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(54) Title: (20S)-2-METHYLENE-19-NOR-22-DIMETHYL-1α,25- DIHYDROXYVITAMIN D3 AND (20R)-2-METHYLENE-19-NOR-22- DIMETHYL-1α,25-HYDROXYVITAMIN D3
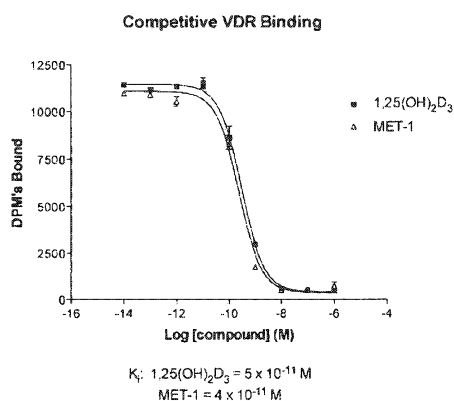
(57) Abstract: Compounds of formula I are provided where X^1, X^2 and X^3 are independently selected from H or hydroxy protecting groups. Such compounds may be used in preparing pharmaceutical compositions and are useful in treating a variety of biological conditions.

FIG. 1

Competitive VDR Binding

K_i: 1,25(OH)$_2$D$_3$ = 5 x 10^{-11} M
MET-1 = 4 x 10^{-11} M

I
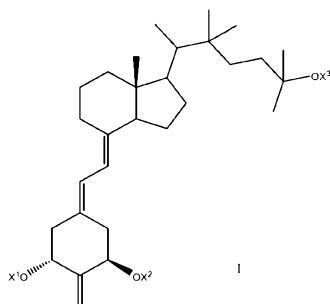
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(20S)-2-METHYLENE-19-NOR-22-DIMETHYL-1α,25-DIHYDROXYVITAMIN D₃ AND (20R)-2-METHYLENE-19-NOR-22-DIMETHYL-1α,25-HYDROXYVITAMIN D₃

CROSS REFERENCE TO RELATED APPLICATIONS

[0001]   This application claims priority to U.S. Provisional Application No. 61/316,631 filed March 23, 2010, the entire disclosure of which is hereby incorporated by reference and for all purposes in its entirety as if fully set forth herein.

FIELD

[0002]   This present technology relates to vitamin D compounds, and more particularly to (20S)-2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D₃ and (20R)- 2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D₃ and derivatives thereof, and to pharmaceutical formulations that include this compound. The present technology also relates to the use of these compounds in the treatment of various diseases and in the preparation of medicaments for use in treating various diseases.

BACKGROUND

[0003]   The natural hormone, 1α,25-dihydroxyvitamin D₃ (also referred to as 1α,25-dihydroxycholecalciferol and calcitriol) and its analog in the ergosterol series, i.e. 1α,25-dihydroxyvitamin D₂, are known to be highly potent regulators of calcium homeostasis in animals and humans, and their activity in cellular differentiation has also been established, Ostrem *et al., Proc. Natl. Acad. Sci. USA, 84*, 2610 (1987). Many structural analogs of these metabolites have been prepared and tested, including 1α-hydroxyvitamin D₃, 1α-hydroxyvitamin D₂, various side chain homologated vitamins, and fluorinated analogs. Some of these compounds exhibit an interesting separation of activities in cell differentiation and calcium regulation. This difference in activity may be useful in the treatment of a variety of

diseases such as renal osteodystrophy, vitamin D-resistant rickets, osteoporosis, psoriasis, and certain malignancies. The structure of 1α,25-dihydroxyvitamin D₃ and the numbering system used to denote the carbon atoms in this compound are shown below.
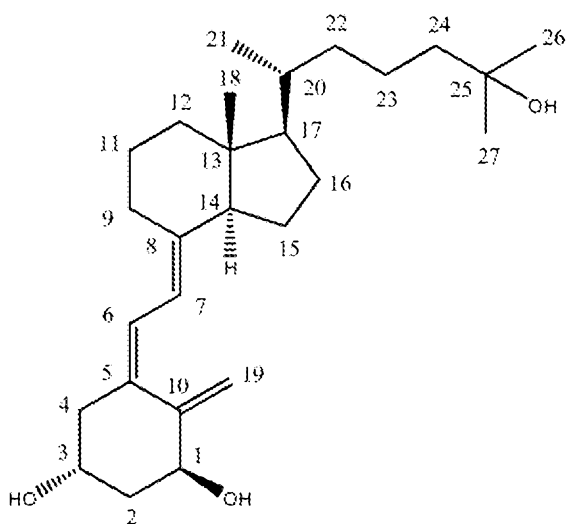
1α,25-Dihydroxyvitamin D₃ = 1α,25-Dihydroxycholecalciferol = Calcitriol

Summary

[0004]   According to a first aspect of the present invention, there is provided a compound having the formula I:

I
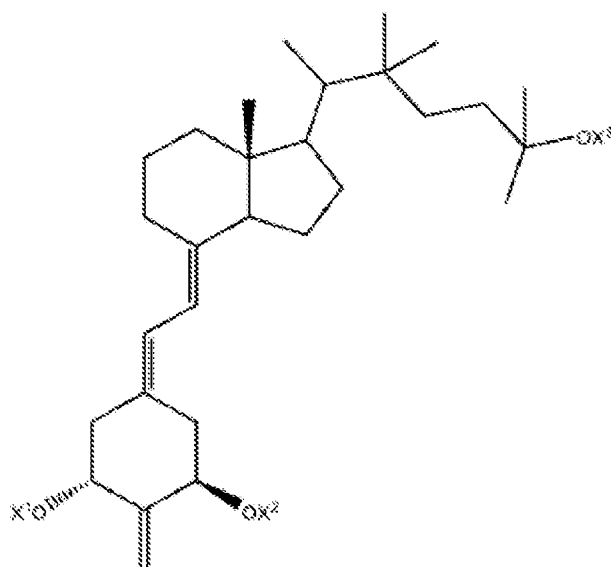
wherein X ^{1}, X^2 and X^3 are independently selected from H and hydroxy protecting groups.

[0004a]   According to a second aspect of the present invention, there is provided a compound having the formula II:
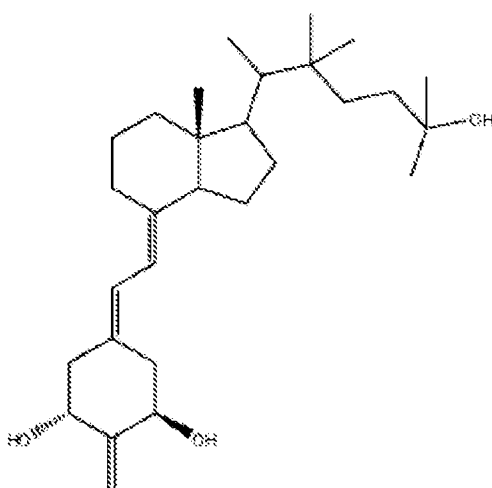
II

[0004b]   According to a third aspect of the present invention, there is provided a pharmaceutical composition, comprising an effective amount of the compound in accordance with the second aspect of the present invention and a pharmaceutically acceptable carrier.

[0004c]   According to a fourth aspect of the present invention, there is provided a method of treating a subject suffering from a biological condition, comprising administering an effective amount of the compound in accordance with the second aspect of the present invention to the subject, wherein the biological condition is 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, 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; or osteoporosis.

[0004d]   The present technology provides (20R)-2-methylene-19-nor-22-dimethyl-$1\alpha,25$-dihydroxyvitamin D_3 and (20S)- 2-methylene-19-nor-22-dimethyl-$1\alpha,25$-dihydroxyvitamin D_3 and related compounds, pharmaceutical formulations that include (20S)-2-methylene-19-nor-22-dimethyl-$1\alpha,25$-dihydroxyvitamin D_3 or (20R)-2-methylene-19-nor-22-dimethyl-$1\alpha,25$-dihydroxyvitamin D_3, methods of treating various disease states using this compound, and the use of this compound in the preparation of medicaments for treating various disease states.

[0005]   Therefore, in one aspect, the present technology provides a compound having the formula I shown below:
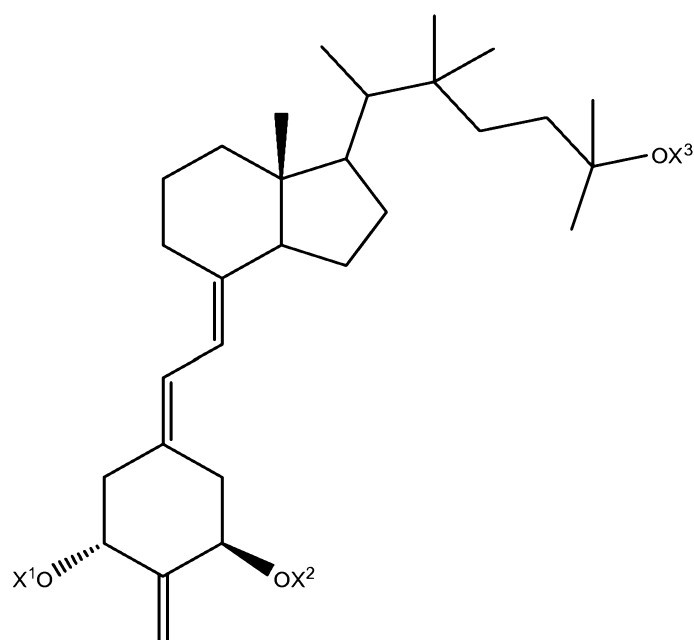
I

where X^1, X^2 and X^3 may be the same or different and are independently selected from H or hydroxy-protecting groups. In some embodiments, the carbon at position 20 has the S-configuration as shown in the compound of formula IA and in others it has the R-configuration as shown in the compound of formula IB:
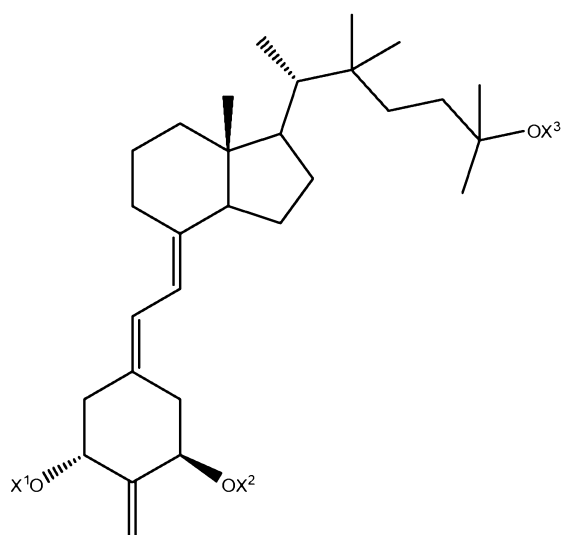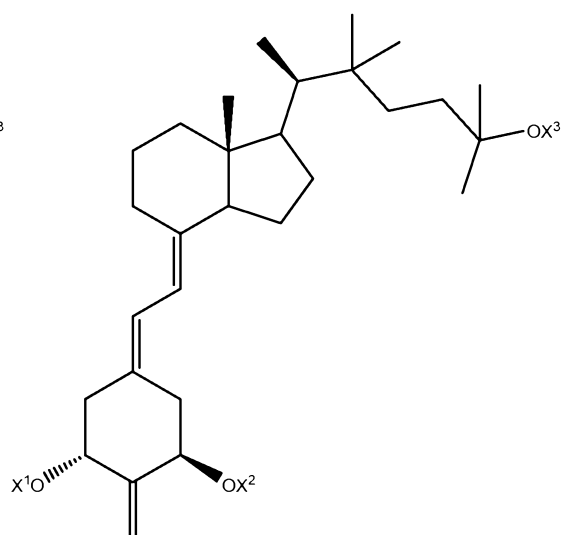
IA   IB

[0006] In some embodiments of compounds of formulas I, IA, or IB, X^1, X^2 and X^3 are both hydroxy protecting groups such as silyl groups. In some such embodiments, X^1 and X^2 are both t-butyldimethylsilyl groups and X^3 is a triethylsilyl group.

