[0006] In a continuing effort to explore the 19-nor class of pharmacologically important vitamin D compounds, their analogs which are characterized by the transposition of the ring A exocyclic methylene group from carbon 10 (C-10) to carbon 2 (C-2), i.e. 2-methylene-19-nor-vitamin D compounds have been recently synthesized and tested (Sicinski *et al., J. Med. Chem., 41*, 4662 (1998); Sicinski *et al., Steroids 67*, 247 (2002); DeLuca *et al.,* U.S. Pat. Nos. 5,843,928, 5,936,133 and 6,382,071). Molecular mechanics studies, performed on these analogs, showed that a change of ring-A conformation can be expected resulting in the "flattening" of the cyclohexanediol ring. From molecular mechanics calculations and NMR studies of these compounds, the A-ring conformational equilibrium was established to be about 6:4 in favor of the conformer that has an equatorial 1α-OH. Introduction of the 2-methylene group into the 19-nor-vitamin D carbon skeleton changes the character of its (1α- and 3β-) A-ring hydroxyl groups; they are both now in the allylic positions, similar to the 1α-hydroxyl group (important for biological activity) in the natural hormone, 1α,25-$(OH)_2D_3$. 1α,25-Dihydroxy-2-methylene-19-norvitamin D analogs are characterized by significant biological potency which is enhanced in compounds with the “unnatural” (20*S*)-configuration.

[0007] In a continuing effort to explore the 19-nor class of pharmacologically important vitamin D compounds, analogs which are characterized by the presence of a methylene substituent at carbon 2 (C-2), a hydroxyl group at carbon 1 (C-1), and a shortened side chain attached to carbon 20 (C-20) have also been synthesized and tested. 1α-Hydroxy-2-methylene-19-

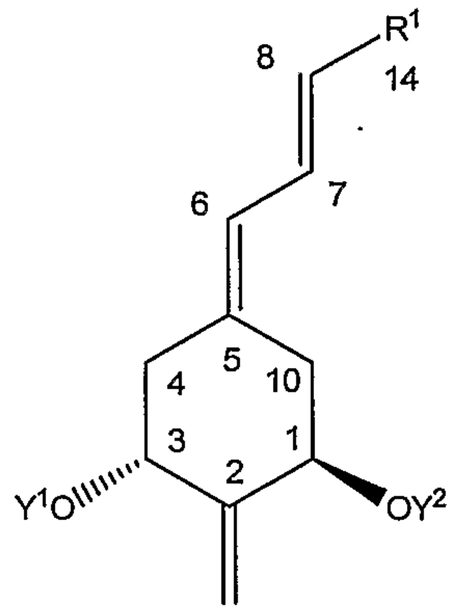
nor-pregnacalciferol is described in U.S. Patent No. 6,566,352 while 1α-hydroxy-2-methylene-19-nor-(20S)-homopregnacalciferol is described in U.S. Patent No. 6,579,861 and 1α-hydroxy-2-methylene-19-nor-bishomopregnacalciferol is described in U.S. Patent No. 6,627,622. All three of these compounds have relatively high binding activity to the vitamin D receptor 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.

[0008] An interesting modification of the vitamin D skeleton is removal of its C and D rings. The first compound (retiferol) lacking the C,D-substructure was disclosed by Kutner *et al.* ten years ago (Kutner *et al., Bioorg. Chem., 23*, 22 (1995). Several other *des*-C,D vitamin D_3 derivatives, including 19-nor analogs, have been disclosed (Bauer *et al.*, U.S. Pat. No. 5,969,190; Barbier *et al.*, U.S. Pat. No. 6,184,422) and some of them (Ro 65-2299) have been reported to show improved biological activities [Hilpert and Wirz, *Tetrahedron, 57*, 681 (2001)].

SUMMARY OF THE INVENTION

[0009] The invention provides compounds that are analogs of 1α,25-dihydroxy-19-norvitamin D_3 that lack the C and D rings such as *des*-C,D analogs of 2-methylene-19-norvitamin D_3, pharmaceutical formulations that include the compounds, and the use of these compounds or mixtures thereof in the preparation of medicaments for use in treating various disease states.

[0010] Therefore, in one aspect, the invention provides a 2-methylene-19-norvitamin D_3 analog that lacks the C and D rings. In some embodiments, the invention provides compounds of formula 1 having the structure shown below:

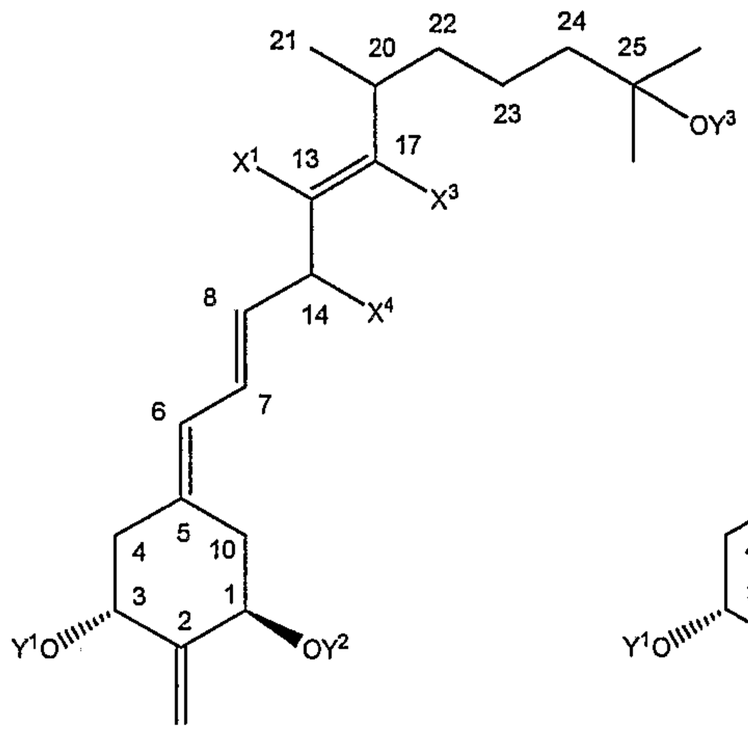


wherein,

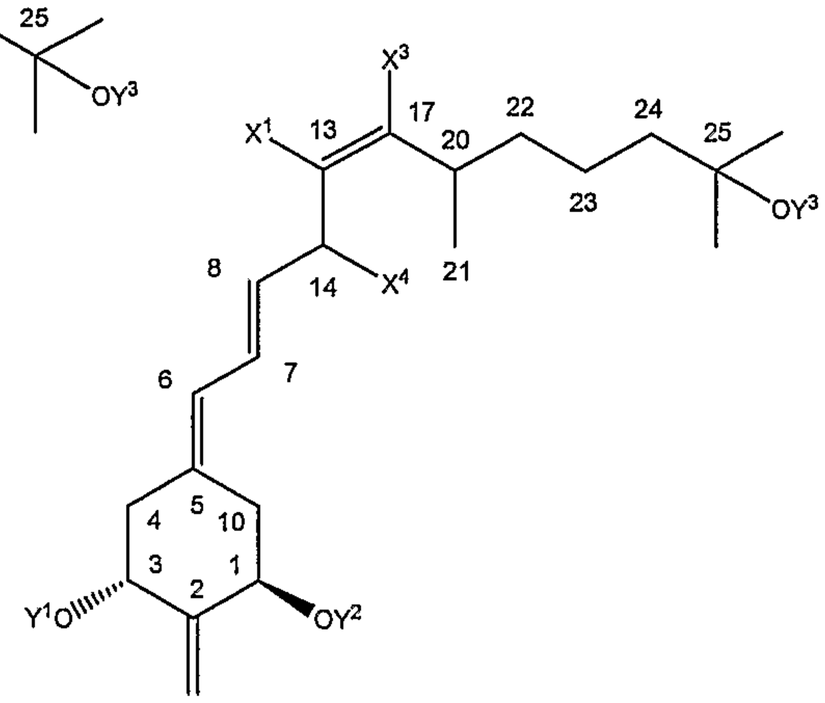
R^1 is a straight or branched chain alkyl or alkylene group having from 8 to 27 carbons and bearing an OY^3 group; and

Y^1, Y^2 and Y^3 are independently selected from H or hydroxy-protecting groups.

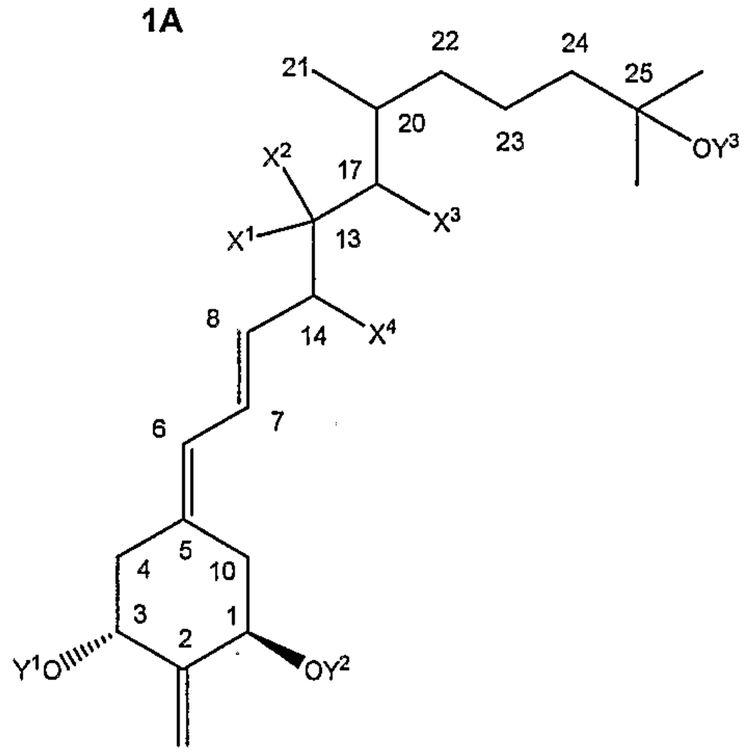
[0011] In some embodiments, the invention provides compounds having the formula 1A, formula 1B, formula 1C, or a mixture thereof as shown below:



1A



1B



1C

wherein,

X^1, X^2, X^3, and X^4 are independently selected from H and straight and branched chain alkyl groups having from 1 to 4 carbon atoms including methyl, ethyl, propyl, isopropyl, and butyl groups;

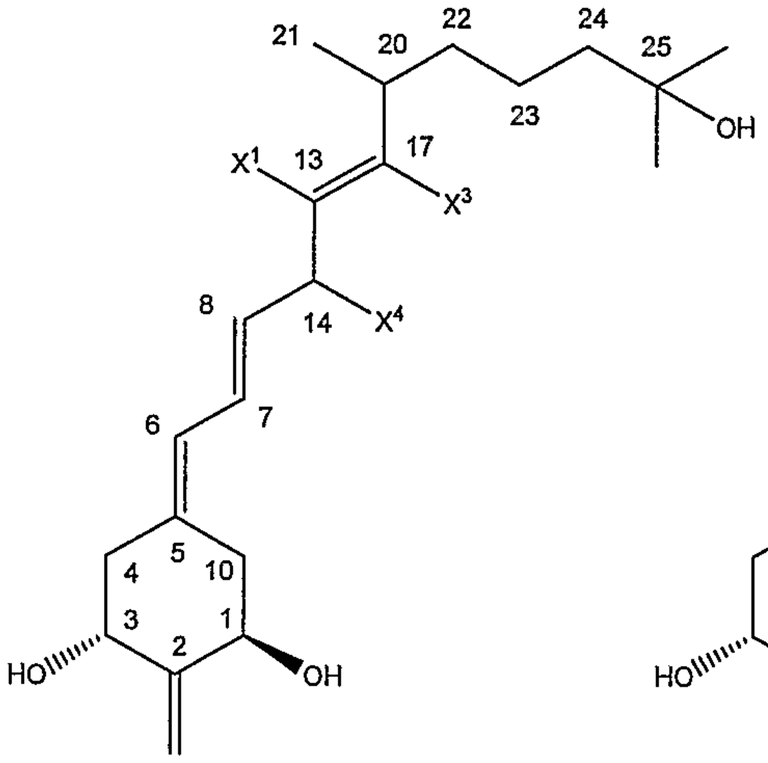
Y^1, Y^2, and Y^3 are independently selected from H or hydroxy-protecting groups;

the carbon atoms at positions 14 and 20 may independently have either the R or S configuration in the compounds of formula 1A and formula 1B; and

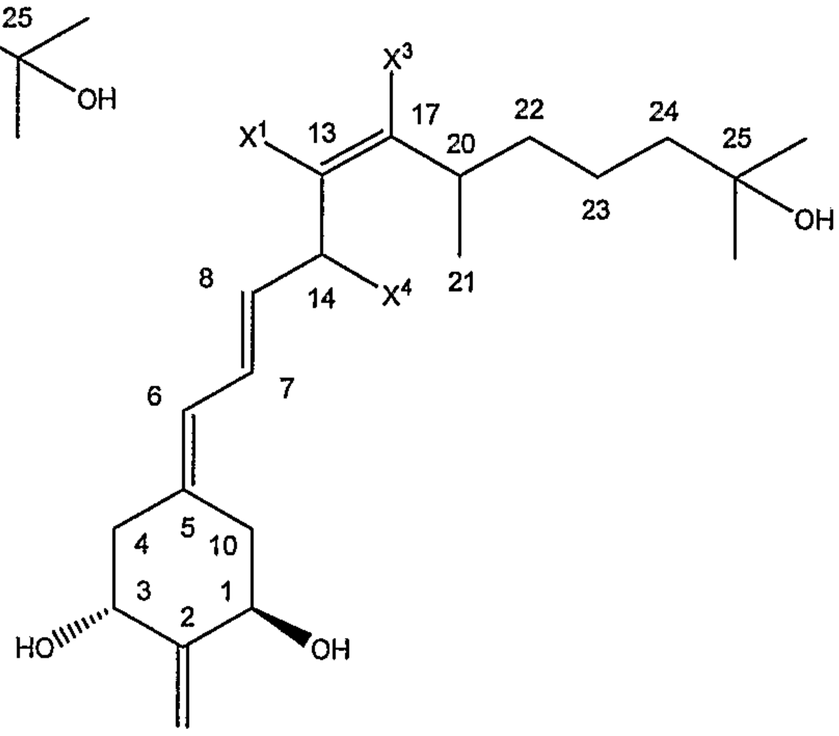
the carbon atoms at positions 13, 14, 17, and 20 may independently have either the R or S configuration in the compounds of formula 1C.

[0012] In some embodiments, Y^1 and Y^2 are both hydroxy protecting groups such as silyl groups. In some such embodiments, Y^1 and Y^2 are both t-butyldimethylsilyl groups. In some embodiments, Y^3 is a trialkylsilyl group such

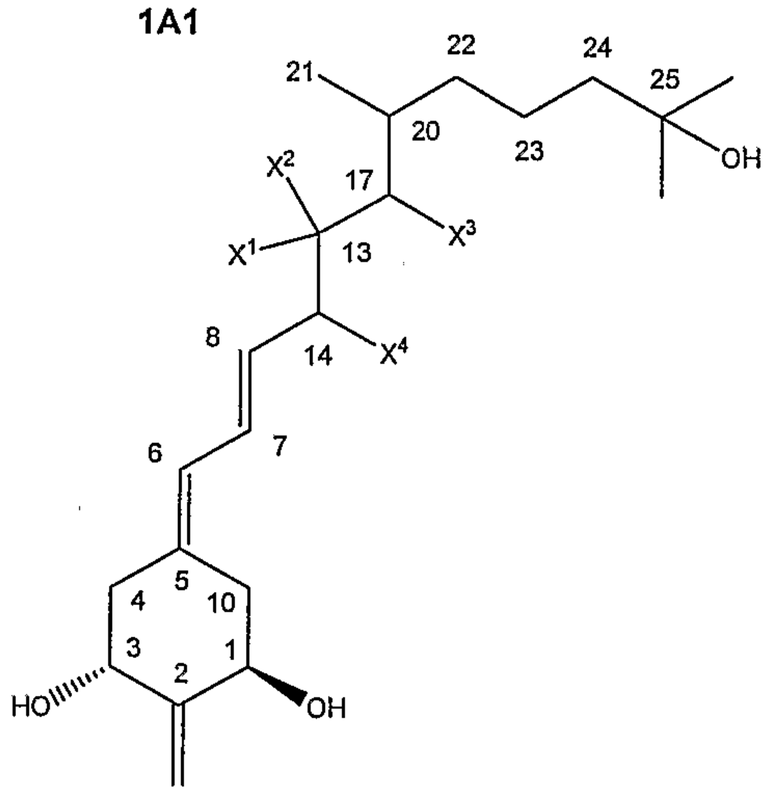
as a trimethylsilyl or trimethylsilyl group. In other embodiments, Y^1, Y^2, and Y^3 are all H such that the compound has the formula 1A1, 1B1, or 1C1 as shown below. In some such embodiments, each of X^1, X^2, X^3, and X^4 is independently selected from H or a methyl group.