[0007] In some embodiments, the compound has the formula II.
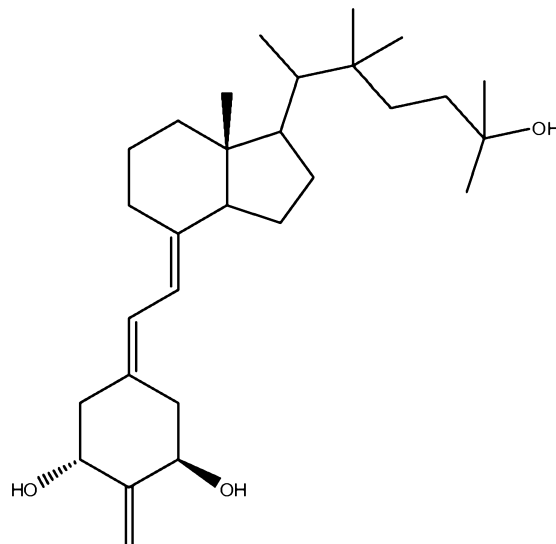
II

[0008] In some embodiments, the compound is (20S)-2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D₃ having the formula IIA as shown below or the compound is (20R)-2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D₃ having the formula IIB as shown below:

IIA   IIB

[0009]   In some embodiments, the compound of formula IIA is a compound of formula IIC (MET-1), and in other embodiments, the compound of formula IIB is a compound of formula IID (MET-2) and have the structures shown below:

IIC   IID

[0010]   Compounds of the present technology show a highly advantageous pattern of biological activity, including strong binding to the vitamin D receptor, strong cell differentiation and induction of 24-hydroxylase activity, yet low to very low calcemic activity. Thus the present compounds may be used in methods of treating a subject suffering from certain biological conditions. The methods include administering an effective amount of a compound of the present technology to the subject, wherein the biological condition is 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, or inflammatory bowel diseases; a skin condition selected from wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration, or insufficient sebum secretion.

[0011]   A compound of the present technology may be present in a composition to treat the above-noted diseases and disorders in an effective amount and optionally including a pharmaceutically acceptable carrier. In some embodiments, the amount of compound includes from about 0.01 μg per gram of composition to about 1 mg per gram of the composition, preferably from about 0.1 μg per gram to about 500 μg per gram of the composition, and may be administered topically, transdermally, orally, or parenterally in

dosages of from about 0.01 μg per day to about 1 mg per day, preferably from about 0.1 μg per day to about 500 μg per day.

[0012]   Further features and advantages of the present technology will be apparent from the following detailed description and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013]   Figures 1-5 illustrate various biological activities of (20S)-2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D_3 (referred to as "MET-1" in the figures) compared with those of the native hormone 1α,25-dihydroxyvitamin D_3 (referred to as "1,25(OH)$_2$D$_3$" in the figures). Figures 6-10 illustrate various biological activities of (20R)-2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D_3 (referred to as "MET-2" in the figures) compared with those of the native hormone, 1,25(OH)$_2$D$_3$.

[0014]   Fig. 1 shows a graph of competitive binding to the nuclear vitamin D hormone receptor between MET-1 and the native hormone, 1,25(OH)$_2$D$_3$. MET-1 binds to the nuclear vitamin D hormone receptor with the same affinity as 1,25(OH)$_2$D$_3$.

[0015]   Fig. 2 is a graph comparing the percent HL-60 cell differentiation as a function of the concentration of MET-1 with that of 1,25(OH)$_2$D$_3$. MET-1 has the about four times the potency of 1,25(OH)$_2$D$_3$ in causing the differentiation of HL-60 cells into monocytes.

[0016]   Fig. 3 is a graph comparing the *in vitro* transcription activity of MET-1 with that of 1,25(OH)$_2$D$_3$. MET-1 is about ten times more potent than 1,25(OH)$_2$D$_3$ in increasing transcription of the 24-hydroxylase gene.

[0017]   Fig. 4 is a bar graph comparing the bone calcium mobilization activity of MET-1 with that of 1,25(OH)$_2$D$_3$ in rat. MET-1 is approximately 20 times less potent than 1,25(OH)$_2$D$_3$ in releasing bone calcium stores.

[0018]   Fig. 5 is a bar graph comparing the intestinal calcium transport activity of MET-1 with that of 1,25(OH)$_2$D$_3$. MET-1 is less potent than 1,25(OH)$_2$D$_3$ in promoting active calcium transport in the rat gut.

[0019]   Fig. 6 shows a graph of competitive binding to the nuclear vitamin D hormone receptor between MET-2 and the native hormone, $1,25(OH)_2D_3$. MET-2 binds to the nuclear vitamin D hormone receptor with the same affinity as $1,25(OH)_2D_3$.

[0020]   Fig. 7 is a graph comparing the percent HL-60 cell differentiation as a function of the concentration of MET-2 with that of $1,25(OH)_2D_3$. MET-2 has the about three times the potency of $1,25(OH)_2D_3$ in causing the differentiation of HL-60 cells into monocytes.

[0021]   Fig. 8 is a graph comparing the *in vitro* transcription activity of MET-2 with that of $1,25(OH)_2D_3$. MET-2 is about three times more potent than $1,25(OH)_2D_3$ in increasing transcription of the 24-hydroxylase gene.

[0022]   Fig. 9 is a bar graph comparing the bone calcium mobilization activity of MET-2 with that of $1,25(OH)_2D_3$ in rat. MET-2 is approximately 16 times less potent than $1,25(OH)_2D_3$ in releasing bone calcium stores.

[0023]   Fig. 10 is a bar graph comparing the intestinal calcium transport activity of MET-2 with that of $1,25(OH)_2D_3$. MET-2 is less potent than $1,25(OH)_2D_3$ in promoting active calcium transport in the rat gut.

DETAILED DESCRIPTION

[0024]   (20S)-2-Methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D_3 and (20R)-2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D_3 were synthesized, and tested, and found to be useful in treating a variety of biological conditions as described herein. Structurally, these compounds have the formulas IIA and IIB as shown below:
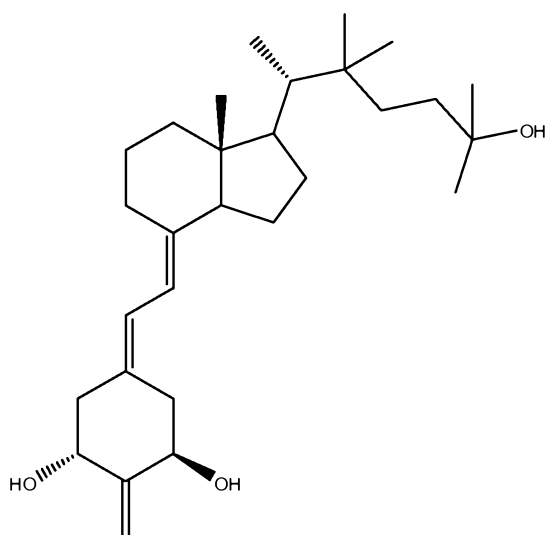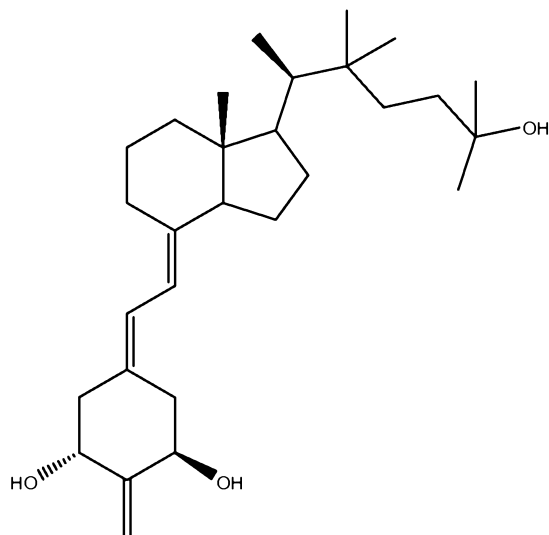
IIA   IIB

[0025]   Preparation of (20S)-2-methylene-19-nor-22-dimethyl-1α,25-

dihydroxyvitamin D_3 and (20R)-2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D_3

can be accomplished by condensing an appropriate bicyclic Windaus-Grundmann type ketone

(IIIA or IIIB) with the allylic phosphine oxide IV followed by deprotection (removal of the

Y, Y_1 and Y_2 hydroxy protecting groups).
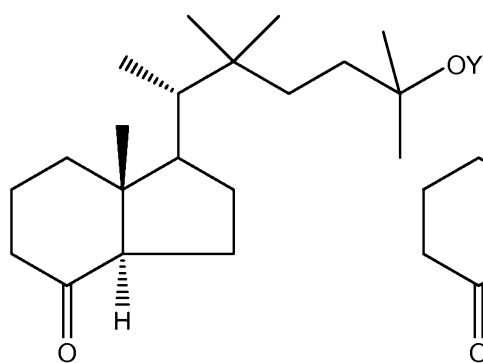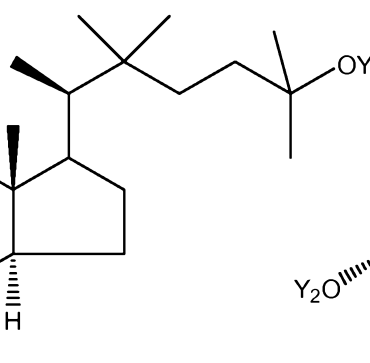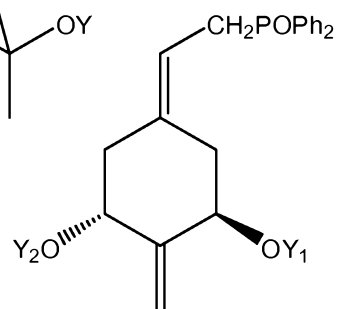
IIIA   IIIB   IV

[0026]   Hydraindanones of structure IIIA and IIIB can prepared by slight modification

of known methods as will be readily apparent to one of skill in the art and described herein.

Specific examples of methods used to synthesize bicyclic ketones for 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). An overall process for synthesizing 2-alkylidene-19-nor-

vitamin D compounds is illustrated and described in U.S. Patent No. 5,843,928 which is

hereby incorporated by reference in its entirety and for all purposes as if fully set forth herein. Details of preparing hydrinanones IIIA and IIIB are found in the Examples herein.

[0027]   In phosphine oxide IV, Y_1 and Y_2 are hydroxy-protecting groups such as silyl protecting groups. The t-butyldimethylsilyl (TBDMS) group is an example of a particularly useful hydroxy-protecting group. 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).

Scheme 1
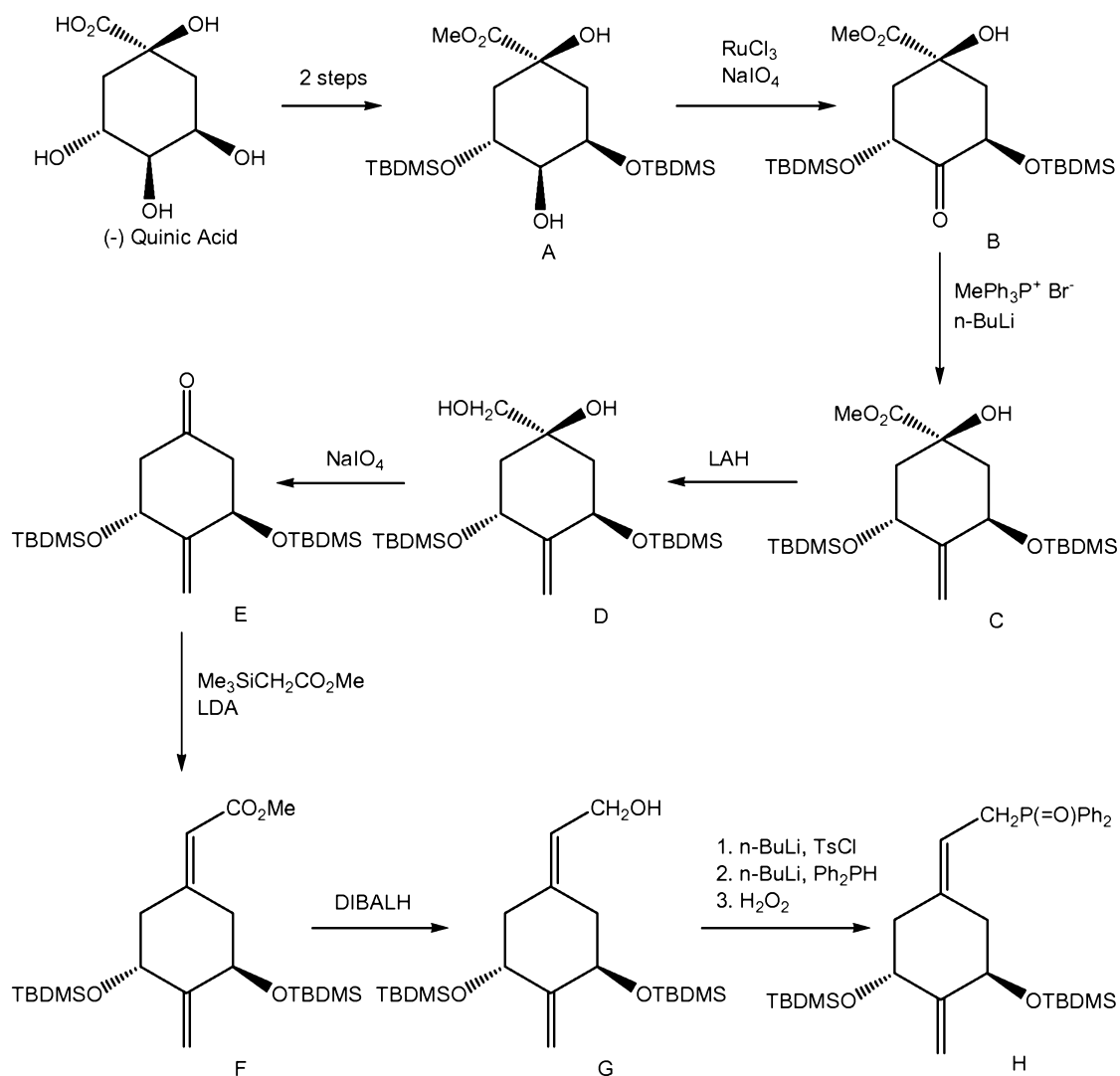
[0028]   Phosphine oxide IV is a convenient reagent that may be prepared according to the procedures described by Sicinski *et al., J. Med. Chem., 41*, 4662 (1998), DeLuca *et al.*, U.S. Patent No. 5,843,928; Perlman *et al., Tetrahedron Lett. 32*, 7663 (1991); and DeLuca *et al.*, U.S. Patent No. 5,086,191. Scheme 1 shows the general procedure for synthesizing phosphine oxide 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.

[0029]   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 and which is hereby incorporated by reference in its entirety and for all purposes as if fully set forth herein.

[0030]   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.

[0031]   Compounds of the present technology exhibit desirable, and highly advantageous, patterns of biological activity. These compounds are characterized by relatively high binding to vitamin D receptors (see Figs. 1 and 5) and high activity in HL-60 differentiation, but very low ability to mobilize calcium from bone (see Figs. 4 and 9) and relatively low intestinal calcium transport activity (see Figs. 5 and 10), as compared to that of $1\alpha,25$-dihydroxyvitamin D_3. Hence, these compounds can be characterized as having little, if any, calcemic activity at the dosages that $1\alpha,25$-dihydroxyvitamin D_3 displays significant calcemic activity. Thus, the may be useful as a therapy for suppression of secondary hyperparathyroidism type renal osteodystrophy.

[0032]   The compounds of the present technology are also 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 may be treated with the compounds of the present technology.

[0033]   The above compounds are also characterized by cell differentiation activity either equal to or significantly higher than that of $1\alpha,25(OH)_2 D_3$ (see Figs. 2 and 7). 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 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.

[0034]   The compounds of the present technology may be used to prepare pharmaceutical formulations or medicaments that include a compound of the present technology 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. 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.

[0035]   For treatment purposes, the compounds defined by formulas I, IA, IB, II, IIA, IIB, IIC, and IID 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 present technology. 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.

[0036]   The compounds may be administered orally, topically, parenterally, 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 about 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 about 0.01 μg to about 1 mg per day of the compound. In other such embodiments an appropriate and effective dose may range from about 0.1 μg to about 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.

[0037]   Compositions for use in the present technology include an effective amount of (20S)-2-Methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D_3 and/or (20R)-2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D_3 as the active ingredient, and a suitable carrier. An effective amount of a compound herein for use in accordance with some embodiments of the present technology will generally be a dosage amount such as those described herein, and may be administered topically, transdermally, orally, nasally, rectally, or parenterally.

[0038]   The compounds of formula IIA, IIB, IIC and IID may be advantageously administered in amounts sufficient to effect the differentiation of promyelocytes to normal macrophages. Dosages as described above are suitable, it being understood that the amounts given are to be adjusted in accordance with the severity of the disease, and the condition and response of the subject as is well understood in the art.

[0039]   The 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.

[0040]   The formulations of the present technology 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.

[0041]   Formulations of the present technology 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.

[0042]   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.

[0043]   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.

[0044]   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.

[0045]   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.

[0046]   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

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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.

[0047]   All references cited herein are specifically incorporated by reference in their entireties and for all purposes as if fully set forth herein.

EXAMPLES

### Example 1: Synthesis of (20S)-2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D₃

[0048]   Compounds of the present technology, including (20S)-2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D_3, were prepared using the methods shown in Schemes 1-3. As shown in Scheme 2, compound **2** is obtained by ozonolysis of vitamin D_2 (compound **1**) as described by Sicinski *et al.* (*J. Med. Chem. 41*, 4662-4672, 1998), followed by reduction with borohydride. Treatment of the dialcohol **2** with tosyl chloride in pyridine provides the tosylate compound **3**. Compound **3** is protected by treatment with triethylsilyl triflate (TESOTf) and 2,6-lutidine in dichloromethane to give compound **4**. The tosylate of compound **4** was displaced with cyanide in dimethyl sulfoxide (DMSO) to give cyano compound **5**. Reaction of compound **5** with lithium diisopropyl amide (LDA) in tetrahydrofuran (THF) and alkylation with methyl iodide provided compound 6, which was subsequently reduced with diisobutyl aluminum hydride (DIBAL) in dichloromethane to provide aldehyde **7**.

[0049]   Scheme 3 illustrates the conversion of compound **7** to the title compound of Formula IIA (compound 14). First, the aldehyde **7** is reacted with triethylphosphonoacetate **8** in the presence of LDA to provide alkene **9**. Compound 9 was hydrogenated over Pd/C in methanol to give compound **10**, and the latter compound was reacted with methyl Grignard reagent to give the tertiary alcohol, **11**. Oxidation with tetrapropylperruthenate in the presence of N-methylmorpholine N-oxide, followed by protection of the remaining alcohol with TESOTf under the same conditions as before led to ketone **12**. Compound **12** was coupled with the A-ring phosphonium salt (compound H from Scheme 1) using phenyl lithium to produce compound **13**, the silyl protected vitamin derivative (a compound of formula I and IA). Removal of all the silyl protecting groups was effected with HF in acetonitrile (ACN) to give compound **14** (a compound of formula I and IIA). This product was fully characterized as described below.