1A1

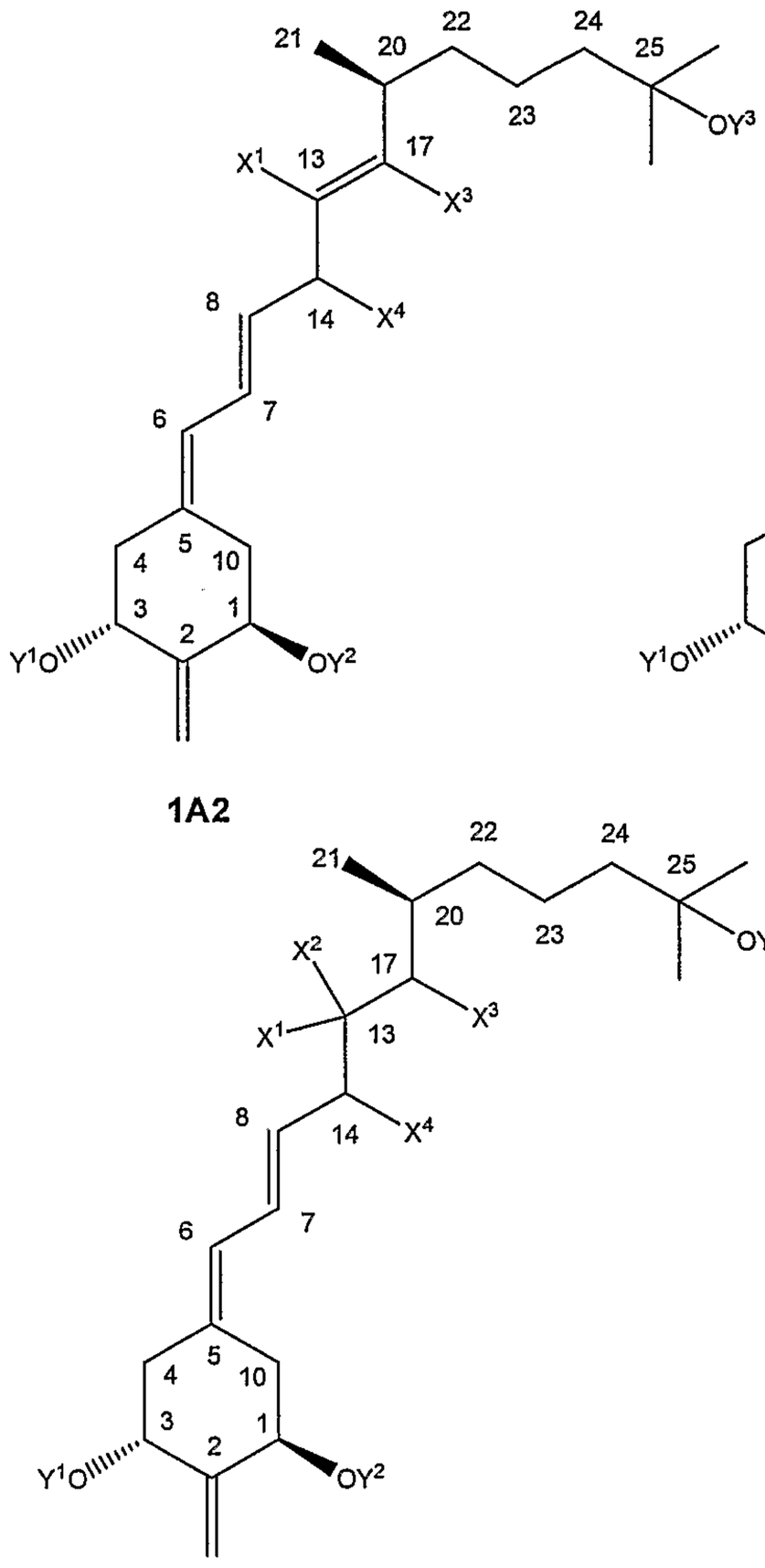


1B1

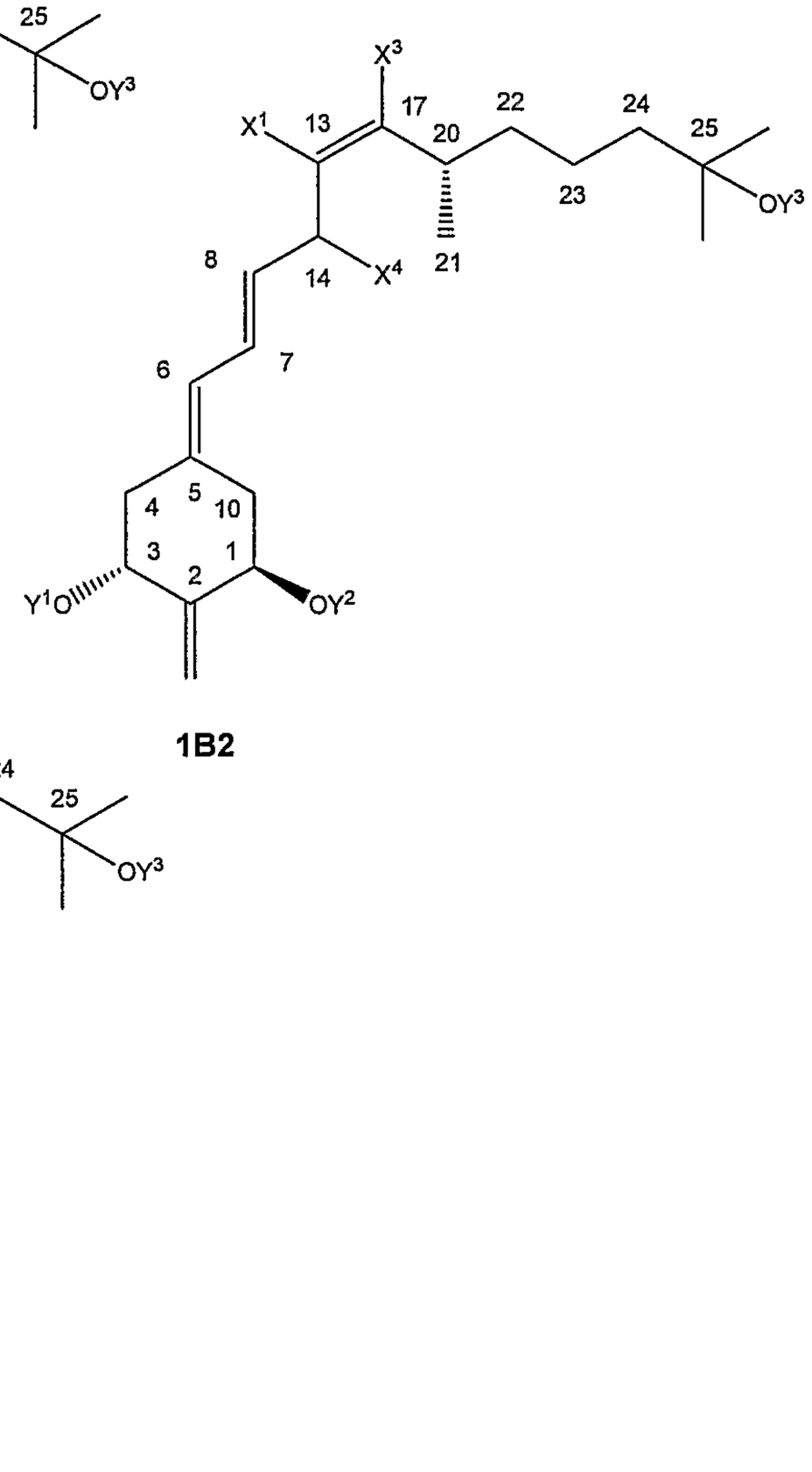


1C1

[0013] In some embodiments, the compounds of formula 1A, 1B, and 1C have the formula 1A2, 1B2, or 1C2 as shown below:



1A2



1B2

1C2

wherein,

X^1, X^2, X^3, and X^4 are independently selected from H and straight and branched chin alkyl groups having from 1 to 4 carbon atoms;

Y^1, Y^2, and Y^3 are independently selected from H or hydroxy-protecting groups;

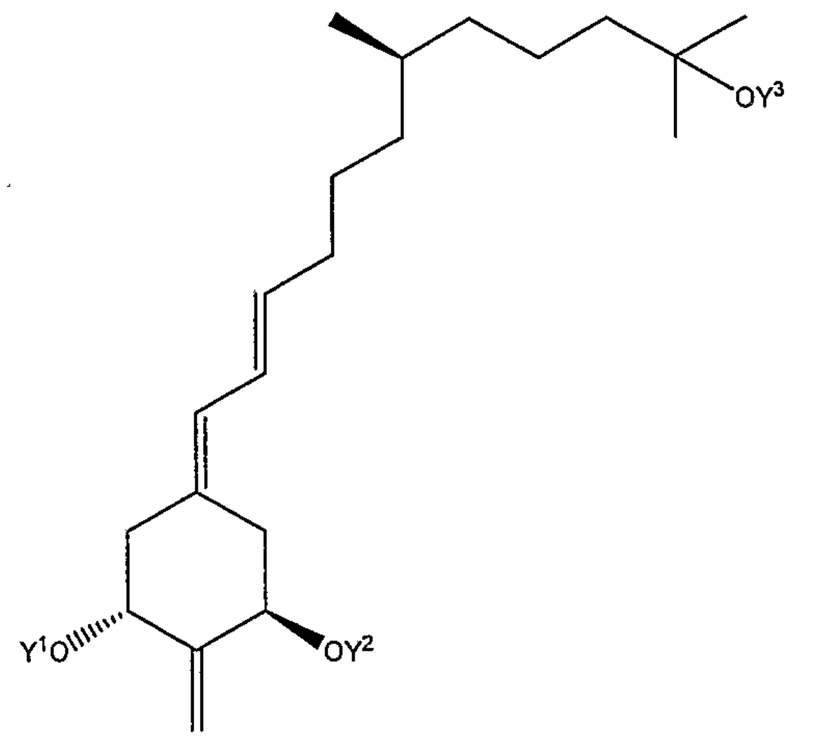
the carbon atoms at position 14 have either the R or S configuration in the compounds of formula 1A2 and formula 1B2; and

the carbon atoms at positions 13, 14, and 17 may independently have either the R or S configuration in the compounds of formula 1C2.

In some such embodiments, each of Y^1, Y^2, and Y^3 is H. In some embodiments

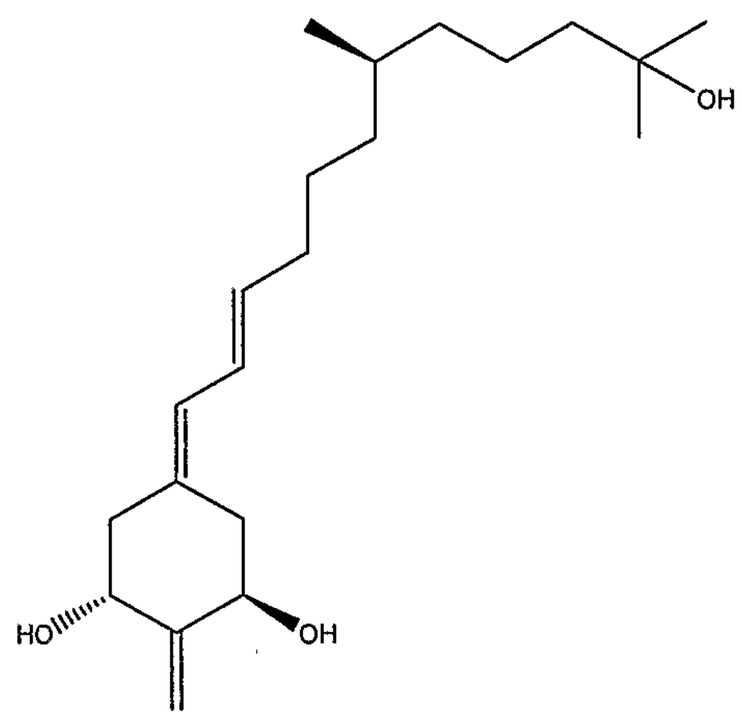
each of X^1, X^2, X^3, and X^4 is independently selected from H or a methyl group.

[0014] In some embodiments, the invention provides compounds of formula 1C having the formula 1C3 as shown below:



1C3

wherein Y^1, Y^2, and Y^3 are independently selected from H or hydroxy-protecting groups. In some such embodiments, Y^1, Y^2, and Y^3 are all hydroxy protecting groups such as silyl groups. In some such embodiments, Y^1 and Y^2 are t-butyldimethylsilyl groups and Y^3 is a trialkylsilyl group such as a triethylsilyl group. In other embodiments, Y^1, Y^2, and Y^3 are all H such that the compound has the formula 1C4 as shown below:



1C4

[0015] In some embodiments, the compounds of any of the embodiments may be present in a purified form. In other embodiments, the compounds in a

composition may be present as a mixture. In some embodiments, the mixture includes a first compound of the invention and a second compound of the invention, and the ratio of the first compound to the second compound ranges from 50:50 to 99.9:0.1. In some such embodiments, the ratio of the first compound to the second compound ranges from 70:30 to 99.9:0.1, from 80:20 to 99.9:0.1, from 90:10 to 99.9:0.1, or from 95:5 to 99.9:0.1.

[0016] The above compounds were/are tested and found to exhibit desired, and highly advantageous, patterns of biological activity with respect to intestinal calcium transport activity, ability to mobilize calcium from bone, and ability to bind to the vitamin D receptor. The compounds may thus find use in treating cancer, skin conditions, and autoimmune disorders. Therefore, in some embodiments, these compounds or pharmaceutical formulations that include one or more compounds of the invention may be employed as therapeutic agents for the treatment of diseases or disorders such as cancer, autoimmune diseases, skin conditions, and secondary hyperparathyroidism. In some embodiments, the treatment may be transdermal, oral, or parenteral.

[0017] The compounds of the invention may also be especially suited for treatment and prophylaxis of human disorders which are characterized by an imbalance in the immune system, e.g., in autoimmune diseases, including multiple sclerosis, diabetes mellitus, host versus graft reaction, and rejection of transplants; and additionally, for the treatment of inflammatory diseases, such as rheumatoid arthritis and asthma, as well as the improvement of bone fracture healing and improved bone grafts. Acne, alopecia, skin conditions such as dry skin (lack of dermal hydration), undue skin slackness (insufficient skin firmness), insufficient sebum secretion and wrinkles, and hypertension are other conditions which may be treated with the compounds of the invention.

[0018] The compounds described herein were also tested and found to moderate cell differentiation activity. Thus, these compounds may also be used as therapeutic agents for the treatment of psoriasis and/or as anti-cancer agents, especially against leukemia, colon cancer, breast cancer and prostate cancer. In some embodiments, the compounds and compositions of the invention are used

to treat a biological condition selected from psoriasis; leukemia; colon cancer; breast cancer; prostate cancer; multiple sclerosis; lupus; diabetes mellitus; host versus graft reaction; rejection of organ transplants; an inflammatory disease selected from rheumatoid arthritis, asthma, eczema, or inflammatory bowel diseases; a skin condition selected from wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration, or insufficient sebum secretion; or secondary hyperparathyroidism.

[0019] In some embodiments of the methods of the invention, the compound or pharmaceutical composition is administered orally, rectally, parenterally, transdermally, or topically. In other embodiments, the compound or pharmaceutical formulations is administered in an aerosol which may be accomplished using an inhaler or a nebulizer.

[0020] The compounds of the invention may be used to prepare pharmaceutical formulations or medicaments that include a compound or a mixture of the compounds of the invention in combination with a pharmaceutically acceptable carrier. Such pharmaceutical formulations and medicaments may be 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. "Subject," as used herein, refers to any animal that may experience the beneficial effects of a compound of the invention upon administration of the compound to the animal. 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. In some embodiments, the compounds are used to prepare an aerosol which may include a glycol compound such as propylene glycol.

[0021] The compounds may be present in a composition to treat the

above-noted diseases and disorders in an amount from about 0.01 µg/gm to about 1 mg/gm of the composition, preferably from about 0.1 µg/gm to about 500 µg/gm of the composition, and may be administered topically, transdermally, orally, rectally, or parenterally in dosages of from about 0.01 µg/day to about 1 mg/day, preferably from about 0.1 µg/day to about 500 µg/day.

[0022] Further objects, features and advantages of the invention will be apparent from the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] Figures 1-4 illustrate various biological activities of the compound of formula 1C4 (referred to as “Des-C,D” 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).

[0024] Figure 1 is a graph comparing the relative activity of Des-C,D 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.

[0025] Figure 2 is a graph comparing the percent HL-60 cell differentiation as a function of the concentration of Des-C,D with that of $1,25(OH)_2D_3$.

[0026] Figure 3 is a graph comparing the *in vitro* transcription activity of Des-C,D with that of $1,25(OH)_2D_3$.