Scheme 2
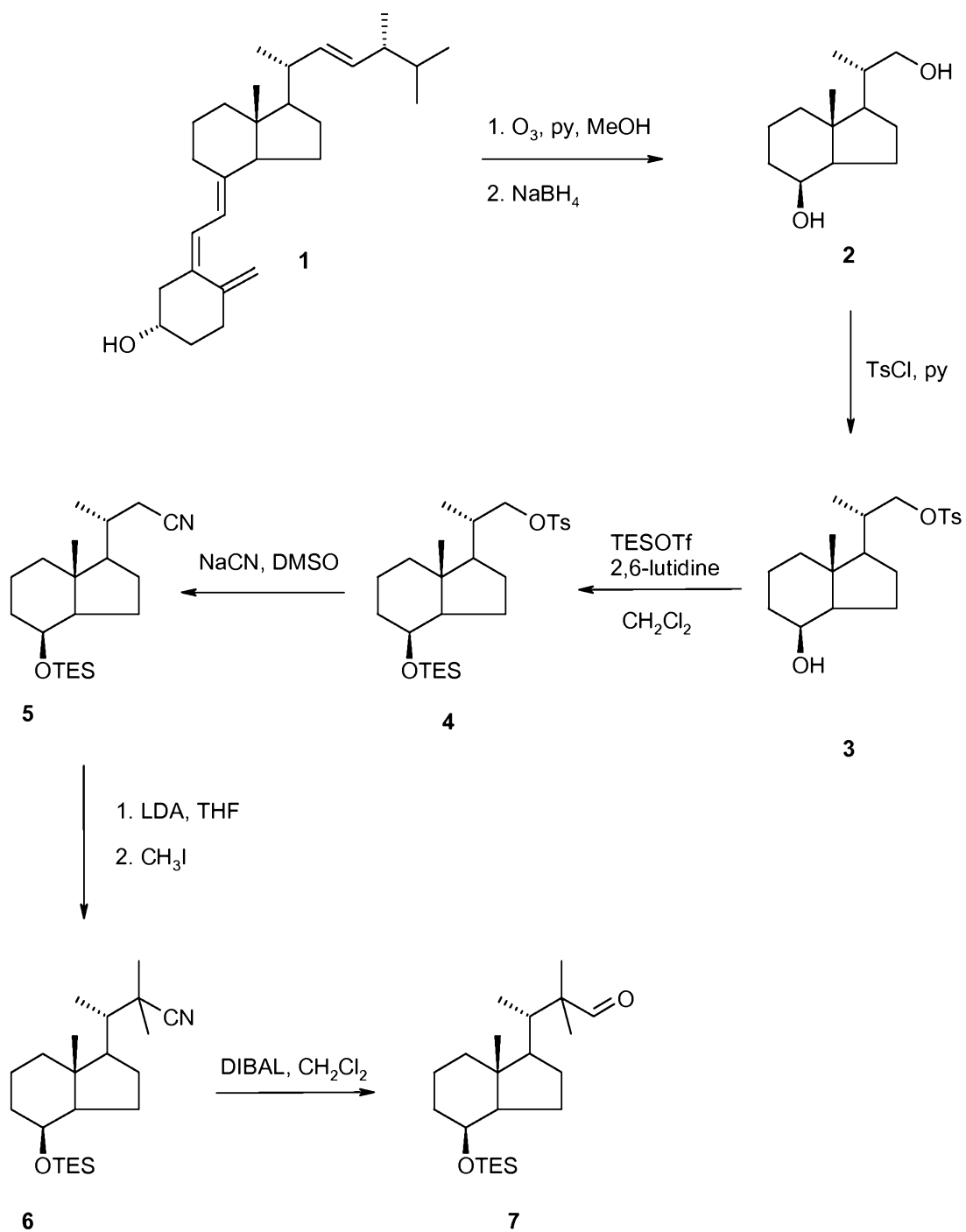
Scheme 3
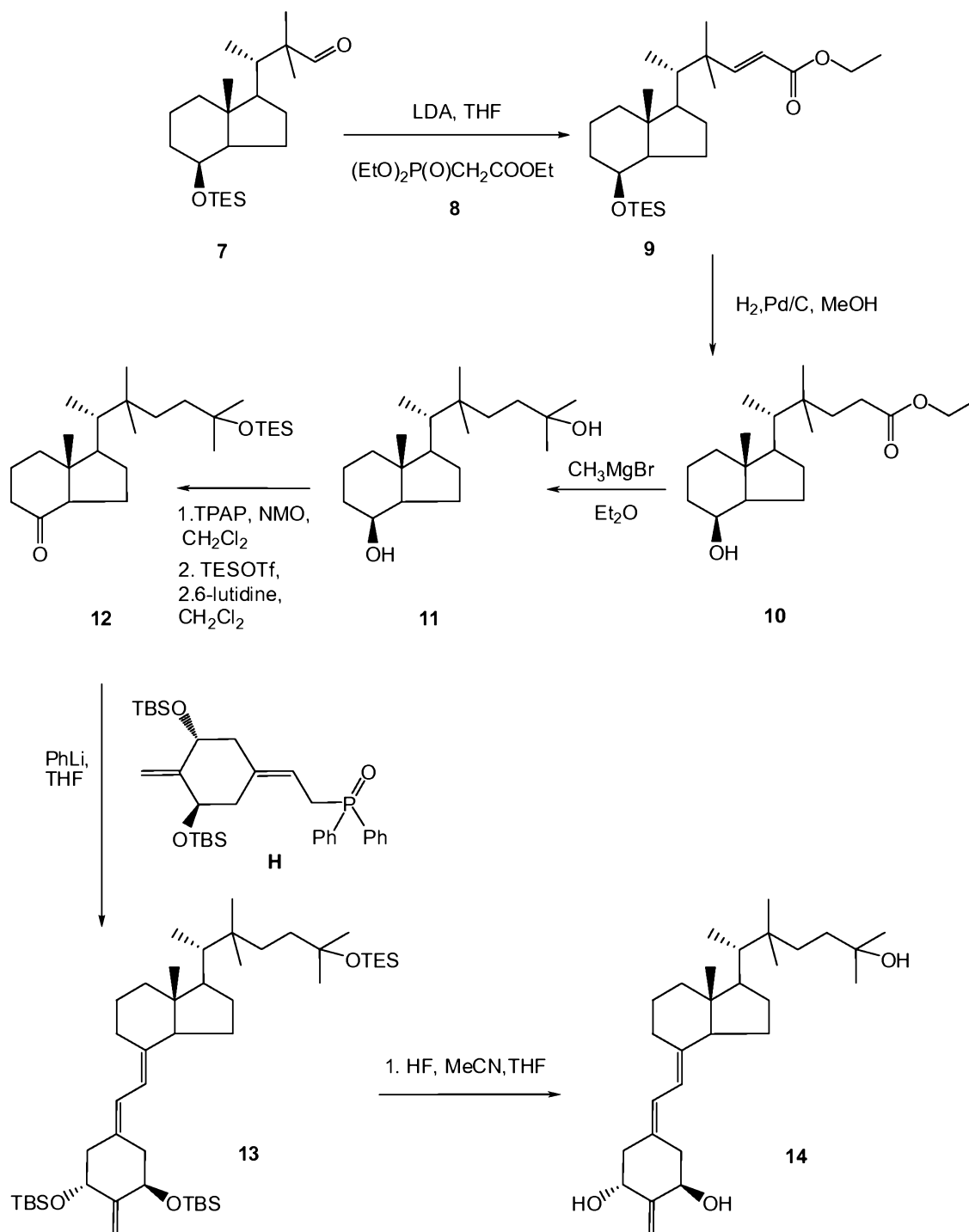
(8S,20S)-Des-A,B-20-(hydroxymethyl)-pregnan-8-ol (2)

[0050]   Ozone was passed through a solution of vitamin D$_2$ **1** (5g, 12.6 mmol) and pyridine (5 mL, 4.89 g, 62 mmol) in methanol (400 mL) at -78°C. When the reaction mixture turned deep blue it was flushed with oxygen for 15 min to remove the residual ozone and

then it was treated with NaBH$_4$ (1.5 g, 40 mmol). After 15 min the second portion of NaBH$_4$ (1.5 g, 40 mmol) was added and the mixture was allowed to warm to room temperature. The third portion of NaBH$_4$ (1.5 g, 40 mmol) was added and the reaction mixture was stirred for 18 hours. The reaction was quenched with water, concentrated under reduced pressure and extracted with dichloromethane. The combined organic phases were washed with 1M aqueous HCl, saturated aqueous NaHCO$_3$ and dried (Na$_2$SO$_4$) and concentrated. The residue was purified by column chromatography on silica gel (30%, then 50% ethyl acetate/hexane) to give the diol **2** (2.61 g, 49%) as colorless crystals.

m.p. 107 °C (from ethyl acetate/hexane); $[\alpha]_D$ +32.9 (*c* 1.0, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.07 (1H, d, J = 2.5 Hz), 3.62 (1H, dd, J = 10.5, 3.2 Hz), 3.37 (1H, dd, J = 10.5, 6.8 Hz), 1.98 (1H, m), 1.80 (3H, m), 1.02 (3H, d, J = 6.6 Hz), 0.94 (3H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ 69.21, 67.81, 52.91, 52.34, 41.84, 40.20, 38.22, 33.55, 26.64, 22.55, 17.38, 16.60, 13.56; MS (EI) *m/z* 212 (1, M$^+$), 194 (28, M$^+$- H$_2$O), 179 (29), 163 (22), 147 (15), 135 (42), 125 (48), 111 (100), 97 (51); exact mass calculated for C$_{13}$H$_{22}$O (M$^+$-H$_2$O) 194.1671, found 194.1673.

(8S,20S)-Des-A,B-20-[(p-toluenesulfonyl)oxy]methyl-pregnan-8-ol (3)

[0051]   A precooled (-20 °C) solution of tosyl chloride (0.9 g, 4.73 mmol) in pyridine (2 mL) was added to a mixture of the diol **2** (0.52 g, 2.45 mmol) in dry pyridine (5 mL) at -20 °C. The reaction mixture was stirred for 3 h at -20 °C, then it was warmed to 0 °C and stirred for 18 h. The mixture was pulled into a saturated aqueous CuSO$_4$ solution and extracted with dichloromethane. Combined organic phases were washed with a saturated aqueous CuSO$_4$ solution and dried (Na$_2$SO$_4$) and concentrated. The residue was purified by column chromatography on silica gel (20% ethyl acetate/hexane) to afford of tosylate **3** (0.86 g, 96% yield) as colorless crystals.

m.p. 95 °C (from ethyl acetate/hexane); $[\alpha]_D$ +17.4 (*c* 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.77 (2H, d, J = 8.2 Hz), 7.34 (2H, d, J = 8.2 Hz), 4.06 (1H, s), 3.94 (1H, dd, J = 9.2, 3.1 Hz), 3.80 (1H, dd, J = 9.2, 6.2 Hz), 2.44 (3H, s), 1.90 (1H, m), 1.78 (2H, m), 0.95 (3H, d, J = 6.6 Hz), 0.88 (3H, s); ^{13}C NMR (100 MHz, CDCl$_3$) δ 144.59, 133.01, 129.73, 127.86, 75.56, 68.98, 52.18, 41.81, 40.00, 35.66, 33.50, 26.36, 22.40, 21.60, 17.29, 16.69, 13.43; MS (EI) *m/z* 367 (6, MH$^+$), 348 (5, M$^+$ - H$_2$O), 307 (2), 194 (18), 179 (23), 150 (17), 135 (16), 125 (34), 111 (100), 91 (50); MS (ESI) *m/z* 389 (100, [M+Na]$^+$), 755 (90,

$[2M+Na]^+$), 1121 (60, $[3M+Na]^+$); exact mass (ESI) calculated for $C_{20}H_{30}O_4SNa$ $[M+Na]^+$ 389.1763, found 389.1758.

(8S,20S)-Des-A,B-8-[(triethylsilyl)oxy]-20-[(p-toluenesulfonyl)oxy]methyl-pregnane (4)

[0052]   Triethylsilyl trifluoromethanesulfonate (0.6 mL, 0.70 g, 2.65 mmol) was added to a solution of the tosylate **3** (0.65 g; 1.78 mmol) and 2,6-lutidine (0.3 mL, 0.28 g, 2.58 mmol) in dichloromethane (6 mL) at 0 °C. The reaction mixture was stirred for 15 min and it was diluted with dichloromethane. The organic phase was washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (20% ethyl acetate/hexane) to give the product **4** (0.84 g, 99% yield) as a light yellow oil. $[\alpha]_D$ +20.6 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, J = 8.2 Hz), 7.34 (2H, d, J = 8.2 Hz), 4.01 (1H, d, J = 2.0 Hz), 3.96 (1H, dd, J = 9.2, 3.0 Hz), 3.79 (1H, dd, J = 9.2, 6.5 Hz), 2.45 (3H, s), 1.87 (1H, m), 0.94 (3H, d, J = 5.9 Hz), 0.93 (9H, t, J = 7.9 Hz), 0.86 (3H, s), 0.54 (6H, q, J = 7.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.55 (0), 133.10 (0), 129.73 (1), 127.91 (1), 75.76 (2), 69.11 (1), 52.70 (1), 52.36 (1), 42.12 (0), 40.39 (2), 35.72 (1), 34.47 (2), 26.52 (2), 22.88 (2), 21.63 (3), 17.56 (2), 16.76 (3), 13.46 (3), 6.91 (3), 4.89 (2); MS (EI) *m/z* no M^+, 319 (46), 291 (9), 265 (9), 246 (5), 217 (100), 189 (81), 161 (69), 133 (54), 103 (38), 94 (39); MS (ESI) *m/z* 503 (100, $[M+Na]^+$), 983 (40, $[2M+Na]^+$), 1463 (71, $[3M+Na]^+$); exact mass (ESI) calculated for $C_{26}H_{44}O_4SSiNa$ $[M+Na]^+$ 503.2627, found 503.2629.

(8S,20R)-Des-A,B-8-[(triethylsilyl)oxy]-20-(cyanomethyl)-pregnane (5)

[0053]   Sodium cyanide (2 g, 41 mmol) was added to a solution of tosylate **4** (0.84 g, 1.75 mmol) in dry DMSO (8 mL). The resulting mixture was stirred at 90 °C for 3 h, then it was cooled, diluted with water and extracted with ethyl acetate. Combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (10% ethyl acetate/hexane) to give the cyanide **5** (0.57 g, 97% yield) as a colorless oil.

$[\alpha]_D$ +16.6 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.04 (1H, d, J = 2.1 Hz), 2.34 (1H, dd, J = 16.6, 3.7 Hz), 2.23 (1H, dd, J = 16.6, 7.0 Hz), 1.92 (1H, m), 1.13 (3H, d, J = 6.6 Hz), 0.942 (9H, t, J = 7.9 Hz), 0.921 (3H, s), 0.55 (6H, q, J = 7.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 119.09 (0), 69.12 (1), 55.34 (1), 52.86 (1), 42.18 (0), 40.35 (2), 34.40 (2), 33.09 (1), 27.19 (2), 24.69 (2), 22.82 (2), 19.23 (3), 17.53 (2), 13.63 (3), 6.91 (3), 4.89 (2); MS (EI) *m/z*

335 (10), 320 (3), 306 (100), 292 (28), 225 (7), 202 (20), 188 (10), 161 (17), 135 (14), 103 (55); exact mass calculated for $C_{20}H_{37}ONSi$ (M^+) 335.2644, found 335.2656.

(8S,20S)-Des-A,B-8-[(triethylsilyl)oxy]-20-(1'-methyl-1'-cyano-ethyl)-pregnane (6)

[0054]   n-Butyllithium (1.6 M in hexane, 3.4 mL, 5.4 mmol) was added to a solution of diisopropylamine (0.76 mL, 0.544 g, 5.4 mmol) in THF (1 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, then it was cooled to -78 °C and a solution of cyanide 5 (0.45 g, 1.34 mmol) in THF (2 mL) was added. The mixture was stirred at -78 °C for 30 min and then iodomethane (0.9 mL, 2.04 g, 14.4 mmol) was added. The reaction mixture was stirred at -78 °C for 1 h and then at room temperature for 1 h. It was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate. Combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (10%, then 20% ethyl acetate/hexane) to give the product 6 (0.49 g, 100% yield).

$[\alpha]_D$ +34.5 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (1H, d, J = 2.5 Hz), 1.37 (3H, s), 1.28 (3H, s), 0.99 (3H, d, J = 6.9 Hz), 0.97 (3H, s), 0.95 (9H, t, J = 7.9 Hz), 0.55 (6H, q, J = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.28 (0), 69.26 (1), 54.06 (1), 52.33 (1), 43.55 (0), 42.77 (1), 41.17 (2), 35.67 (0), 34.48 (2), 27.97 (2), 27.43 (3), 23.45 (2), 22.70 (3), 17.69 (2), 14.60 (3), 13.17 (3), 6.92 (3), 4.91 (2); MS (EI) m/z 363 (28, M^+), 349 (14), 334 (100), 321 (65), 306 (27), 261 (11), 225 (27), 183 (14), 163 (36), 135 (47), 103 (99), 75 (58); exact mass calculated for $C_{22}H_{41}ONSi$ (M^+) 363.2957, found 363.2957.

(8S,20S)-Des-A,B-8-[(triethylsilyl)oxy]-20-(1'-methyl-1'-formyl-ethyl)-pregnane (7)

[0055]   Diisobutylaluminium hydride (1.0 M in dichloromethane, 2.5 mL, 2.5 mmol) was added to a solution of the compound 6 (0.49 g, 1.35 mmol) in dichloromethane (3 mL) at -10 °C. The reaction mixture was stirred at -10 °C for 1 hour, then it was quenched with a saturated aqueous sodium potassium tartrate solution (5 mL). The water phase was extracted with dichloromethane. Combined organic layers were washed with brine and dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (10%, then 20% ethyl acetate/hexane) to give the aldehyde 7 (0.47 g, 95% yield) as colorless crystals. m.p. 71-72 °C (EtOAc); $[\alpha]_D$ +12.8 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ

9.48 (1H, s), 4.00 (1H, d, J = 2.2 Hz), 2.00 (1H, m), 0.95 (6H, s), 0.94 (9H, t, J = 7.8 Hz), 0.94 (3H, d, J = 6.9 Hz), 0.93 (3H, s), 0.54 (6H, q, J = 7.8 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 207.03 (1), 69.30 (1), 54.46 (1), 52.65 (1), 50.05 (0), 43.02 (0), 41.22 (2), 40.21 (1), 34.57 (2), 28.73 (2), 23.34 (2), 22.74 (3), 17.72 (2), 15.20 (3), 13.61 (3), 13.22 (3), 6.92 (3), 4.92 (2); MS (EI) m/z 366 (3, M$^+$), 337 (10), 323 (4), 295 (10), 281 (5), 253 (6), 239 (8), 225 (38), 203 (6), 186 (22), 163 (100), 135 (56), 103 (87), 75 (63); exact mass (ESI) calculated for C$_{22}$H$_{42}$O$_2$SiNa [M+Na]$^+$ 389.2852, found 389.2855.

(8S,20S)-Des-A,B-8-[(triethylsilyl)oxy]-20-(1'-dimethyl-3'-ethyloxycarbonyl-2'-propenyl)-pregnane (9)

[0056]   n-Butyllithium (1.6 M in hexane, 1.1 mL, 1.76 mmol) was added to a solution of diisopropylamine (0.24 mL, 0.172 g, 1.70 mmol) in dry THF (1mL) at 0 °C. After 30 min the mixture was cooled to -10 °C and triethylphosphonoacetate **8** (0.38 mL, 0.426 g, 1.9 mmol) was added. The reaction mixture was stirred at -10 °C for 30 min and then a solution of aldehyde **7** (31.4 mg, 0.086 mmol) in anhydrous THF (1 mL + 0.5 mL) was added *via* cannula. The mixture was stirred under argon at -10 °C for 1 h, then it was heated to 37 °C for 2.5 h and later it was stirred at room temperature overnight. Dichloromethane was added and the organic phase was washed with water, dried (Na$_2$SO$_4$) and concentrated. The product was purified on Sep-Pak cartridge (5g). The cartridge was washed with hexane/ethyl acetate (2%) to give **9** (34.1 mg, 91% yield) as a colorless oil. [α]$_D$ -4.6 (c 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.07 (1H, d, J = 16.0 Hz), 5.64 (1H, d, J = 16.0 Hz), 4.19 (2H, q, J = 7.1 Hz), 4.00 (1H, d, J = 2.1 Hz), 2.00 (1H, m), 1.30 (3H, t, J = 7.1 Hz), 1.00 (3H, s), 0.98 (3H, s), 0.94 (9H, t, J = 7.9 Hz), 0.93 (3H, s), 0.93 (3H, d, J = 8.0 Hz), 0.54 (6H, q, J = 7.9 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.52 (0), 162.38 (1), 115.17 (1), 69.44 (1), 60.04 (2), 54.44 (1), 52.45 (1), 45.28 (1), 43.45 (0), 41.30 (2), 40.91 (0), 34.59 (2), 29.75 (2), 27.44 (3), 23.79 (2), 21.34 (3), 17.74 (2), 15.03 (3), 14.29 (3), 13.01 (3), 6.92 (3), 4.92 (2); MS (EI) m/z 437 (4, MH$^+$), 421 (4), 407 (43), 366 (5), 337 (5), 295 (42), 281 (13), 256 (42), 225 (18), 191 (27), 163 (100); MS (ESI) m/z 459 (81, [M+Na]$^+$), 895 (75, [2M+Na]$^+$), 1331 (94, [3M+Na]$^+$), exact mass (ESI) calculated for C$_{26}$H$_{48}$O$_3$SiNa [M+Na]$^+$ 459.3270, found 459.3254.