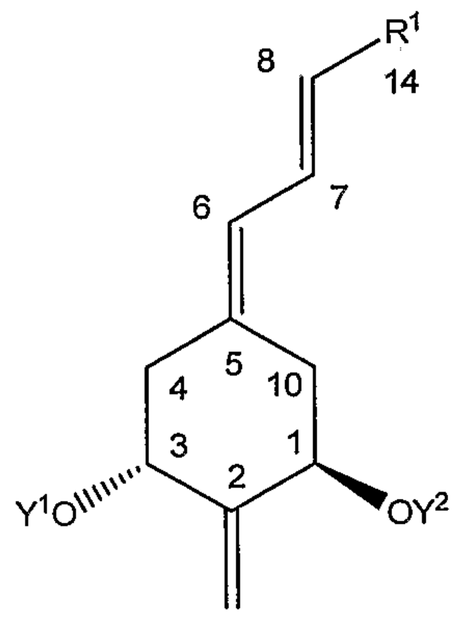
[0027] Figure 4 is a bar graph comparing the bone calcium mobilization activity of Des-C,D with that of $1,25(OH)_2D_3$.

DETAILED DESCRIPTION OF THE INVENTION

[0028] Generally, the invention provides compounds that are analogs of 1α,25-dihydroxy-19-norvitamin D_3 that lack the C and D rings (*des*-C,D compounds) such as *des*-C,D analogs of 2-methylene-1α,25-dihydroxy-19-norvitamin D_3, pharmaceutical formulations that include the compounds, and the

use of these compounds or mixtures thereof in the preparation of medicaments for use in treating various disease states.

[0029] In one aspect, the invention provides a 2-methylene-19-norvitamin D_3 analog that lacks the C and D rings (a *des*-C,D-2-methylene-19-norvitamin D_3 analog) such as *des*-C,D-2-methylene-1α,25-dihydroxy-19-norvitamin D_3. By 2-methylene-19-norvitamin D_3 analog is meant a compound that is an agonist of the vitamin D receptor and at least comprises the 2-methylene-19-norvitamin D_3 A ring. In some embodiments, the invention provides compounds of formula 1 having the structure shown below:



1

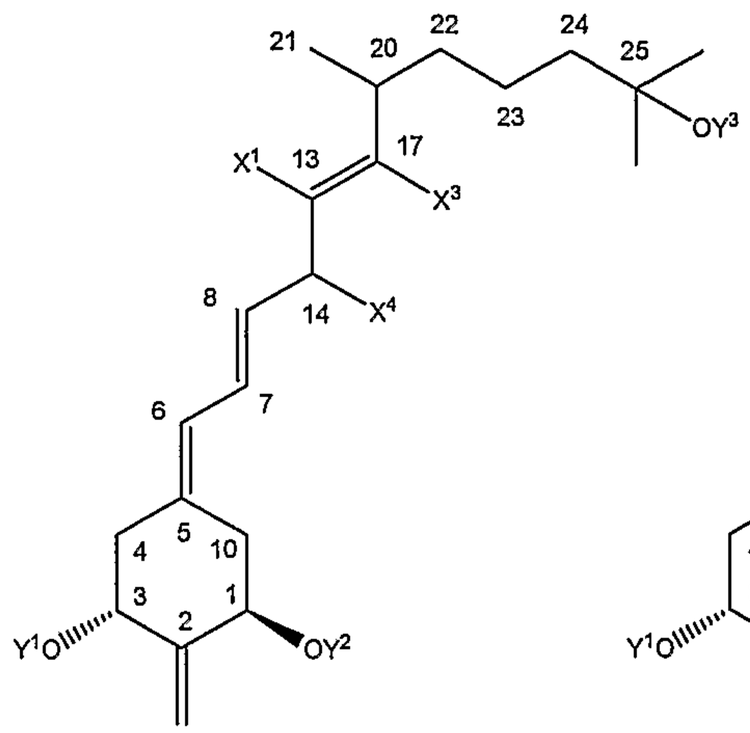
wherein,

R^1 is a straight or branched chain alkyl or alkylene group having from 8 to 27 carbons and bearing an OY^3 group; and

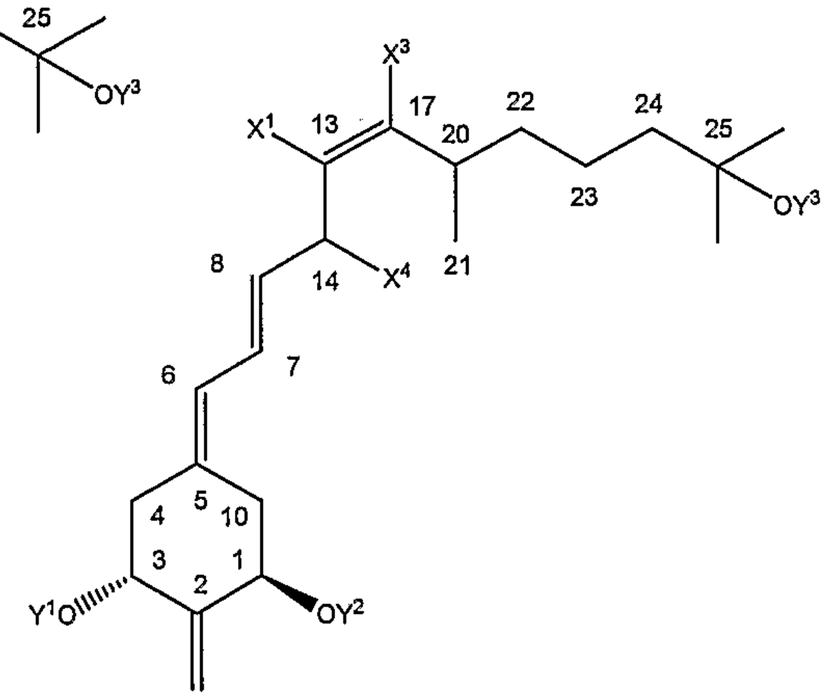
Y^1, Y^2 and Y^3 are independently selected from H or hydroxy-protecting groups.

[0030] In some embodiments of the compound of formula 1, R^1 is a straight or branched chain alkyl or alkylene group having from 8 to 20 carbons and bearing an OY^3 group. In some such embodiments, the alkyl or alkylene group has 8 to 11, 8 to 12 or 8 to 15 carbons.

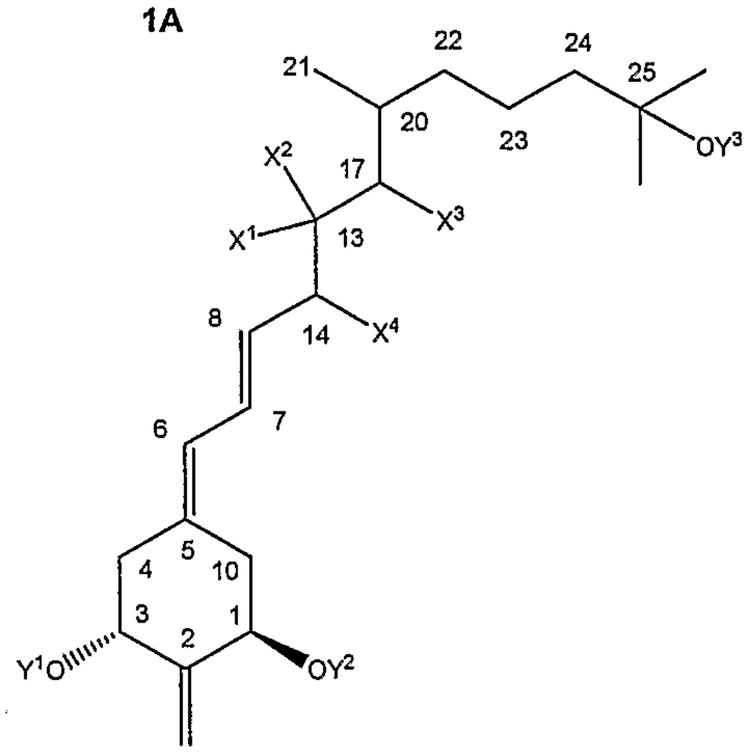
[0031] In some embodiments, the invention provides compounds having the formula 1A, formula 1B, formula 1C, or a mixture thereof as shown below:



1A



1B



1C

wherein,

X^1, X^2, X^3, and X^4 are independently selected from H and straight and branched chain alkyl groups having from 1 to 4 carbon atoms including methyl, ethyl, propyl, isopropyl, and butyl groups;

Y^1, Y^2, and Y^3 are independently selected from H or hydroxy-protecting groups;

the carbon atoms at positions 14 and 20 may independently have either the R or S configuration in the compounds of formula 1A and formula 1B; and

the carbon atoms at positions 13, 14, 17, and 20 may independently have either the R or S configuration in the compounds of formula 1C.

[0032] As used herein, the phrase "straight and branched chain alkyl groups" refers to groups that include carbon and hydrogen atoms that only include carbon-carbon single bonds and carbon-hydrogen single bonds. Thus,

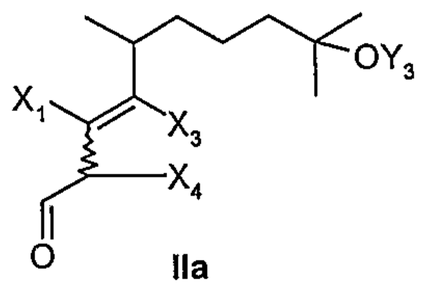
the phrase “straight and branched chain alkyl groups” having 1 to 4 carbon atoms includes alkyl groups such as methyl, ethyl, propyl, i-propyl, and butyl groups.

[0033] 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 groups 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 may be 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.

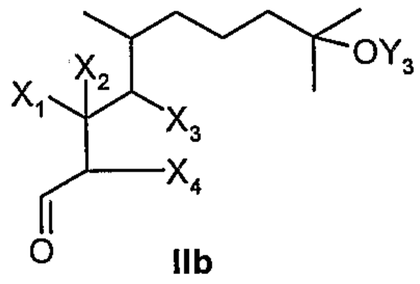
[0034] A “protected hydroxy” group is a hydroxy group derivatized or protected by any of the above groups commonly used for the temporary or permanent protection of hydroxy functional groups, e.g., the silyl, alkoxyalkyl, acyl or alkoxycarbonyl groups, as previously defined.

[0035] The preparation of *des*-C,D-19-nor-vitamin D compounds of formula 1A, 1B, and 1C can be accomplished using either of two general

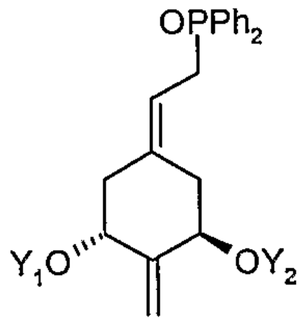
methods. In the first method, the Wittig-Horner coupling of an aldehyde (IIa or IIb) with an allylic phosphine oxide (III) is employed. In an alternative procedure, Julia olefination is performed and includes coupling of an unsaturated sulfone (IVa or IVb), easily prepared from the aldehydes IIa or IIb, with the cyclohexanone derivative V. Compounds IIA, IIB, III, IVa, IVb, and V are shown below where the variables have the same meanings as defined above with respect to the compounds of formula 1A, 1B, and 1C, and the wavy lines indicate that both cis and trans isomers are represented in formula IIA and IVA:



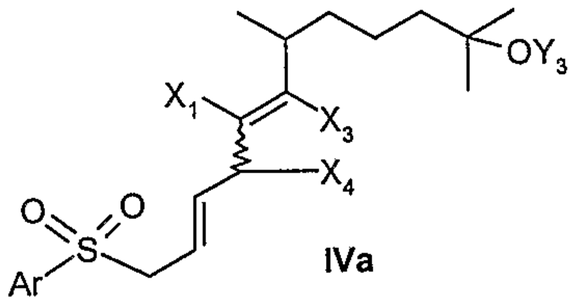
IIa



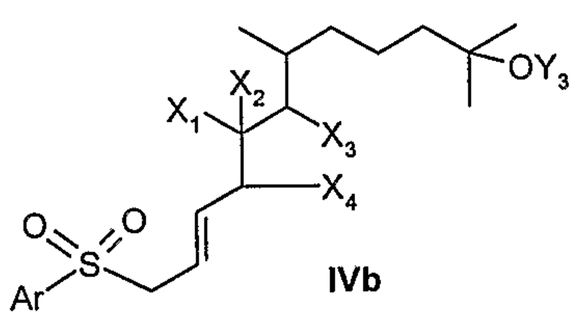
IIb



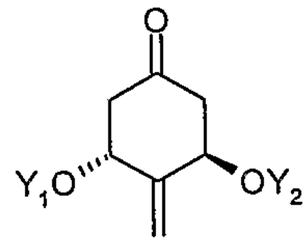
III



IVa



IVb



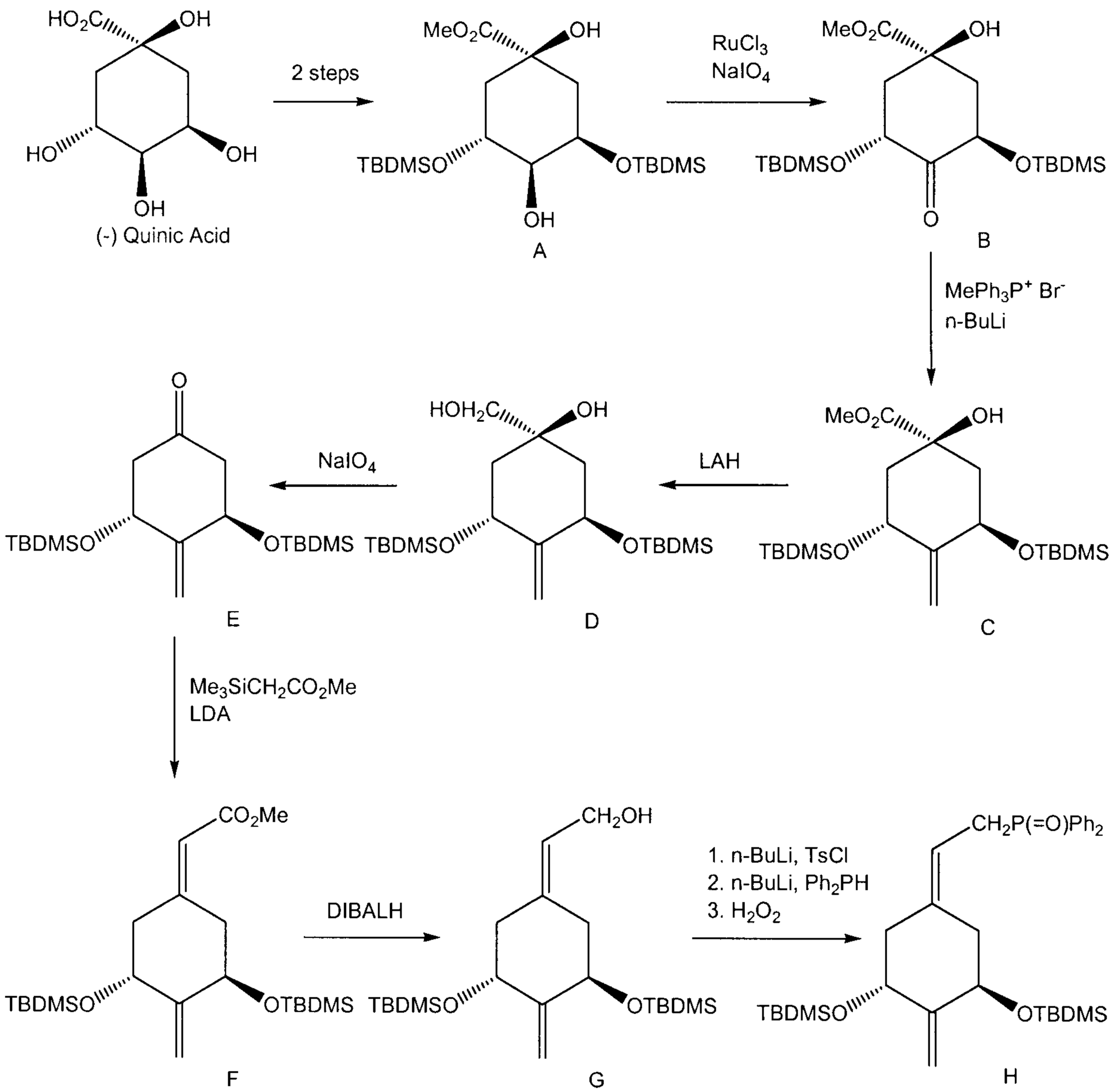
V

In the structures shown above, Ar represents an aromatic group such as a phenyl, a substituted phenyl, a 2-phenyltetrazolyl, a 2-benzothiazolyl group, and other aromatic groups that are suitable for the Julia olefination process. Those skilled in the art will recognize that any functionalities in the Ar group that might be sensitive to, or interfere with, the condensation reaction, should be avoided. In phosphine oxide **III**, and cyclohexanone **V**, Y_1 and Y_2 are preferably hydroxy-protecting groups such as silyl protecting groups. The t-butyldimethylsilyl (TBDMS) group is an example of a particularly useful hydroxy-protecting group. The general procedures described above represent an application of the convergent synthesis concept, which has been applied effectively for the preparation of vitamin D compounds (e.g. Kittaka *et al., Synlett, 8*, 1175 (2003), and *J. Org. Chem., 68*, 7407 (2003).