(8S,20S)-Des-A,B-20-(1'-dimethyl-3'-ethyloxycarbonyl-propyl)-pregnan-8-ol (10)

[0057]   A solution of the ester **9** (34.1 mg, 0.078 mmol) in methanol (5 mL) was hydrogenated in the presence of 10% palladium on powdered charcoal (10 mg) at room temperature for 20 h. The reaction mixture was filtered through a Waters silica Sep-Pak cartridge (2 g), which was further washed with methanol. After removal of the solvent the ester **10** (24.0 mg, 95%) was obtained as a colorless oil. $[\alpha]_D$ +7.1 (*c* 1.0, CHCl₃); ^{1}H NMR (500 MHz, CDCl₃) δ 4.12 (2H, q, J = 7.1 Hz), 4.07 (1H, d, J = 2.1 Hz), 2.25 (2H, m), 2.10 (1H, m), 1.26 (3H, t, J = 7.1 Hz), 0.99 (3H, s), 0.92 (3H, d, J = 7.1 Hz), 0.91 (3H, s), 0.86 (3H, s); ^{13}C NMR (125 MHz, CDCl₃) δ 174.60 (0), 69.47 (1), 60.23 (2), 53.30 (1), 51.90 (1), 43.53 (0), 43.14 (1), 40.90 (2), 36.34 (0), 36.25 (2), 33.57 (2), 29.94 (2), 29.44 (2), 27.49 (3), 26.21 (3), 23.36 (2), 17.48 (2), 14.89 (3), 14.22 (3), 13.08 (3); MS (EI) *m/z* 325 (3, MH$^+$), 306 (5), 278 (8), 261 (7), 224 (7), 181 (15), 163 (56), 143 (100), 111 (76), 97 (62); MS (ESI) *m/z* 347 (85, [M+Na]$^+$), 671 (9, [2M+Na]$^+$), exact mass calculated for naC₂₀H₃₆O₃Na [M+Na]$^+$ 347.2562, found 347.2556.

(8S,20S)-Des-A,B-22-dimethyl-cholestan-8,25-diol (11)

[0058]   Methylmagnesium bromide (3.0 M solution in diethyl ether, 65μL, 0.195 mmol) was added to a solution of the ester **10** (24 mg, 0.074 mmol) in anhydrous diethyl ether (1.8 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 18 h. It was quenched with saturated aqueous NH₄Cl solution, extracted with ethyl acetate, dried (Na₂SO₄) and concentrated. The residue was applied to a Waters silica Sep-Pak cartridge (5 g). Elution with ethyl acetete/hexane (1:1) gave the diol **11** (19.2 mg, 84%). $[\alpha]_D$ +4.8 (*c* 1.0, CHCl₃); ^{1}H NMR (400 MHz, CDCl₃) δ 4.07 (1H, d, J = 2.1 Hz), 2.10 (1H, m), 1.21 (6H, s), 0.99 (3H, s), 0.91 (3H, s), 0.90 (3H, d, J = 8.2 Hz), 0.84 (3H, s); ^{13}C NMR (100 MHz, CDCl₃) δ 71.19 (0), 69.51 (1), 53.43 (1), 51.91 (1), 43.51 (0), 42.65 (1), 40.91 (2), 37.59 (2), 36.29 (2), 36.24 (0), 33.55 (2), 29.89 (2), 29.23 (3), 29.17 (3), 28.04 (3), 26.29 (3), 23.38 (2), 17.49 (2), 14.87 (3), 13.10 (3); MS (EI) *m/z* no M$^+$, 292 (5), 259 (2), 223 (3), 205 (7), 181 (8), 163 (28), 129 (25), 111 (100), 95 (23); MS (ESI) *m/z* 333 (95, [M+Na]$^+$), 643 (11, [2M+Na]$^+$), exact mass (ESI) calculated for naC₂₀H₃₈O₂Na [M+Na]$^+$ 333.2770, found 333.2774.

(20S)-Des-A,B-22-dimethyl-25-[(triethylsilyl)oxy]-cholestan-8-one (12)

[0059] Molecular sieves A4 (100 mg) were added to a solution of 4-methylmorpholine oxide (150 mg, 1.28 mmol) in dichloromethane (600 μL). The mixture was stirred at room temperature for 15 min and tetrapropylammonium perruthenate (8 mg, 22.8 μmol) was added, followed by a solution of diol **11** (19 mg, 0.061 mmol) in dichloromethane (400 + 200 μL). The resulting suspension was stirred at room temperature for 1 h. The reaction mixture was filtered through a Waters silica Sep-Pak cartridge (2 g) that was further washed with ethyl acetate. After removal of the solvent the ketone (19 mg) was obtained as a colorless oil.

Triethylsilyl trifluoromethanesulfonate (20 μL, 23 mg, 0.088 mmol) was added dropwise to a solution of the ketone (19 mg, 0.062 mmol) and 2,6-lutidine (60 μL, 55 mg, 0.515 mmol) in dichloromethane (1.2 mL) at -40 °C. The reaction mixture was stirred at -40 °C for 15 min, then it was diluted with dichloromethane and washed with water. The organic layer was dried (Na$_2$SO$_4$) and concentrated. The residue was applied to a Waters silica Sep-Pak cartridge (5 g). Elution with hexane/ethyl acetate (1%, then 2%) gave the protected ketone **12** (20.2 mg, 78% yield).

$[\alpha]_D$ -19.2 (c 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.33 (1H, d, J = 11.5, 7.5 Hz), 2.24 (3H, m), 1.19 (6H, s), 0.95 (9H, t, J = 7.9 Hz), 0.95 (3H, d, J = 6.9 Hz), 0.89 (3H, s), 0.84 (3H, s), 0.71 (3H, s), 0.56 (6H, q, J = 7.9 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 212.46 (0), 73.40 (0), 61.73 (1), 53.18 (1), 51.09 (0), 43.36 (1), 41.08 (2), 39.48 (2), 38.77 (2), 36.15 (0), 35.76 (2), 30.76 (2), 29.87 (3), 27.70 (3), 26.24 (3), 23.94 (2), 19.96 (2), 14.72 (3), 12.87 (3), 7.14 (3), 6.81 (2); MS (EI) m/z no M$^+$, 407 (10), 393 (28), 364 (11), 294 (12), 273 (10), 173 (48), 163 (28), 111 (100); MS (ESI) m/z 445 (8, [M+Na]$^+$), exact mass (ESI) calculated for C$_{26}$H$_{50}$O$_2$SiNa [M+Na]$^+$ 445.3478, found 445.3486.

(20S)-2-Methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D$_3$ (14)

[0060] Phenyllithium (1.83 M in di-n-buthylether, 0.1 mL, 0.183 mmol) was added to a stirred solution of the phosphine oxide **H** (110 mg, 0.189 mmol) in anhydrous THF (1 mL) at -30 °C. After 30 min the mixture was cooled to -78 °C and a precooled solution of the ketone **12** (20 mg, 47.4 μmol) in anhydrous THF (200 + 100 μL) was added. The reaction mixture was stirred under argon at -78 °C for 4 hours and then at +4 °C for 19 h. Ethyl acetate was added and the organic phase was washed with brine, dried (Na$_2$SO$_4$) and concentrated. The residue was applied to a Waters silica Sep-Pak cartridge (5 g). The

cartridge was washed with hexane and ethyl acetate/hexane (1:99) to give the crude product. The vitamin was further purified by straight phase HPLC [9.4 × 250 mm Zorbax Silica column, 4 mL/min, hexane/2-propanol (0.1%) solvent system, R_t = 3.4 min.] to give the pure protected compound **13** (33.83 mg, 91% yield).

UV (in hexane) λ_{max} 263.5, 253.5, 245.5 nm; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.22 (1H, d, J = 11.1 Hz, 6-H), 5.85 (1H, d, J = 11.1 Hz, 7-H), 4.97 (1H, s, =CH$_2$), 4.92 (1H, s, =CH$_2$), 4.43 (2H, m, 1β-H and 3α-H), 2.81 (1H, dm, J = 12.6 Hz), 2.52 (1H, dd, J = 13.3, 5.9 Hz, 10α-H), 2.47 (1H, dd, J = 12.6, 4.5 Hz, 4α-H), 2.34 (1H, dd, J = 13.3, 2.8 Hz, 10β-H), 2.18 (1H, dd, J = 12.6, 8.3 Hz, 4β-H), 2.09 (1H, m), 1.97 (2H, m), 1.19 (6H, bs, 26-H$_3$, 27-H$_3$), 0.95 (9H, t, J = 7.9 Hz), 0.93 (3H, d, J = 6.8 Hz, 21-H$_3$), 0.897 (9H, s, t-BuSi), 0.868 (9H, s, t-BuSi), 0.889 and 0.833 (each 3H, each s, 28-H$_3$, 30-H$_3$), 0.62 (3H, s, 18-H$_3$), 0.57 (6H, q, J = 7.9 Hz), 0.080 (3H, s, SiMe), 0.068 (3H, s, SiMe), 0.049 (3H, s, SiMe), 0.027 (3H, s, SiMe); ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.98 (0, C-2), 141.40 (0, C-8), 132.77 (0, C-5), 122.46 (1, C-6), 116.43 (1, C-7), 106.25 (2, =CH$_2$), 73.52 (0, C-25), 72.53 and 71.64 (each 1, C-1, C-3), 56.02 (1), 52.84 (1), 47.60 (2), 46.96 (0, C-13), 44.18 (1), 41.14 (2), 38.84 (2), 38.57 (2), 36.23 (0, C-22) , 35.85 (2), 31.28 (2), 29.91 and 29.86 (each 3, C-26, C-27), 28.84 (2), 27.75 (3), 26.22 (3), 25.84 (3), 25.78 (3), 23.53 (2), 23.17 (2), 18.25 (0), 18.17 (0), 14.70 (3), 12.53 (3), 7.15 (3), 6.84 (2), -4.86 (3), -5.10 (3); MS (ESI) *m/z* 809 (2, [M+Na]$^+$), exact mass (ESI) calculated for C$_{47}$H$_{90}$O$_3$Si$_3$Na [M+Na]$^+$ 809.6096, found 809.6086.

[0061]   The protected compound **13** (33.82 mg, 43.0   mol) was dissolved in THF (4 mL) and acetonitrile (3 mL). A solution of aqueous 48% HF in acetonitrile (1:9 ratio, 4 mL) was added at 0 °C and the resulting mixture was stirred at room temperature for 3 h. Saturated aqueous NaHCO$_3$ solution was added and the reaction mixture was extracted with dichloromethane. The combined organic phases were dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residue was diluted with 2 mL of hexane/ethyl acetate (7:3) and applied to a Waters silica Sep-Pak cartridge (5 g). An elution with hexane/ethyl acetate (7:3, then 1:1) gave the crude product **14**. The vitamin **14** was further purified by straight phase HPLC [9.4 × 250 mm Zorbax Silica column, 4 mL/min, hexane/2-propanol (85:15) solvent system, R_t = 7.8 min.] and reverse phase HPLC [9.4 × 250 mm Zorbax RX-C18 column, 3 mL/min, methanol/water (85:15) solvent system, R_t = 15.7 min.] to give the pure compound **14** (14.336 mg, 75% yield).

UV (in EtOH) λ_{max} 261.5, 252.0, 244.5 nm; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.35 (1H, d, J = 11.2 Hz, 6-H), 5.89 (1H, d, J = 11.2 Hz, 7-H), 5.10 (1H, s, =CH$_2$), 5.08 (1H, s, =CH$_2$), 4.48 (2H, m, 1β-H and 3α-H), 2.84 (1H, dd, J = 13.0, 4.3 Hz, 10β-H), 2.80 (1H, dd, J = 13.3, 4.1 Hz, 9β-H), 2.56 (1H, dd, J = 13.4, 3.3 Hz, 4α-H), 2.32 (1H, dd, J = 13.4, 6.1 Hz, 4β-H), 2.28 (1H, dd, J = 13.0 Hz, 8.4 Hz, 10α-H), 2.08 (1H, m), 1.21 (6H, s, 26-H$_3$, 27-H$_3$), 0.92 (3H, d, J = 7.0 Hz, 21-H$_3$), 0.91 and 0.84 (each 3H, each s, 28-H$_3$, 30-H$_3$), 0.62 (3H, 18-H$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) δ 151.97 (0, C-2), 143.44 (0, C-8), 130.52 (0, C-5), 124.23 (1, C-6), 115.65 (1, C-7), 107.71 (2, =CH$_2$), 71.79 and 70.63 (each 1, C-1, C-3), 71.23 (0, C-25), 56.01 (1), 52.77 (1), 47.07 (0, C-13), 45.77 (2), 43.90 (1), 40.98 (2), 38.15 (2), 37.64 (2), 36.28 (0, C-22), 36.00 (2), 31.20 (2), 29.23 and 29.20 (each 3, C-26, C-27), 29.02 (2), 27.77 (3), 25.97 (3), 23.55 (2), 23.22 (2), 14.71 (3), 12.59 (3); MS (EI) m/z 444 (30, M$^+$), 426 (7, M$^+$- H$_2$O), 411 (2), 341 (4), 315 (20), 297 (10), 269 (12), 247 (20), 223 (4), 192 (4), 175 (6), 161 (14), 135 (40), 111 (56), 91 (100), 69 (24); MS (ESI) m/z 467 (49, [M+Na]$^+$), 911 (11, [2M+Na]$^+$), exact mass (ESI) calculated for C$_{29}$H$_{48}$O$_3$Na [M+Na]$^+$ 467.3501, found 467.3507.

Example 2: Synthesis of (20R)-2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D$_3$

[0062]   Compounds of the present technology, including (20R)-2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D$_3$, were prepared using the methods shown in Schemes 4-6. As shown in Scheme 4, compound **4** is obtained by the same steps shown in Scheme 2 and described in Example 1. Kornblum oxidation of tosylate **4** with sodium bicarbonate in DMSO provided aldehyde **15**. Compound **15** was epimerized at position **20** by treatment with tetrabutylammonium hydroxide to give compound **16** and reduced with sodium borohydride to give a mixture of diastereomers, from which compound **17**, with the 20R stereochemistry, was isolated.

[0063]   As shown in Scheme 5, compound **17** was subjected to an analogous series of synthetic steps to those shown in Schemes 2 and 3 to provide compound **25**, the 20R diastereomer of compound **11**. Likewise, as shown in Scheme 6, compound **25** was subjected to the same series of oxidation, protection, triethylphosphonoacetate condensation and deprotection steps as compound **11** in Scheme 3, to provide compound **28**, (20R)-2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D$_3$. This product was fully characterized as described below.
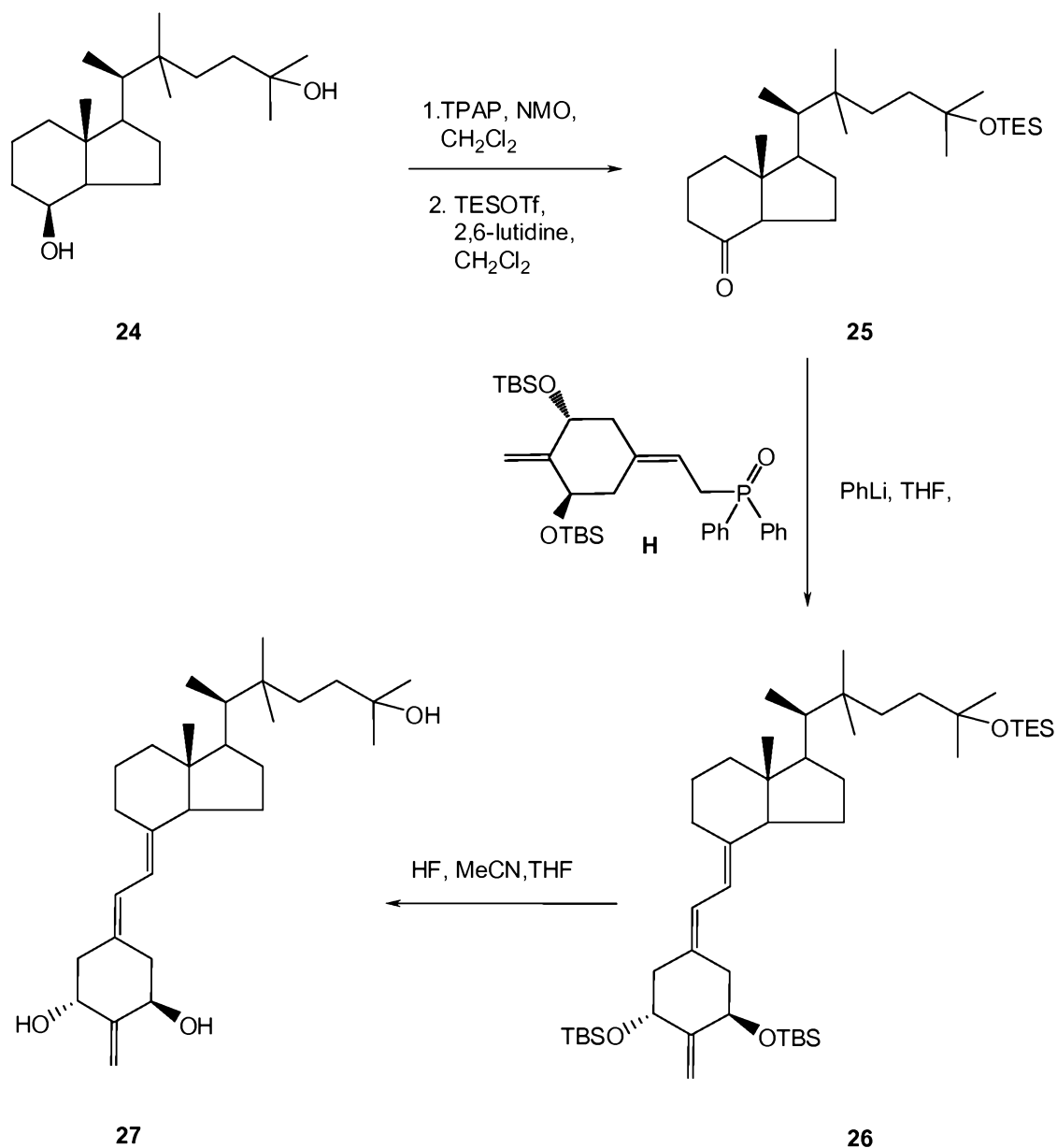
Scheme 4
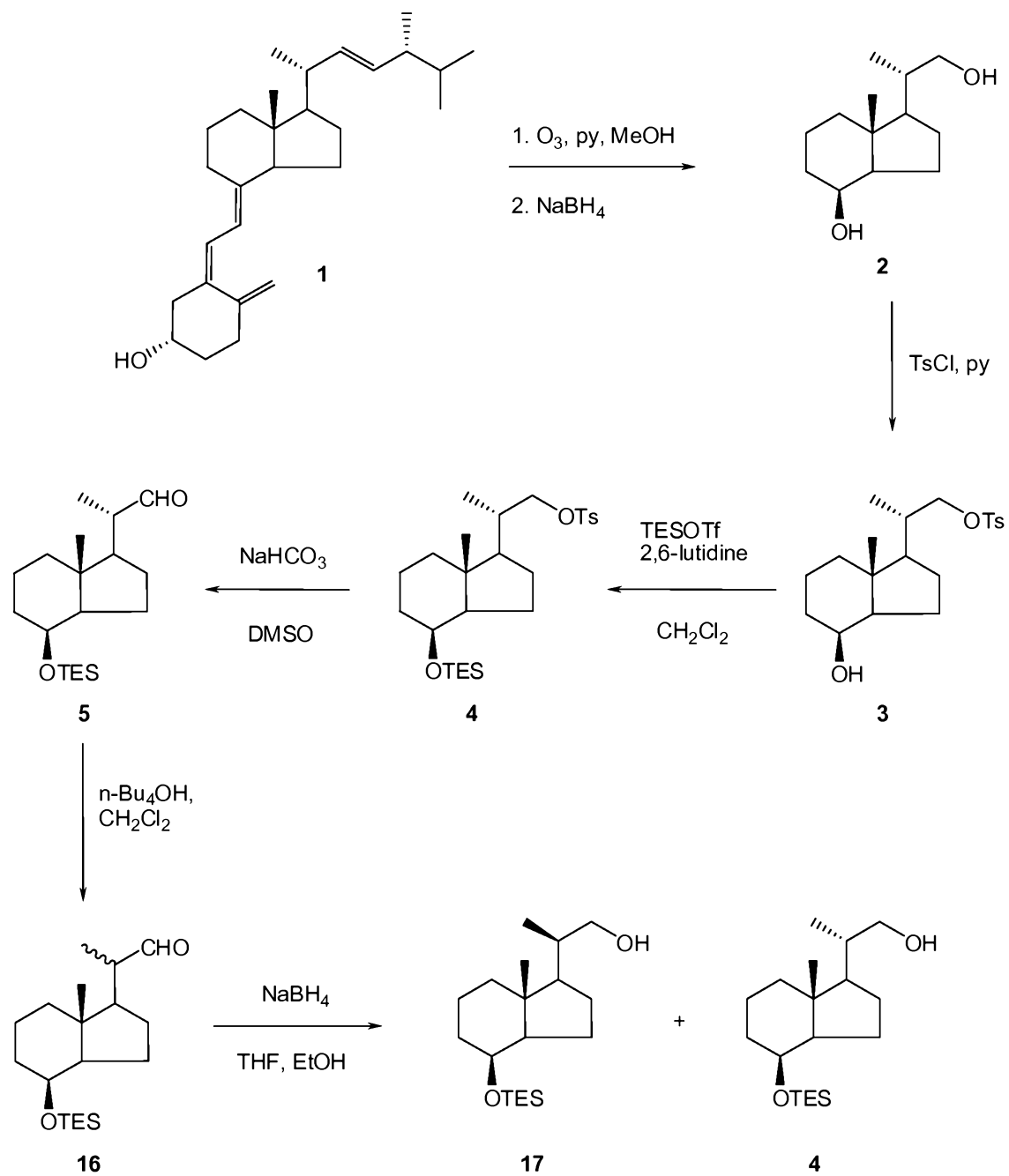
Scheme 5
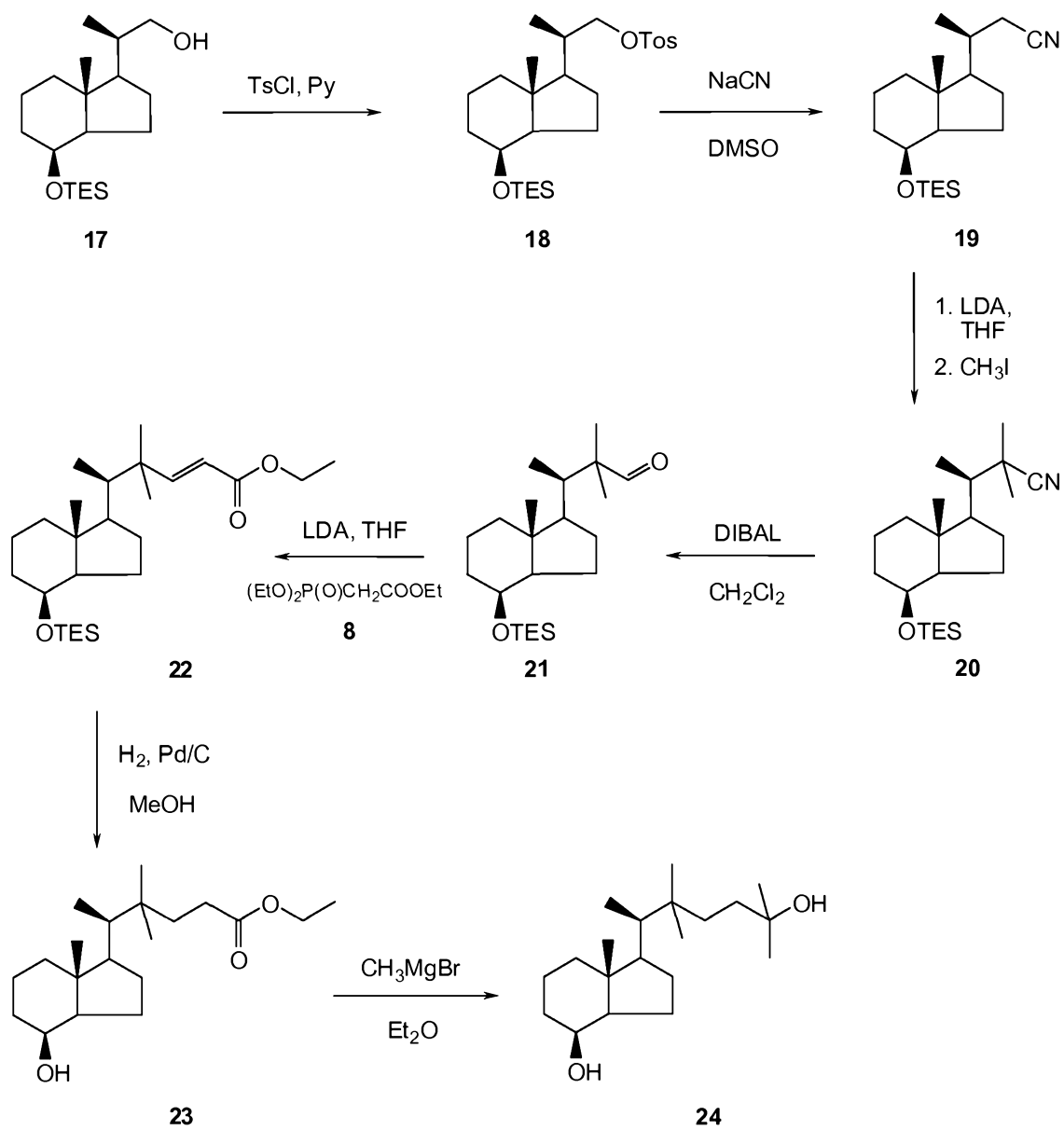
Scheme 6