[0036] Phosphine oxide **III** and cyclohexanone **V** are convenient reagents that can be used to prepare a large number of 19-nor vitamin D compounds including *des*-C,D analogs. These compounds may be 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 1 shows the general procedure for synthesizing phosphine oxide **III** (See Scheme 1, compound H) and cyclohexanone **V** (See Scheme 1, compound D) as outlined in U.S. Patent No. 5,843,928. Modification of the method shown in Scheme 1 may be 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 may be 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 1. Alternatively, an alkene analogous to compound C of Scheme 1 may be 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). Therefore, the procedure for forming the phosphine oxide shown in Scheme 1 may be used to prepare a wide variety of vitamin D analogs in addition to the compounds of the present invention.

[0037] Reference should be made to the following description as well as to Schemes 1, 2, and 3 for a detailed illustration of the preparation of compounds of formula 1A, 1B, and 1C and specifically 2-methylene-1α,25-dihydroxy-*des*-C,D-19-norvitamin D_3.

Scheme I



EXAMPLES

[0038] The synthesis and characteristics of various 19-nor vitamin D analogs is described in numerous United States patents including 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.

[0039] Melting points (uncorrected) were determined using a Thomas-Hoover capillary melting-point apparatus. Ultraviolet (UV) absorption spectra were recorded with a Perkin-Elmer Lambda 3B* UV-VIS spectrophotometer in ethanol. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded at 400 and 500 MHz using Bruker Instruments DMX-400 and DMX-500 Avance* console spectrometers in $CDCl_3$. ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 125 MHz with a Bruker Instruments DMX-500 Avance console spectrometer in $CDCl_3$. Chemical shifts (δ) are 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.

[0040] Schemes 1, 2, and 3 outline the synthetic procedures described below, in detail.

Preparation of 2-Methylene-1α,25-Dihydroxy-*des*-C,D-19-norvitamin D_3 analog 19

A. Protection of 3-Hydroxy Group of Ester 1 (Scheme 2)

(2*R*)-3-Benzyloxymethoxy-2-methyl-propionic acid methyl ester (2)

[0041] To a solution of *R*-(-)-methyl-3-hydroxy-2-methylpropionate **1** (4 mL, 4.26 g, 0.036 mol) in anhydrous CH_2Cl_2 (30 mL) was added *N,N*-diisopropylethylamine (11.8 mL, 8.75 g, 0.06 mol) at room temperature. The mixture was cooled to -78°C and benzyl chloromethyl ether (5.6 mL, 6.29 g, 0.04 mol) was added dropwise via cannula. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 16 hours. Tetrabutylammonium iodide (50 mg) and benzyl chloromethyl ether (2 mL, 3.15 g, 0.02 mol) were then added to the reaction mixture. The mixture was stirred at room temperature for 3 hours, poured into water, and extracted with methylene

*Trade-mark

chloride. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel using hexane/EtOAc (9:1) as an eluent to give product **2** (8.29 g, 97%) as a colorless oil.

[0042] **2**: $[\alpha]^{24}_D$ –3° (*c* 0.17, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.19 (3H, d, J = 7.1 Hz, CH-C<u>H</u>$_3$), 2.77 (1H, m, C<u>H</u>-CH_3), 3.64 (1H, dd, J = 9.4, 5.4 Hz, one of C<u>H</u>$_2$-CH), 3.70 (3H, s, CH_3O), 3.78 (1H, dd, J = 9.4, 7.8 Hz, one of C<u>H</u>$_2$-CH), 4.57 (2H, s, OCH_2O), 4.74 (2H, s, CH_2Ph), 7.29 (1H, m, Ar-H_{para}), 7.35 (4H, m, Ar-$H_{ortho,meta}$); ^{13}C NMR (125 MHz) δ 13.91 (CH_3), 39.99 (<u>C</u>H-CH_3), 51.70 (CH_3O), 69.22 and 69.60 (<u>C</u>H_2CH and CH_2-Ph), 94.50 (OCH_2O), 127.63, 127.84 and 128.33 ($Ar_{ortho,meta,para}$), 137.61 (Ar_{ipso}); MS (EI) m/z (relative intensity) no M^+, 207(M^+ - OCH_3, 2), 131 (34), 120 (64), 91 (100); HRMS (ESI) exact mass calculated for $C_{13}H_{18}O_4Na$ (M^+ + Na) 261.1103, measured 261.1110.

B. Reduction of Ester 2

(2*R*)-3-Benzyloxymethoxy-2-methyl-propan-1-ol (3)

[0043] A solution of ester **2** (0.5 g, 2.1 mmol) in anhydrous THF (4 mL) was added dropwise to a suspension of lithium aluminum hydride (0.16 g, 4.2 mmol) in anhydrous THF (10 mL) at 0°C. The cooling bath was removed, and the reaction was stirred at room temperature overnight, quenched with cold water, and extracted with EtOAc. The solvents were removed in vacuum and the crude oil was purified by silica gel chromatography using hexane/EtOAc (8:2) as an eluent to afford oily diol **3** (0.29 g, 66%).

[0044] **3**: $[\alpha]^{24}_D$ –3° (*c* 0.17, $CHCl_3$);); ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, d, J = 7.1 Hz, CH-<u>C</u>H_3), 2.02 (1H, m, C<u>H</u>-CH_3), 2.39 (1H, s, OH), 3.54 (1H, dd, J = 9.4, 7.6 Hz, one of C<u>H</u>$_2$-CH), 3.60 (d, J = 9.4 Hz, CH_2OH), 3.65 (1H, dd, J = 9.4, 4.8 Hz, one of C<u>H</u>$_2$-CH), 4.6 (2H, s, OCH_2O), 4.75 (2H, s, CH_2Ph), 7.30 (1H, m, Ar-H_{para}), 7.35 (4H, d, J = 4.3 Hz, Ar-$H_{ortho,meta}$); ^{13}C NMR (125 MHz) δ 13.61 (CH_3), 35.62 (<u>C</u>H-CH_3), 67.19 (CH_2OH), 69.58 (<u>C</u>H_2CH), 72.38 (CH_2-Ph), 94.79 (OCH_2O), 127.82, 127.90 and 128.49 ($Ar_{ortho,meta,para}$), 137.58 (Ar_{ipso}); MS

(EI) m/z (relative intensity) no M^+, 180 (8), 120 (100), 108 (95), 89 (72); HRMS (ESI) exact mass calculated for $C_{12}H_{18}O_3Na$ (M^+ + Na) 233.1154, measured 233.1158.

C. Tosylation of Hydroxy Compound 3

(*R*)-Toluene-4-sulfonic acid 3-benzyloxymethoxy-2-methyl-propyl ester (4)

[0045] To a mixture of diol **3** (29.2 mmol, 6.13 g), DMAP (0.82 mmol, 100 mg) and triethylamine (116.7 mmol, 16.2 mL, 11.8 g) in anhydrous CH_2Cl_2 (60 mL) was added tosyl chloride (37.9 mmol, 7.23 g) at 0°C. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. The mixture was then diluted with CH_2Cl_2 (100 mL) and was then washed with a saturated aqueous solution of $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a silica gel using hexane/EtOAc (7:3) as an eluent to give the oily tosylate **4** (10.2 g, 97%).

[0046] **4**: $[\alpha]^{24}_D$ –5° (*c* 0.15, $CHCl_3$); ^1H NMR (500 Hz, $CDCl_3$) δ 0.94 (3H, d, J = 7.1 Hz, CH-C<u>H</u>$_3$), 2.09 (1H, m, C<u>H</u>-CH_3), 2.42 (3H, s, CH_3Ph), 3.42 (1H, dd, J = 9.4, 6.6 Hz, one of C<u>H</u>$_2$-CH), 3.47 (1H, dd, J = 9.4, 5.1 Hz, one of C<u>H</u>$_2$-CH), 3.97 (1H, dd, J = 9.4, 5.8 Hz, one of C<u>H</u>$_2$-OTs), 4.03 (1H, dd, J = 9.4, 5.8 Hz, one of C<u>H</u>$_2$-OTs), 4.51 (2H, s, OCH_2O), 4.65 (2H, s, CH_2Ph), 7.30 (7H, br m, Ar-H), 7.78 (2H, d, J = 8.2 Hz, Ar-H_{ortho} from tosyl); ^{13}C NMR (125 MHz) δ 13.58 (CH_3), 21.60 (Ph-CH_3), 33.45 (<u>C</u>H-CH_3), 68.61 (<u>C</u>H_2CH), 69.27 (CH_2OTs), 71.96 (CH_2-Ph), 94.56 (OCH_2O), 127.68, 127.82, 128.36, 129.75, 132.6, 137.58 and 144.66 (Ar); MS (EI) m/z (relative intensity) no M^+, 257(M^+ - OCH_2Ph, 65), 245 (55), 227 (81), 86 (100); HRMS (ESI) exact mass calculated for $C_{19}H_{24}O_5SNa$ (M^+ + Na) 387.1242, measured 387.1252.

D. Reaction of Tosylate 4 with Grignard Reagent

(*S*)-1-Benzyloxymethoxy-2,6-dimethyl-hept-5-ene (5)

[0047] 4-Chloro-2-methyl-2-butane (15.5 mL, 14.4 g, 137.5 mmol) was

added dropwise to stirred magnesium turnings (6.75 g, 225 mmol) in anhydrous THF (465 mL) under argon at 0°C. The stirring was continued 0°C for 1 hour. The cooling bath was removed, and the mixture was stirred at room temperature for an additional 1.5 hours. The mixture was then cooled to -78°C and the formed Grignard reagent was added via cannula to a solution of tosylate **4** (10 g, 27.5 mmol) in anhydrous THF (70 mL). Li_2CuCl_4 (160mL) [previously prepared from LiCl (1.36 g, 32.1 mmol) and $CuCl_2$ (2.17 g, 16.1 mmol)] was then added to the reaction mixture. The cooling bath was removed, and the reaction was stirred at room temperature for 17 hours. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with NH_4Cl and $NaHCO_3$, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel using hexane/EtOAc (7:3) as an eluent to give oily product **5** (5.65 g, 78%).

[0048] **5**: $[\alpha]^{24}_D$ +2° (*c* 0.24, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$) δ 0.94 (3H, d, J = 6.6 Hz, CH-C<u>H</u>$_3$), 1.18 and 1.46 (1H and 1H, each m), 1.60 and 1.68 [3H and 3H, each s, =C(CH_3)$_2$], 1.87 (1H, m, C<u>H</u>-CH_3), 2.05 (2H, m, =C<u>H</u>$_2$), 3.37 (1H, dd, J = 9.4, 6.8 Hz, one of C<u>H</u>$_2$-CH), 3.44 (1H, dd, J = 9.4, 5.8 Hz, one of C<u>H</u>$_2$-CH), 4.60 (2H, s, OCH_2O), 4.76 (2H, s, CH_2Ph), 5.10 (1H, br t, J ~ 7 Hz, CH=C), 7.30 (1H, m, Ar-H_{para}), 7.34 (4H, m, Ar-$H_{ortho,meta}$); ^{13}C NMR (125 MHz) δ 16.96 (CH-<u>C</u>H_3), 17.53 (one of <u>C</u>H_3C=), 25.60 (one of <u>C</u>H_3C=), 32.92 (<u>C</u>H-CH_3), 33.57 (CH_2<u>C</u>H_2CH), 69.27 (<u>C</u>H_2-Ph), 73.37 (<u>C</u>H_2CH), 94.64 (OCH_2O), 124.49 (<u>C</u>-CH_3), 127.52, 127.77, 128.28, ($Ar_{ortho,meta,para}$), 137.95 [=<u>C</u>(CH_3)$_2$]; MS (EI) m/z (relative intensity) 262 (M^+, 22), 232.2 (65), 154.1 (100); HRMS (ESI) exact mass calculated for $C_{17}H_{26}O_2Na$ (M^+ + Na) 285.1830, measured 285.1837.

E. Epoxidation of Olefin 5

(2*S*)-1-Benzyloxymethoxy-2,6-dimethyl-5,6-epoxy-heptane (6)

[0049] Olefin **5** (3.2 g, 12.2 mmol) was dissolved in anhydrous CH_2Cl_2 (60 mL), and $NaHCO_3$ (1.6 g, 18.4 mmol) was added. Then, 3-chloroperoxybenzoic acid (60%, 12.8 g, 36.6 mmol) was added at room temperature with stirring. The stirring was continued for 24 hours, and the mixture was diluted with ether, and

shaken with water and 2M NaOH. The organic layer was washed with water and saturated NH_4Cl, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel using hexane/EtOAc (9:1) as an eluent to give the oily product **6** (2.5 g, 74%).

[0050] **6**: $[\alpha]^{24}_D$ –1.7° (*c* 0.88, $CHCl_3$); ^1H NMR (500 Hz, $CDCl_3$) δ 0.96 (3H, d, J = 6.7 Hz, CH-C<u>H</u>$_3$), 1.25 (1H, m), 1.27 and 1.31 [3H and 3H, each s, $C(CH_3)_2$], 1.5 – 1.7 (3H, br m), 1.79 (1H, m, C<u>H</u>-CH_3), 2.73 (1H, m, CH_2C<u>H</u>O), 3.45 (2H, br m, C<u>H</u>$_2$-CH), 4.60 (2H, s, OCH_2O), 4.76 (2H, s, CH_2Ph), 7.29 (1H, m, Ar-H_{para}), 7.34 (4H, d, J = 4.3 Hz, Ar-$H_{ortho,meta}$).

F. Reduction of Epoxide 6

***(S)*-7-Benzyloxymethoxy-2,6-dimethyl-heptan-2-ol (7)**

[0051] To a solution of the epoxide **6** (2.5 g, 9 mmol) in anhydrous ether (75 mL) at 0°C was added lithium aluminum hydride (1.7 g, 67.5 mmol). The cooling bath was removed and the reaction was stirred at room temperature overnight. The reaction was then quenched with cold water and aqueous NH_4Cl, and extracted with CH_2Cl_2. The solvents were removed under reduced pressure and the crude oil was chromatographed on a silica gel using hexane/EtOAc (9:1) as an eluent to give an oily alcohol **7** (2 g, 80%).

[0052] **7:** $[\alpha]^{24}_D$ -4° (*c* 0.19, $CHCl_3$); ^1H NMR (200 Hz, $CDCl_3$) δ 0.94 (3H, d, J = 6.5 Hz, CH-C<u>H</u>$_3$), 1.20 [6H, s, $(CH_3)_2$COH], 1.75 (1H, m, C<u>H</u>-CH_3), 3.38 (1H, dd, J = 10.8, 6.6 Hz, one of C<u>H</u>$_2$-CH), 3.46 (1H, dd, J = 10.8, 6.0 Hz, one of C<u>H</u>$_2$-CH), 4.60 (2H, s, OCH_2O), 4.76 (2H, s, CH_2Ph), ca. 7.3 (5H, m, Ar-H); HRMS (ESI) exact mass calculated for $C_{17}H_{28}O_3Na$ (M^+ + Na) 303.1936, measured 303.1947.

G. Removal of BOM Protecting Group

2,6-Dimethyl-heptane-1,6-diol (8)

[0053] To a solution of an alcohol **7** (1.8 g, 0.01 mol) in ethyl acetate (20

mL) was added Pd/C (10 %, 100 mg) at room temperature. The reaction mixture was stirred for 5 days and Pd/C (150 mg) was added 3 times per day. The reaction was then filtered, and the solvent was evaporated under reduced pressure. The crude oil was chromatographed on silica gel using hexane/EtOAc (1:1) as an eluent to give an oily diol **8** (0.95 g, 92%).

[0054] **8**: $[\alpha]^{24}_D$ +11° (*c* 1.28, $CHCl_3$); ^1H NMR (200 Hz, $CDCl_3$) δ 0.93 (3H, d, J = 6.6 Hz, CH-C<u>H</u>$_3$), 1.20 [6H, s, $(CH_3)_2$COH], 1.65 (1H, m, C<u>H</u>-CH_3), 3.45 (2H, br m, C<u>H</u>$_2$-CH); ^{13}C NMR (50 MHz) δ 16.63 (CH-<u>C</u>H_3), 21.64 (CH_2-<u>C</u>H_2-CH_2), 29.19 [C(<u>C</u>H_3)], 29.29 [C(<u>C</u>H_3)], 33.62 (CH-<u>C</u>H_2-CH_2), 35.68 (<u>C</u>H-CH_3), 44.03 (<u>C</u>H_2COH), 68.19 (CH_2OH), 71.16 [<u>C</u>$(CH_3)_2$]; MS (ES) 183 (M^+ + Na); HRMS (ESI) exact mass calculated for $C_9H_{20}O_2Na$ (M^+ + Na) 183.1361, measured 183.1351.

H. Oxidation of Diol 8

(*S*)-6-Hydroxy-2,6-dimethyl-heptanal (9)

[0055] Pyridinium dichromate (1.5 g, 3.75 mmol) was added to a stirred solution of diol **8** (110 mg, 0.69 mmol) and pyridinium *p*–toluenesulfonate (33 mg, 0.11 mmol) in CH_2Cl_2 (5 mL). The resulting suspension was stirred for 4 hours at room temperature under argon. The reaction was then filtered through Celite and solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel using hexane/EtOAc (9:1) as an eluent to give an oily aldehyde **9** (65 mg, 60%).

[0056] **9**: $[\alpha]^{24}_D$ -10.5° (*c* 1.1, $CHCl_3$); ^1H NMR (400 Hz, $CDCl_3$) δ 1.06 (3H, d, J = 7.0 Hz, CH-C<u>H</u>$_3$), 1.21 [6H, s, $(CH_3)_2$COH], 2.37 (1H, m, C<u>H</u>-CH_3), 9.62 (1 H, d, J = 1.9 Hz, CHO); ^{13}C NMR (25 MHz) δ 13.33 (CH-<u>C</u>H_3), 21.70 (CH_2-<u>C</u>H_2-CH_2), 29.21 [C(<u>C</u>$H_3)_2$], 30.89 (CH-<u>C</u>H_2), 43.70 (<u>C</u>H_2COH), 46.30 (<u>C</u>HCH_3), 71.16 [<u>C</u>$(CH_3)_2$], 205.25 (CHO).

I. Silylation of Hydroxy Aldehyde 9

(*S*)-2,6-Dimethyl-6-triethylsilanyloxy-heptanal (10)

[0057] To a solution of aldehyde **9** (93.4 mg, 0.6 mmol) and 2,6-lutidine (170 µL, 1.5 mmol) in anhydrous CH_2Cl_2 (3.7 mL) was added dropwise Et_3SiOTf (161 µL, 0.72 mmol) at 0°C under argon. The solution was stirred at 10°C for 3 hours and then at room temperature for 30 minutes. The mixture was quenched with cold water and extracted with CH_2Cl_2. The solvent was removed under reduced pressure, and the residue was chromatographed on silica Sep-Pak* cartridge using hexane/EtOAc (99.7:0.3) as an eluent to give an oily aldehyde **10** (130 mg, 81%).

[0058] **10**: $[\alpha]^{24}_D$ + 4.2° (*c* 1.75, $CHCl_3$); ^1H NMR (500 Hz, $CDCl_3$) δ 0.56 (6H, q, J = 7.8 Hz, 3 x $SiCH_2$), 0.94 (9H, t, J = 7.8 Hz, 3 x $SiCH_2C\underline{H}_3$), 1.10 (3H, d, J = 6.8 Hz, CH-$C\underline{H}_3$), 1.19 [6H, s, $(CH_3)_2CO$], 2.37 (1H, d sext, J = 1.9, 6.8 Hz, CH-CHO), 9.62 (1H, d, J = 1.95 Hz, CHO).

J. Wittig Reaction of Aledhyde 10

(*Z*)-(*S*)-1-(*t*-Butyl-dimethyl-silanyloxy)-5,9-dimethyl-9-triethylsilanyloxy-dec-3-ene (12)

[0059] To a solution of a phosphonium bromide **11** (275 mg, 0.54 mmol) in anhydrous THF (12 mL) was added dropwise *n*-BuLi (2 M in cyclohexane, 270 µL, 0.54 mmol) at -20°C. After 15 minutes of stirring at -20°C, the reaction was cooled to -50°C and 2/3 of the orange solution of the formed Wittig reagent was added via cannula to the stirred solution of aldehyde **10** (50 mg, 0.18 mmol) in anhydrous THF (2 mL). After 1 hour of stirring at -50°C, brine and 1M HCl were added, and the mixture was extracted with EtOAc. The organic layer was washed with water and evaporated. The residue was chromatographed on silica Sep-Pak cartridge eluted with hexane/EtOAc (98.5:1.5) to give an oily compound **12** (59.3 mg, 75%).

*Trade-mark

[0060] **12**: $[\alpha]^{24}_D$ -5.5° (*c* 0.48, $CHCl_3$); ^1H NMR (500 Hz, $CDCl_3$) δ 0.058 (6H, s, 2 x CH_3Si), 0.55 (6H, q, J = 7.8 Hz, 3 x $SiCH_2$), 0.89 [9H, s, $(C\underline{H}_3)_3C$], 0.93 (3H, d, J = 6.8 Hz, $C\underline{H}_3CH$), 0.94 (9H, t, J = 7.8 Hz, 3 x $SiCH_2C\underline{H}_3$), 2.27 (2H, m, $C\underline{H}_2CH$=), 2.42 (1H, m, $C\underline{H}$-CH_3), 3.59 (2H, m, OCH_2), 5.20 (dd, J = 10.8, 9.7 Hz, =$C\underline{H}$-$CHCH_3$), 5.29 (1H, dt, J = 10.8, 7.4 Hz, $CH_2C\underline{H}$=CH); ^{13}C NMR (125 MHz) δ -5.28 [$SiCH_3$], 6.75 ($SiCH_2$), 7.10 ($\underline{C}H_3CH_2Si$), 18.37 [$Si\underline{C}(CH_3)_3$], 21.29 [$SiC(\underline{C}H_3)_3$], 22.32 (CH_2-$\underline{C}H_2$-CH_2), 25.95 (CH-$\underline{C}H_3$), 29.80 and 29.89 [$C(\underline{C}H_3)_2$], 31.41 ($\underline{C}H_2CH$=), 31.90 ($\underline{C}H$-CH_3), 38.06 (CH-$\underline{C}H_2$-CH_2), 45.20 ($\underline{C}H_2CO$), 63.23 (CH_2O), 73.23 [$\underline{C}(CH_3)_2$], 123.82 (CH_2-$\underline{C}H$=), 138.34 (=$\underline{C}HCH$); MS (ES) 451 (M^+ + Na); HRMS (ES) exact mass calculated for $C_{24}H_{52}O_2Si_2Na$ (M^+ + Na) 451.3404, measured 451.3414.

K. Hydrolysis of Silyl Protecting Groups in Diether 12 (Scheme 3)

(3*Z*)-(5*S*)-5,9-Dimethyl-dec-3-ene-1,9-diol (13)

[0061] To a stirred solution of compound **12** (201 mg, 0.4 mmol) in anhydrous CH_2Cl_2 (10 mL) was added hydrofluoric acid (48%, 6 mL). After 40 minutes of stirring at room temperature, water was added, and the organic layer was separated, washed with water and $NaHCO_3$, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica Sep-Pak cartridge using hexane/EtOAc (6:4) as an eluent to give an oily diol **13** (76.4 mg, 92%).

[0062] **13**: ^1H NMR (500 Hz, $CDCl_3$) δ 0.95 (3H, d, J = 6.7 Hz, $C\underline{H}_3CH$), 1.19 and 1.20 [3H and 3H, each s, $C(CH_3)_2$], 2.33 (2H, m, $C\underline{H}_2CH$=), 2.48 (1H, br m, $C\underline{H}$-CH_3), 3.64 (2H, t, J = 6.4 Hz, $C\underline{H}_2OH$), 5.31 (2H, m, CH=CH); ^{13}C NMR (50 MHz) δ 21.63 (CH-$\underline{C}H_3$), 22.26 (CH_2-$\underline{C}H_2$-CH_2), 29.25 and 29.60 [$C(\underline{C}H_3)_3$], 31.27 ($\underline{C}H_2CH$=), 31.87 ($\underline{C}H$-CH_3), 37.96 (CH-$\underline{C}H_2$-CH_2), 44.00 ($\underline{C}H_2CO$), 62.55 (CH_2OH), 71.29 [$\underline{C}(CH_3)_2$], 124.09 (CH_2-$\underline{C}H$=), 139.70 (=$\underline{C}HCH$).

L. Hydrogenation of Unsaturated Diol 13

(5*R*)-5,9-Dimethyl-decane-1,9-diol (14)

[0063] To a solution of diol **13** (55 mg, 0.27 mmol) in ethyl acetate (10 mL) was added Pd/C (10%, 50 mg). The reaction mixture was stirred for 18 hours under a continuous stream of hydrogen at room temperature. The mixture was then filtered, and the solvent was evaporated under reduced pressure. The crude oily product was chromatographed on silica Sep-Pak cartridge eluted with hexane/EtOAc (8:2) to give an oily diol **14** (55 mg, 45%).

[0064] **14**: $[\alpha]^{24}_{D}$ -5.9° (*c* 0.27, $CHCl_3$), ^{1}H NMR (200 Hz, $CDCl_3$) δ 0.87 (3H, d, J = 6.4 Hz, CH-C<u>H</u>$_3$), 1.21 [6H, s, C$(CH_3)_2$], 1.56 (1H, br m, C<u>H</u>-CH_3), 3.64 (2H, t, J = 6.4 Hz, C<u>H</u>$_2$OH); ^{13}C NMR (50 MHz) δ 19.61 (CH-H_3), 21.75 (CH_2), 23.22 (CH_2), 29.24 and 29.29 [C(<u>C</u>$H_3)_3$], 32.75 (<u>C</u>H-CH_3), 33.10 (CH_2), 36.76 (CH_2), 37.48 (CH_2), 44.22 (<u>C</u>H_2CO), 63.07 (CH_2OH), 71.11 [<u>C</u>$(CH_3)_2$]; MS (ES) 225 (M^+ + Na); HRMS (ES) exact mass calculated for $C_{12}H_{24}O_2Na$ (M^+ + Na) 225.1831, measured 225.1823.

M. Oxidation of Diol 14

9-Hydroxy-5,9-dimethyl-decanal (15)

[0065] To a stirred solution of diol **14** (25 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (3.5 mL) was added Dess-Martin reagent (73 mg, 0.15 mmol) at room temperature. The reaction was stirred at room temperature for 1.5 hours. Then, an aqueous solution of sodium thiosulfate (6 mL) and saturated $NaHCO_3$ (6 mL) were added. The reaction was extracted with CH_2Cl_2, solvents were removed under reduced pressure, and the crude oil was purified on silica Sep-Pak using hexane/EtOAc (7:3) as an eluent to give an oily aldehyde **15** (16.5 mg, 67%).

[0066] **15**: ^{1}H NMR (200 Hz, $CDCl_3$) δ 0.88 (3H, d, J = 6.4 Hz, CH-C<u>H</u>$_3$), 1.21 [6H, s, C$(CH_3)_2$], 2.41 (2H, dt, J = 1.7, 7.3 Hz, C<u>H</u>$_2$CHO), 9.77 (1H, t, J = 1.7 Hz, CHO).

N. Silylation of Hydroxy Aldehyde 15

5,9-Dimethyl-9-triethylsilanyloxy-decanal (16)

[0067] To a solution of aldehyde **15** (16.5 mg, 82.5 μmol) and 2,6-lutidine (24 μL, 206 μmol) in anhydrous CH_2Cl_2 (1.1 mL) was added dropwise Et_3SiOTf (42 μL, 165 μmol) at -78°C. The mixture was stirred for 2 hours at -78°C and for one additional hour at -50°C. Water and CH_2Cl_2 were added, the organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica Sep-Pak cartridge using hexane/EtOAc (99.7:0.3) as an eluent to give oily aldehyde **16** (22 mg, 85%). An analytical sample was obtained using HPLC (10 mm x 25 cm Zorbax-Sil* column, 4 mL/min) with a hexane/EtOAc (98:2) solvent system. Analytically pure aldehyde **16** was collected at R_V = 33 mL.

[0068] **16**: ^{1}H NMR (500 Hz, $CDCl_3$) δ 0.55 (6H, q, J = 7.9 Hz, 3 x $SiC\underline{H}_2CH_3$), 0.88 (3H, d, J = 6.4 Hz, CH-$C\underline{H}_3$), 0.94 (9H, t, J = 7.9 Hz, 3 x $SiCH_2C\underline{H}_3$), 1.19 [6H, s, $C(CH_3)_2$], 2.41 (2H, m, $C\underline{H}_2CHO$), 9.77 (1H, t, J = 1.8 Hz, CHO).

O. Wittig-Horner Reaction of Aldehyde 16

(1*R*,3*R*,7'*R*)-1,3-Bis-(tert-butyl-dimethyl-silanoxy)-5-(7',11'-dimethyl-11'-triethylsilanyloxy-dodec-2'-enylidene)-2-methylene-cyclohexane (18)

[0069] To a solution of phosphine oxide **17** (45.7 mg, 78.5 μmol) in anhydrous THF (0.6 mL) at -78°C was slowly added *n*-BuLi (51 μL, 81.8 μmol) under argon with stirring. The solution turned deep orange upon addition. The stirring was continued for 20 minutes at -78°C and then a precooled solution of aldehyde **16** (22 mg, 70 μmol) in anhydrous THF (100 μL) was slowly added. The mixture was stirred for 3 hours at -78°C and at 6°C for 16 hours. EtOAc, saturated $NaHCO_3$ and brine were then added to the reaction vessel. The organic layer was washed with water, dried, and evaporated under reduced pressure. The residue was dissolved in hexane and applied on silica Sep-Pak

*Trade-mark

cartridge using hexane/EtOAc (99.8:0.2) as an eluent to give the crude protected vitamin **18**. The product was then purified by HPLC (10 mm x 25 cm Zorbax-Sil column, 4 mL/min) using a hexane/EtOAc (99.9:0.1) solvent system. Analytically pure vitamin D compound **18** (21.2 mg, 45%) was collected at R_V = 18 mL.

[0070] **18**: UV (hexane) λ_{max} 235.0 (ε 15 900), 242.0 (ε 24 800), 250.0 (ε 22 600) nm; ^{1}H NMR (500 Hz, $CDCl_3$) δ 0.04, 0.05, 0.07 and 0.08 (each 3H, each s, 4 x $SiCH_3$), 0.57 (6H, q, J = 7.9 Hz, 3 x $SiC\underline{H}_2CH_3$), 0.86 (3H, d, J = 7.4 Hz, CH-$C\underline{H}_3$), 0.87 and 0.90 [9H and 9H, each s, 2 x $(CH_3)_3CSi$], 0.95 (9H, t, J = 7.9 Hz, 3 x $SiCH_2C\underline{H}_3$), 1.19 [6H, s, $C(CH_3)_2$], 2.07 (2H, m, 4'-H_2), 2.15 (1H, dd, J = 12.5, 8.1 Hz), 2.35 – 2.5 (3H, br m), 4.43 (2H, m, 1- and 3-H), 4.94 and 4.95 (1H and 1H, each s, $C=CH_2$); 5.63 (1H, dt, J = 15.0, 6.9 Hz, 3'-H), 5.90 (1H, d, J = 10.9 Hz, 1'-H), 6.24 (1H, dd, J = 15.0, 10.9 Hz, 2'-H); MS (EI) m/z (relative intensity) 678 (M^+, 10), 649 (M^+ - Et, 5), 621 (M^+ - tBu, 12), 546 (12), 73 (100); HRMS (ESI) exact mass calculated for $C_{39}H_{78}O_3Si_3$ 678.5259, measured 678.5272.

P. Removal of Protecting Groups of 18

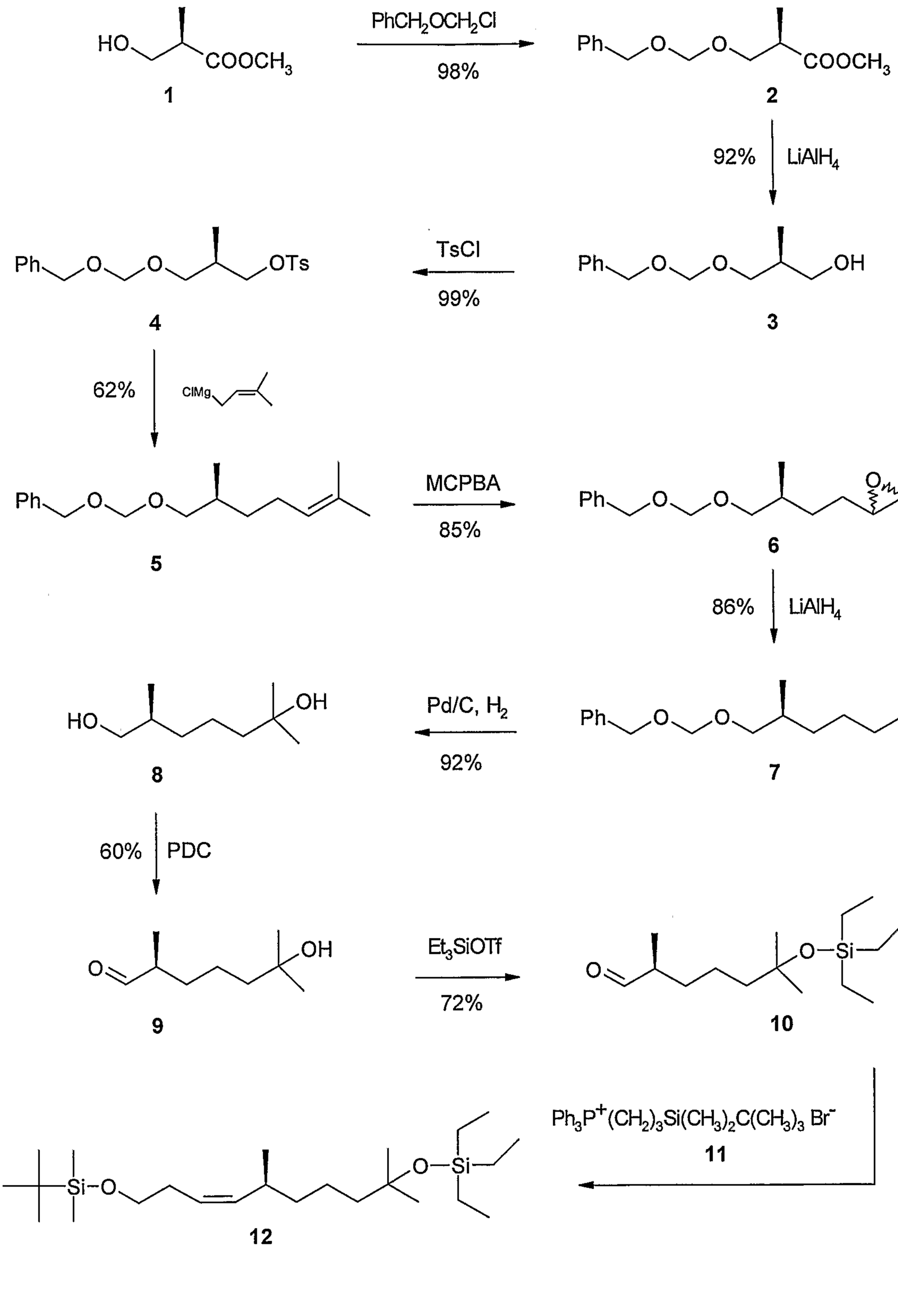
(1*R*,3*R*,7'*R*)-5-(11-Hydroxy-7,11-dimethyl-dodec-2-enylidene)-2-methylene-cyclohexane-1,3-diol (19)

[0071] To a stirred solution of **18** (21.2 mg, 31.2 μmol) in anhydrous THF (3 mL) was added tetrabutylammonium fluoride (1M in THF, 370 μL, 0.37 mmol). The resulting mixture was stirred for 18 hours at room temperature. Solvent was removed in vacuo, and the residue was dissolved in hexane/EtOAc (9:1) and applied on silica Sep-Pak. Elution with hexane/EtOAc (1:1) provided crude product **19**. The vitamin was further purified by HPLC (10 mm x 25 cm Zorbax-Sil column, 4 mL/min) using a hexane/2-propanol (8:2) solvent system. Analytically pure vitamin D compound **19** (6.9 mg, 66%) was collected at R_V = 21 mL.

[0072] **19**: UV (hexane) λ_{max} 234.0 (ε27 800), 241.0 (ε30 200), 248.5 (sh, ε19 900) nm; ^{1}H NMR (400 Hz, $CDCl_3$) δ 0.86 (3H, d, J = 6.5 Hz, CH-$C\underline{H}_3$), 1.21

[6H, s, $C(CH_3)_2$], 2.08 (2H, q, J = 6.9 Hz, 4'-H_2), 2.26 (1H, dd, J = 13.1, 7.1 Hz), 2.39 (1H, dd, J = 13.4, 7.2 Hz), 2.56 (1H, dd, J = 13.5, 4.2 Hz), 2.70 (1H, dd, J = 13.3, 4.3 Hz), 4.48 (2H, m, 1- and 3-H), 5.10 (2H, s, C=C$\underline{H_2}$); 5.70 (1H, dt, J = 15.0, 6.9 Hz, 3'-H), 6.03 (1H, d, J = 10.8 Hz, 1'-H), 6.29 (1H, dd, J = 15.0, 10.8 Hz, 2'-H); MS (EI) m/z (relative intensity) no M^+, 318 (M^+- H_2O, 19), 300 (8), 285 (4), 59 (100); HRMS (ESI) exact mass calculated for $C_{21}H_{34}O_2$ (M^+- H_2O) 318.2559, measured 318.2570.

Scheme 2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98%
Ph
O
O
COOCH3
2
92%
LiAlH4
OH
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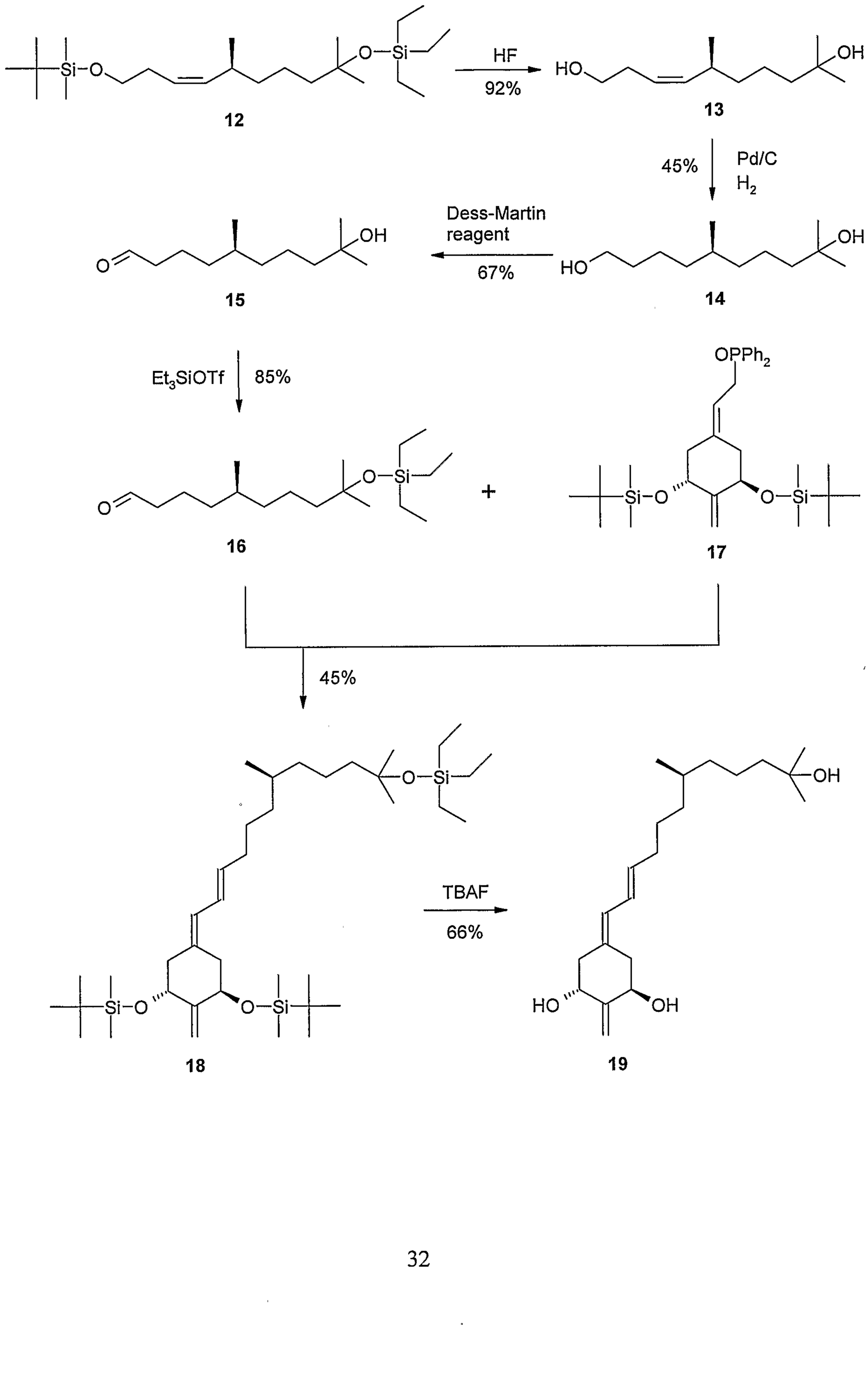
TsCl
99%
OTs
4
62%
ClMg
5
MCPBA
85%
6
86%
LiAlH4
7
Pd/C, H2
92%
8
60%
PDC
9
Et3SiOTf
72%
10
Ph3P+(CH2)3Si(CH3)2C(CH3)3 Br-
11
12

Scheme 3



12 13 14 15 16 17 18 19

BIOLOGICAL ACTIVITY

Vitamin D Receptor Binding

Test Material

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 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, pH 7.4, 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 is bound to the receptor.

Study Drugs

[0074] Unlabeled ligands were dissolved in ethanol and the concentrations were determined using UV spectrophotometry ($1,25(OH)_2D_3$: molar extinction coefficient = 18,200 and λ_{max} = 265 nm). Radiolabeled ligand (^{3}H-$1,25(OH)_2D_3$, ~159 Ci/mmol) was added in ethanol at a final concentration of 1 nM.

Assay Conditions

[0075] 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 was mixed at 10-minute intervals for 30 minutes. The hydroxylapaptite was collected by centrifugation and was then washed three times with Tris-EDTA buffer (50 mM Tris, 1.5 mM EDTA, pH 7.4) containing 0.5% Titron X-100. After the final wash,

the pellets were transferred to scintillation vials containing 4 mL of Biosafe II scintillation cocktail, mixed and placed in a scintillation counter. Total binding was determined from the tubes containing only radiolabeled ligand.

HL-60 Differentiation

Test Material

Study Drugs

[0076] 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 was tested without changing the final concentration of ethanol (≤ 0.2%) present in the cell cultures.

Cells

[0077] Human promyelocytic leukemia (HL60) cells were grown in RPMI-1640 medium containing 10% fetal bovine serum. The cells were incubated at 37°C in the presence of 5% CO_2.

Assay Conditions

[0078] 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 contain intracellular black-blue formazan deposits. Verification of differentiation to monocytic cells was determined by measuring phagocytic activity.

In Vitro Transcription Assay

[0079] 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. 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.

[0080] Antagonism was tested by adding a combination of $1,25(OH)_2D_3$ and the compound in the same well keeping the final ethanol concentration the same.

Intestinal Calcium Transport and Bone Calcium Mobilization

[0081] Male, weanling Sprague-Dawley rats were placed on Diet 11 (Suda et al. J. Nutr. 100:1049, 1970) (0.47% Ca) diet + vitamins 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 was 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. Antagonism was tested by administering a combination of $1,25(OH)_2D_3$ and the compound to the animal simultaneously.

[0082] The compounds of the invention were prepared and studied using the methods described above. The compounds were/are found to exhibit desired, and highly advantageous, patterns of biological activity with respect to intestinal calcium transport activity, ability to mobilize calcium from bone, and ability to bind to the vitamin D receptor. The compounds are also found to moderate cell differentiation activity.

[0083] The compound of formula 1C4 (Des-C,D) does not bind to the vitamin D receptor as strongly as the native hormone $1,25\text{-}(OH)_2D_3$ as shown in Figure 1. Des-C,D does not show as much activity as $1,25\text{-}(OH)_2D_3$ in inducing differentiation of HL-60 cells (Figure 2). Des C,D also does not show as much activity in causing transcription as $1,25\text{-}(OH)_2D_3$ in this respect as shown in

Figure 3. Finally, as shown in Figure 4, Des C,D has no measureable bone calcium mobilizing activity even at the very high dose of 12,480 pmol/day.

[0084] For treatment purposes, the compounds of the invention 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. 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).

[0085] The compounds may be administered orally, topically, parenterally, rectally, 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 may be suitably administered alone, or together with another active vitamin D compound.

[0086] Compositions for use in the invention include an effective amount of a compound of any of the embodiments as the active ingredient or

ingredients, and a suitable carrier. An effective amount of the compound or compounds for use in accordance with some embodiments of the invention will generally be a dosage amount such as those described herein, and may be administered topically, transdermally, orally, nasally, rectally, or parenterally.

[0087] 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. As noted, the compounds of the invention may be present as a mixture of two or more compounds. In some mixtures, the mixture may include a first compound of the invention and a second compound of the invention. In some embodiments, the mixture includes the first compound and the second compound, and the ratio of the first compound to the second compound ranges from 50:50 to 99.9:0.1. In some such embodiments, the ratio of the first compound to the second compound ranges from 70:30 to 99.9:0.1, from 80:20 to 99.9:0.1, from 90:10 to 99.9:0.1, or from 95:5 to 99.9:0.1.

[0088] The compound or compounds may be 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.

[0089] 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.

[0090] 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.

[0091] 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.

[0092] 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.

[0093] 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.

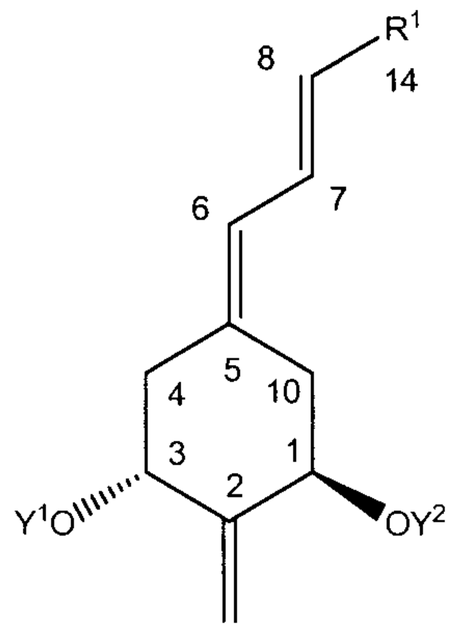
[0094] For nasal administration, inhalation of powder, self-propelling or spray formulations, dispensed with a spray can, a nebulizer or an atomizer can be used. The formulations, when dispensed, preferably have a particle size in the range of 10 to 100 microns.

[0095] 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.

[0096] 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.

CLAIMS:

1. A compound of formula 1:



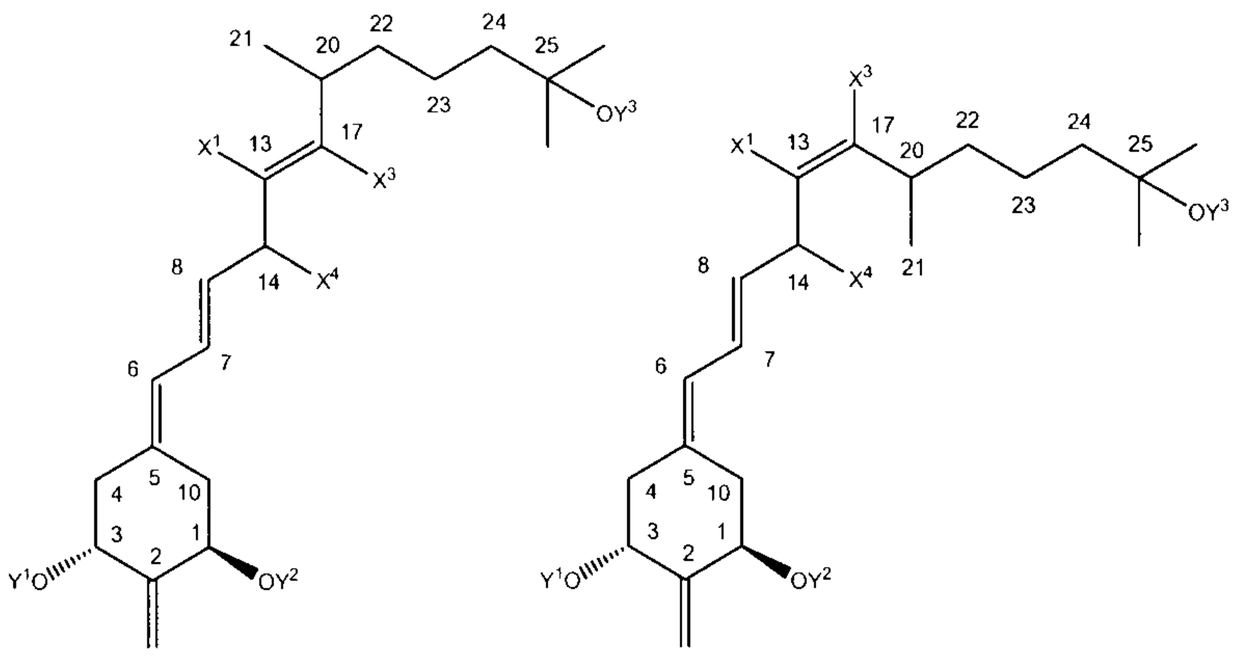
1

wherein,

R^1 is a straight or branched chain alkyl or alkylene group having from 8 to 27 carbons and bearing an OY^3 group; and

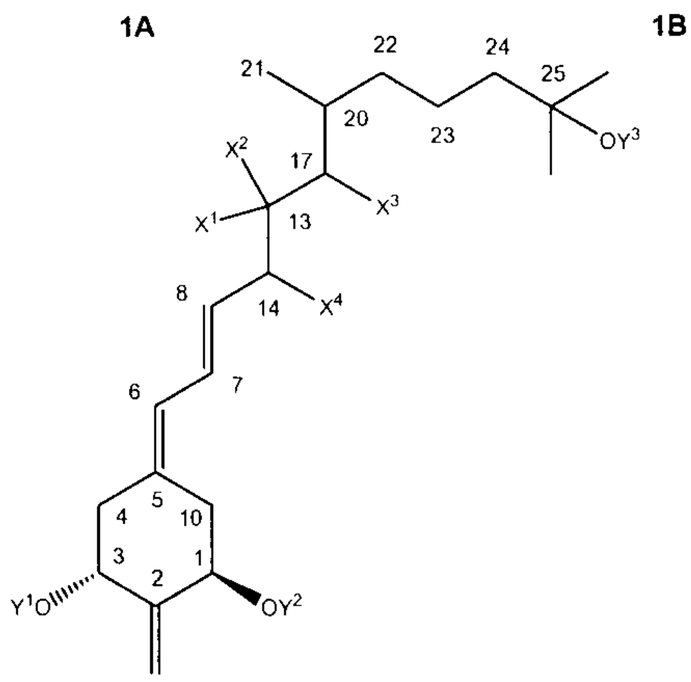
Y^1, Y^2 and Y^3 are independently selected from H or hydroxy-protecting group.

2. The compound of claim 1, wherein the compound has the formula 1A, 1B, or 1C



1A

1B



1C

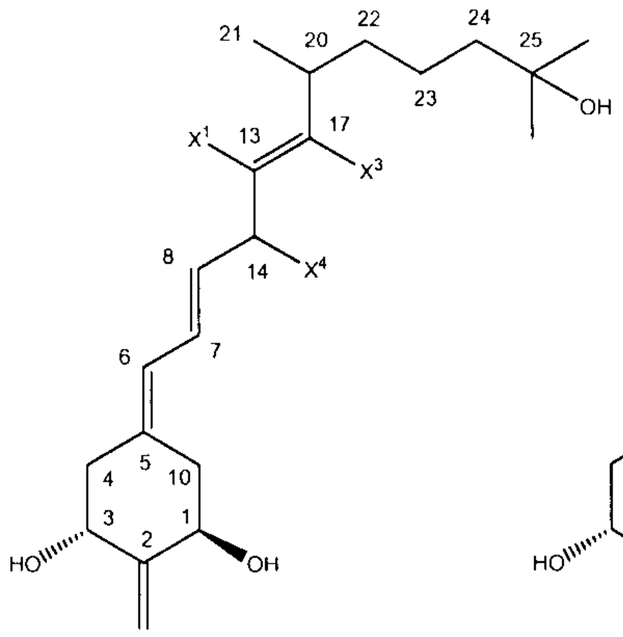
wherein,

X^1, X^2, X^3, and X^4 are independently selected from H or straight or branched chain alkyl groups having from 1 to 4 carbon atoms;

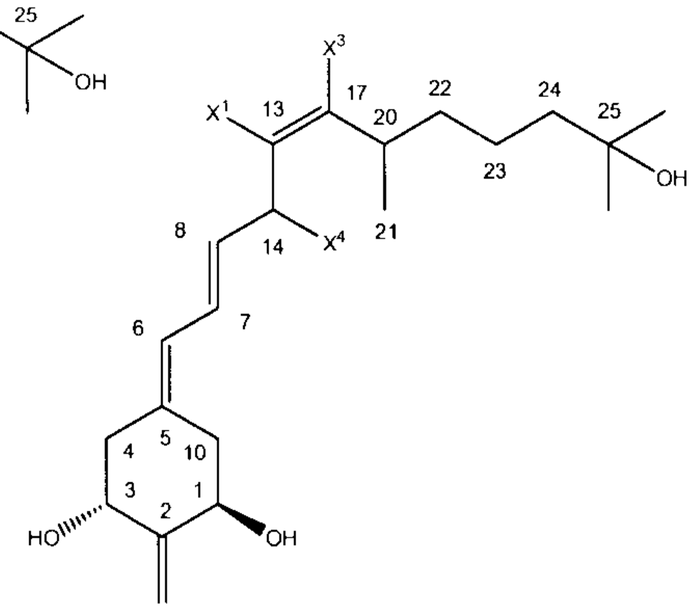
Y^1, Y^2, and Y^3 are independently selected from H or hydroxy-protecting groups; the carbon atoms at positions 14 and 20 may independently have either the R or S configuration in the compound of formula 1A and formula 1B; and

the carbon atoms at positions 13, 14, 17, and 20 may independently have either the R or S configuration in the compound of formula 1C.

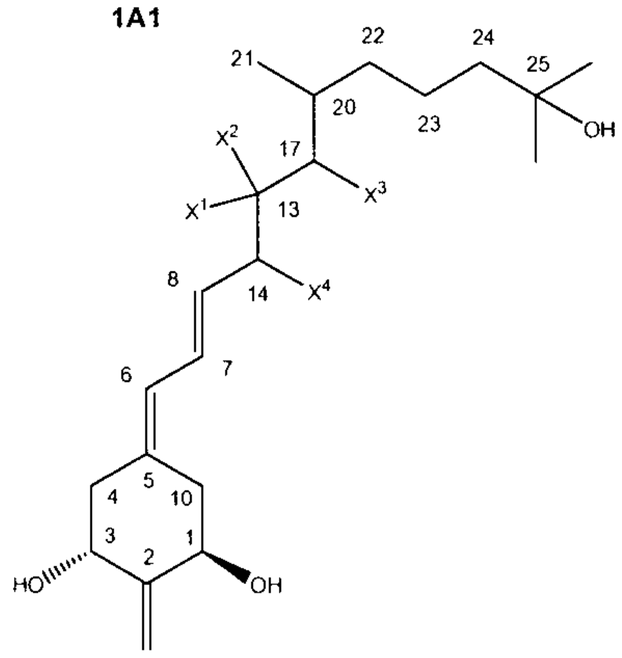
3. The compound of claim 2, wherein Y^1, Y^2, and Y^3 are all H and the compound has the formula 1A1, 1B1, or 1C1



1A1

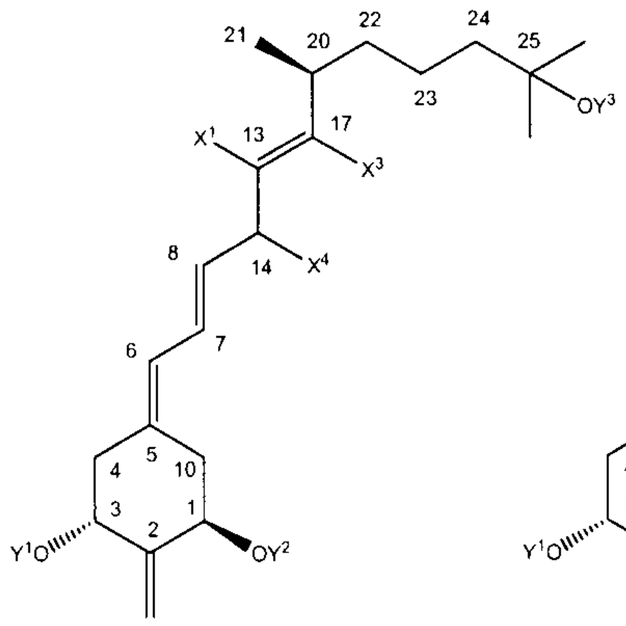


1B1

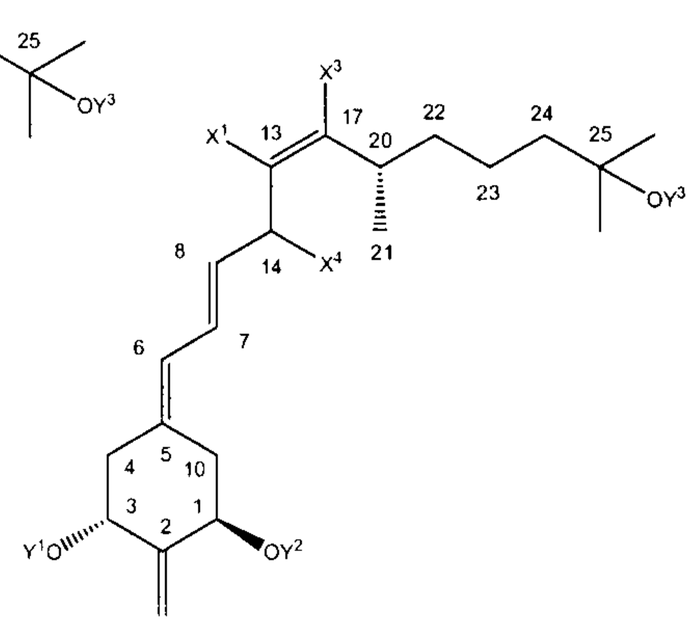


1C1

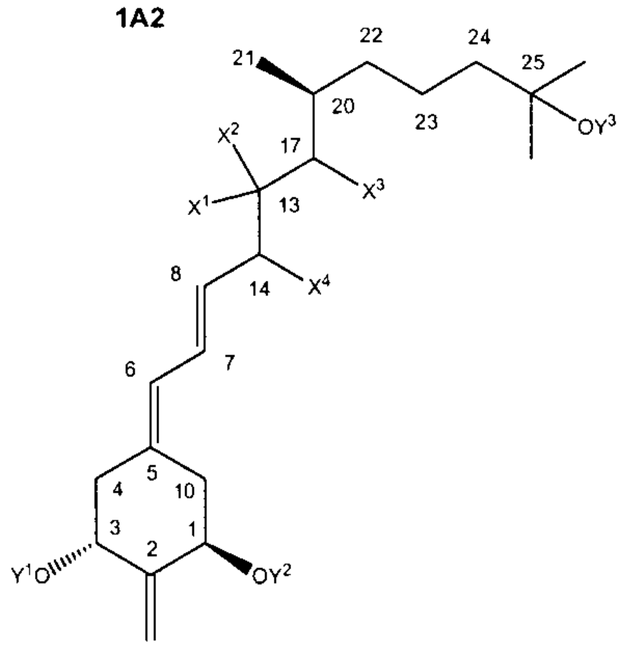
4. The compound of claim 2, wherein the compound has the formula 1A2, 1B2, or 1C2



1A2



1B2

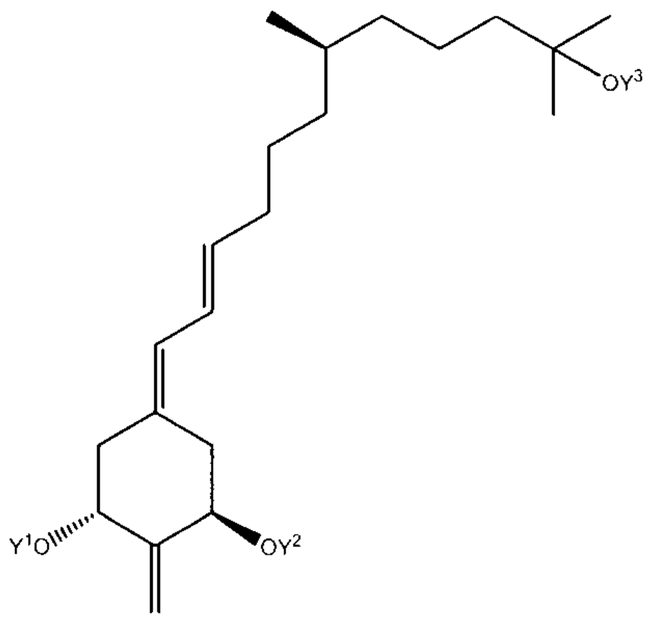


1C2

5. The compound of claim 2, wherein X^1, X^2, X^3, and X^4 are independently selected from H or methyl groups.

6. The compound of claim 2, wherein X^1, X^2, X^3, and X^4 are all H.

7. The compound of claim 2, wherein the compound has the formula 1C3



1C3

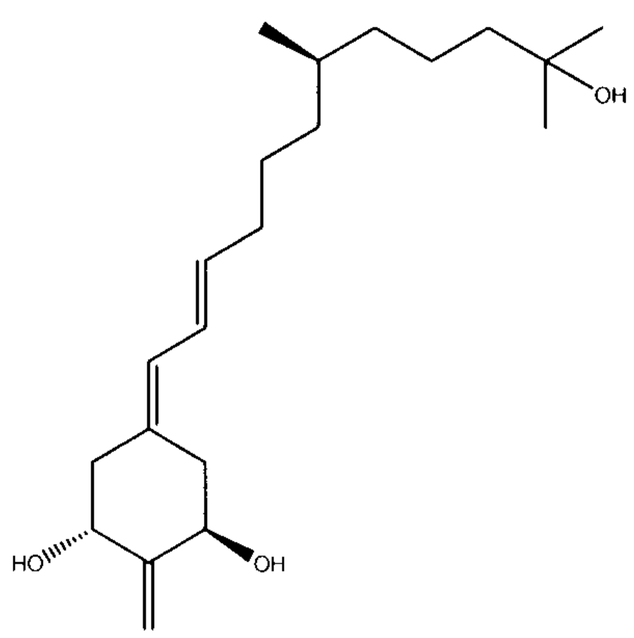
8. The compound of claim 1, wherein Y^1 and Y^2 are both hydroxy protecting groups.

9. The compound of claim 8, wherein Y^1 and Y^2 are both t-butyldimethylsilyl groups.

10. The compound of claim 8, wherein Y^3 is a trialkylsilyl group.

11. The compound of claim 10, wherein Y^3 is a triethylsilyl group.

12. The compound of claim 2, wherein the compound has the formula 1C4



1C4

13. A pharmaceutical formulation, comprising: the compound of any one of claims 1 to 12 and a pharmaceutically acceptable carrier.

14. The pharmaceutical formulation of claim 13, wherein the amount of the compound in the pharmaceutical formulation ranges from about 0.01 µg to about 1 mg per gram of the pharmaceutical formulation.

15. The pharmaceutical formulation of claim 13, wherein the amount of the compound in the pharmaceutical formulation ranges from about 0.1 µg to about 500 µg per gram of the pharmaceutical formulation.

16. Use of an effective amount of the compound of any one of claims 1 to 12 for the treatment of psoriasis; leukemia; colon cancer; breast cancer; prostate cancer; multiple sclerosis; lupus; diabetes mellitus; host versus graft reaction; rejection of organ transplants; an inflammatory disease selected from rheumatoid arthritis, asthma, eczema, or inflammatory bowel diseases; a skin condition selected from wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration, or insufficient sebum secretion; or secondary hyperparathyroidism.

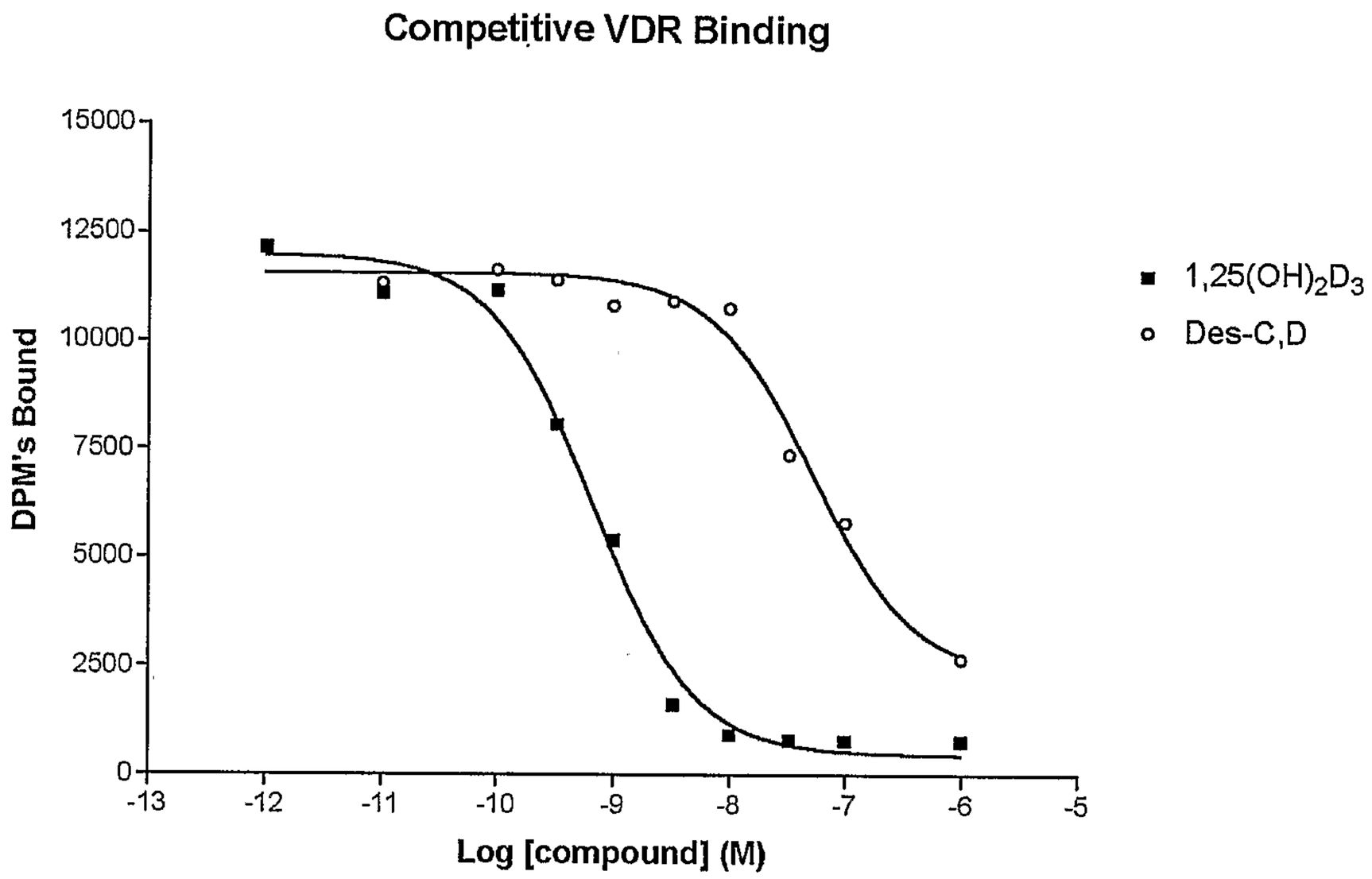
17. Use of the pharmaceutical formulation of claim 13 for the treatment of psoriasis; leukemia; colon cancer; breast cancer; prostate cancer; multiple sclerosis; lupus; diabetes mellitus; host versus graft reaction; rejection of organ transplants; an inflammatory disease selected from rheumatoid arthritis, asthma, eczema, or inflammatory bowel diseases; a skin condition selected from wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration, or insufficient sebum secretion; or secondary hyperparathyroidism.

18. The use of the compound of any one of claims 1 to 12 in the preparation of a medicament for treating psoriasis; leukemia; colon cancer; breast cancer; prostate cancer; multiple sclerosis; lupus; diabetes mellitus; host versus graft reaction; rejection of organ transplants; an inflammatory disease selected from rheumatoid arthritis, asthma, eczema, or inflammatory bowel diseases; a skin condition selected from wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration, or insufficient sebum secretion; or secondary hyperparathyroidism.

19. The use of claim 18, wherein the medicament is in orally, parenterally, rectally, transdermally, or topically administrable form.

20. The use of claim 18, wherein the medicament is for use as an aerosol.

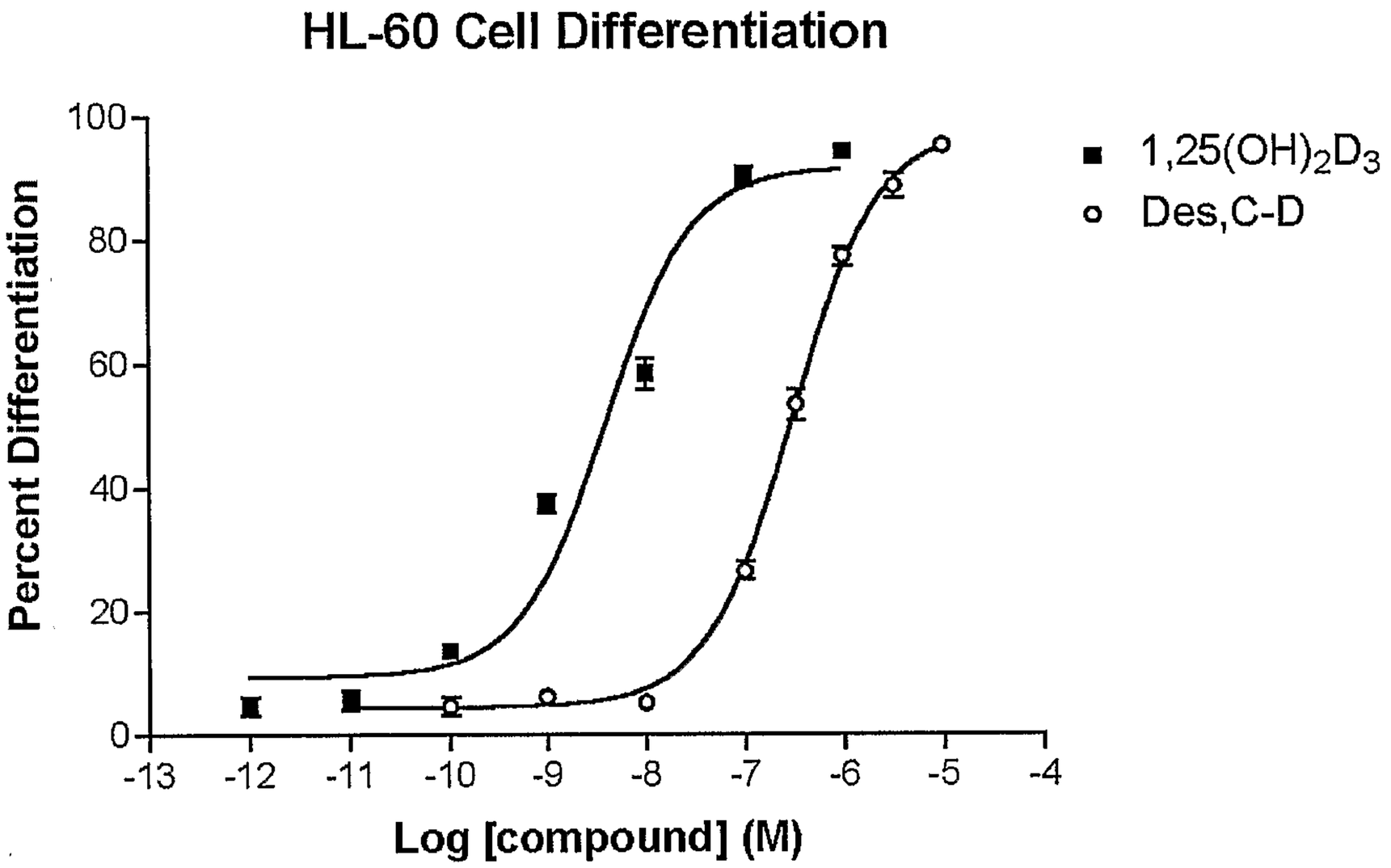
FIGURE 1



K_i: $1,25(OH)_2D_3 = 9.6 \times 10^{-11}$ M

Des-C,D = ~7.5×10^{-9} M

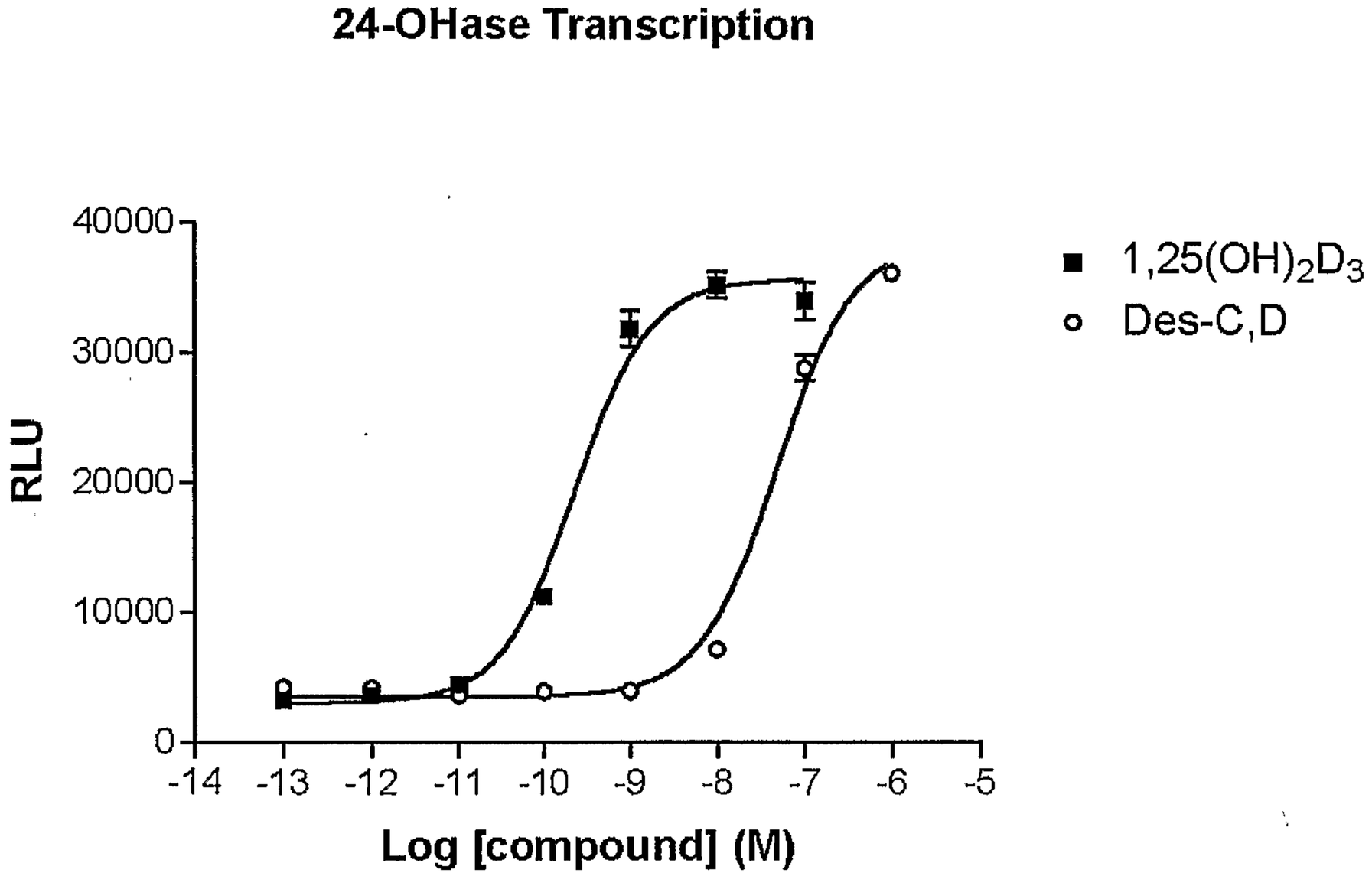
FIGURE 2



EC_{50}: $1,25(OH)_2D_3 = 4 \times 10^{-9}$ M

$Des,C\text{-}D = 3 \times 10^{-7}$ M

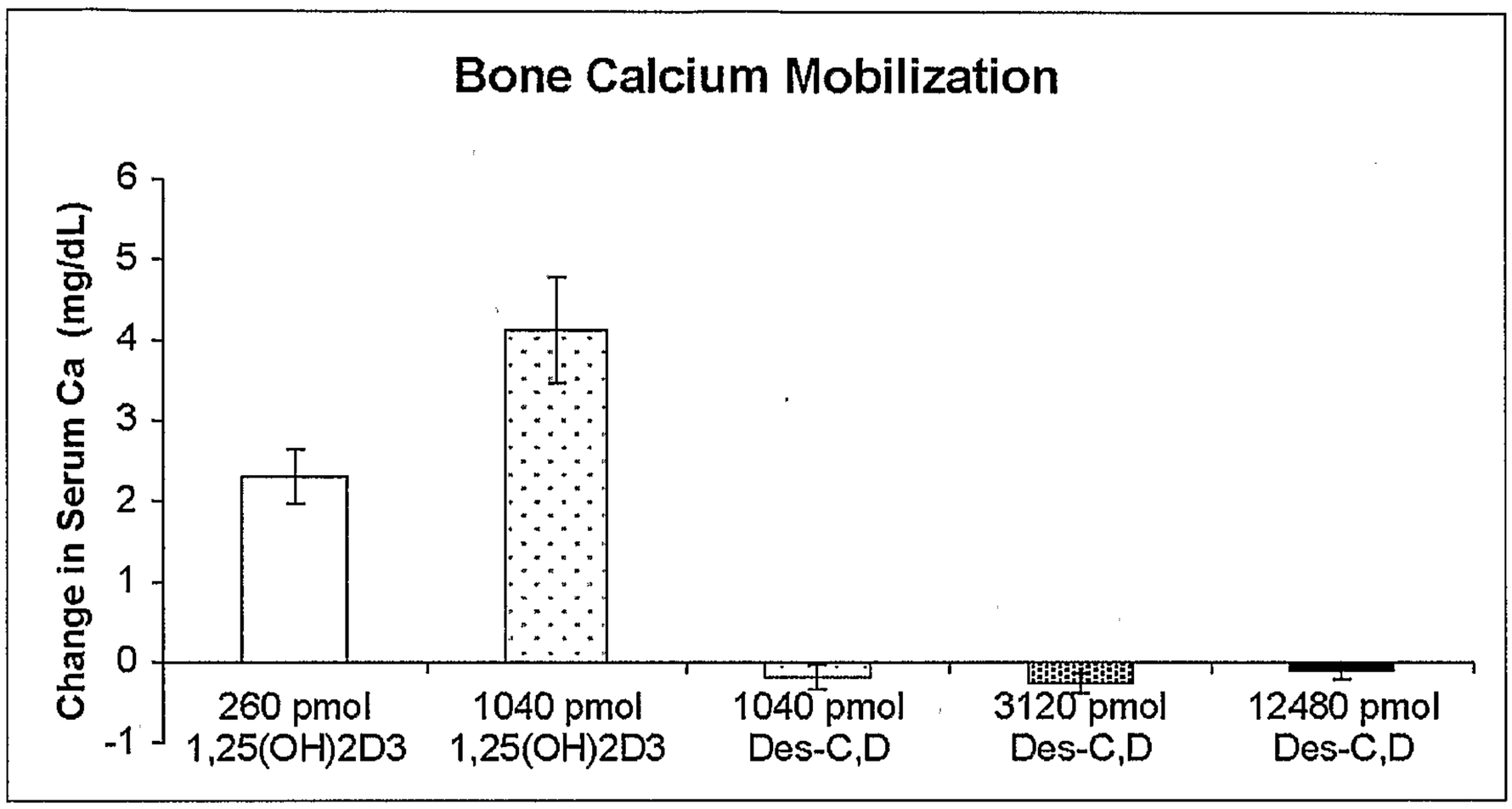
FIGURE 3

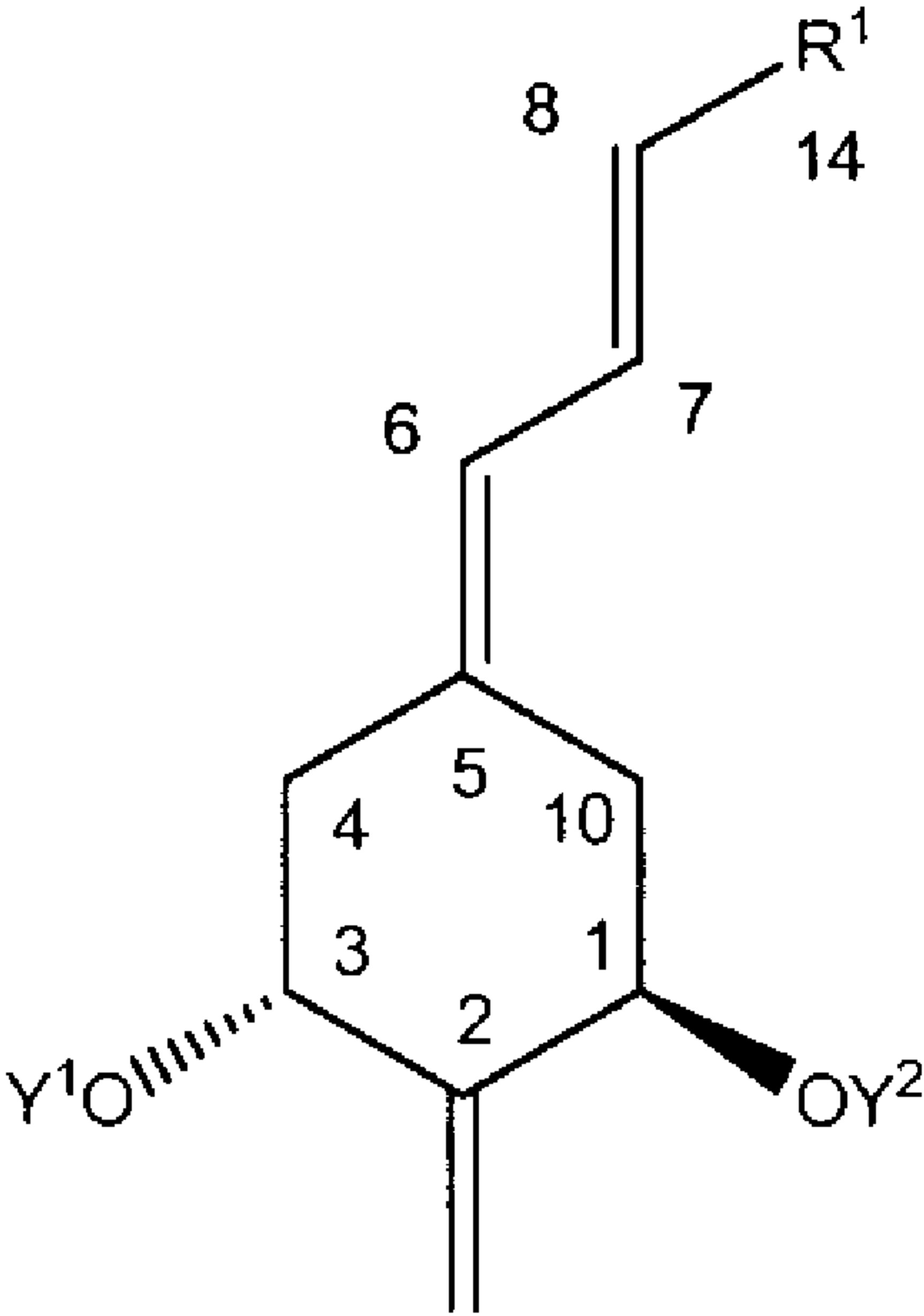


EC_{50}: $1,25(OH)_2D_3 = 2 \times 10^{-10}$ M

Des-C,D = 5×10^{-8} M

FIGURE 4


Bone Calcium Mobilization
Change in Serum Ca (mg/dL)
6
5
4
3
2
1
0
-1
260 pmol 1,25(OH)2D3
1040 pmol 1,25(OH)2D3
1040 pmol Des-C,D
3120 pmol Des-C,D
12480 pmol Des-C,D



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