(8S,20S)-Des-A,B-8-[(triethylsilyl)oxy]-20-(formyl)-pregnane (15)

[0064]   Sodium bicarbonate (5 g, 59.5 mmol) was added to a solution of tosylate **4** (2.31g, 4.81 mmol) in DMSO (15 mL). The reaction mixture was stirred at for 1 hour 15 min 120 $^{\circ}$C and it was diluted with ethyl acetate. The organic phase was washed with brine, dried (Na$_2$SO$_4$) and concentrated. The residue was purified by column chromatography on silica gel (5% ethyl acetate/hexane) to give the product **5** (1.19 g, 76% yield) as a colorless oil.

[α]$_D$ +41.4 (c 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.58 (1H, d, J = 3.2 Hz), 4.06 (1H, d, J = 2.4 Hz), 2.36 (1H, m), 1.09 (3H, d, J = 6.8, 3.0 Hz), 0.96 (3H, s), 0.94 (9H, t, J = 7.9

28

Hz), 0.56 (6H, q, J = 7.9 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 205.40 (1), 69.01 (1), 52.38 (1), 51.69 (1), 49.17 (1), 42.64 (0), 40.49 (2), 34.54 (2), 26.20 (2), 23.28 (2), 17.58 (2), 13.89 (3), 13.32 (3), 6.92 (3), 4.90 (2); MS (EI) m/z 324 (5, M$^+$), 295 (100, M$^+$ - EtOH), 281 (30), 246 (12), 191 (36), 175 (99), 135 (54), 103 (76); MS (ESI) m/z 671 (100, [2M+Na]$^+$), 995 (49, [3M+Na]$^+$); exact mass calculated for C$_{17}$H$_{31}$O$_2$Si [M-Et]$^+$ 295.2093, found 295.2103.

(8S,20R)-Des-A,B-8-[(triethylsilyl)oxy]-20-(hydroxymethyl)-pregnane (17)

[0065]   Tetrabutylammonium hydroxide (40 wt. % solution in water, 4 mL, 3.98 g, 0.015 mol) was added to a solution of aldehyde **5** (0.97 g, 2.99 mmol) in dichloromethane (20 mL). The reaction mixture was stirred for 18 hours at room temperature and it was diluted with dichloromethane. The organic phase was washed with water, dried (Na$_2$SO$_4$) and concentrated. The product was purified by column chromatography on silica gel (3%, then 5% ethyl acetate/hexane) to give a mixture of isomers **16** (0.69 g, 71% yield). Sodium borohydride (0.2 g, 5.29 mmol) was added to a solution of aldehydes **16** (0.69 g, 2.13 mmol) in THF (10 mL) and ethanol (10 mL). The reaction mixture was stirred for 45 min., quenched with saturated NH$_4$Cl, extracted with ethyl acetate and dried (Na$_2$SO$_4$). The residue was purified by column chromatography on silica gel (4%, then 20% ethyl acetate/hexane) to give the pure isomer **17** (0.326 g, 47% yield) and a mixture of both isomers **17** and **4** (0.277 g, 40% yield).

[α]$_D$ +33.6 (c 1.0, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.03 (1H, d, J = 2.5 Hz), 3.72 (1H, dd, J = 10.7, 3.6 Hz), 3.44 (1H, dd, J = 10.7, 7.0 Hz), 0.95 (9H, t, J = 7.9 Hz), 0.94 (3H, d, J = 6.6 Hz), 0.93 (3H, s), 0.55 (6H, q, J = 7.9 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ 69.25 (1), 66.84 (2), 53.01 (1), 41.91 (0), 40.20 (2), 37.49 (1), 34.58 (2), 26.73 (2), 22.81 (2), 17.67 (2), 16.58 (3), 13.88 (3), 6.93 (3), 4.91 (2); MS (EI) m/z 326 (7, M$^+$), 311 (3, M$^+$-CH$_3$), 297 (100, M$^+$-Et), 283 (41), 265 (8), 225 (23), 193 (41), 177 (41), 135 (57), 103 (99); MS (ESI) m/z 327 (100, [M+H]$^+$); exact mass calculated for C$_{17}$H$_{33}$O$_2$Si [M-Et]$^+$ 297.2250, found 297.2244.

(8S,20R)-Des-A,B-8-[(triethylsilyl)oxy]-20-[(p-toluenesulfonyl)oxy]methyl-pregnane (18)

[0066]   A solution of tosyl chloride (0.38 g, 2 mmol) in pyridine (3 mL) was transfered *via* cannula to a solution of alcohol **17** (0.326 g, 1 mmol) in pyridine (5 mL) at -20 °C. The reaction mixture was stirred at -20 °C for 1 hour and then at +4 °C overnight. It was diluted with methylene chloride, washed with a saturated aqueous solution of CuSO$_4$ and dried (Na$_2$SO$_4$). The residue was purified by column chromatography on silica gel (5%, then

10% and 20% ethyl acetate/hexane) to give the tosylate **18** (427 mg, 89% yield) as a colorless oil.

$[\alpha]_D$ +8.8 (*c* 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.78 (1H, d, J = 8.2 Hz), 7.34 (1H, d, J = 8.2 Hz), 4.11 (1H, dd, J = 9.3, 3.4 Hz), 4.00 (1H, d, J = 2.0 Hz), 3.77 (1H, dd, J = 9.3, 7.4 Hz), 2.45 (3H, s), 0.93 (9H, t, J = 7.9 Hz), 0.87 (3H, d, J = 6.7 Hz), 0.81 (3H, s), 0.53 (6H, q, J = 7.9 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 144.53 (0), 133.18 (0), 129.70 (1), 127.93 (1), 74.30 (2), 69.09 (1), 52.74 (1), 52.60 (1), 41.77 (0), 39.95 (2), 34.66 (1), 34.40 (2), 26.61 (2), 22.64 (2), 21.62 (3), 17.54 (2), 16.65 (3), 13.82 (3), 6.91 (3), 4.89 (2); MS (EI) *m/z* 480 (18, M$^+$), 465 (2), 437 (14), 348 (2, M$^+$- Et$_3$SiOH), 309 (1, M$^+$- CH$_3$C$_6$H$_4$SO$_3$), 257 (91), 225 (23), 177 (100), 135 (19), 121 (24); MS (ESI) *m/z* 503 (7, [M+Na]$^+$), 983 (4, [2M+Na]$^+$), 1463 (10, [3M+Na]$^+$); exact mass calculated for C$_{26}$H$_{44}$O$_4$SSiNa [M+Na]$^+$ 503.2627, found 503.2639.

(8S,20S)-Des-A,B-8-[(triethylsilyl)oxy]-20-(cyanomethyl)-pregnane (19)

[0067]   Sodium cyanide (0.9 g, 18.4 mmol) was added to a solution of tosylate **18** (0.412 g, 0.858 mmol) in DMSO (5 mL). The resulting mixture was stirred at 90 °C for 2 h, then it was cooled, diluted with water and extracted with ethyl acetate. Combined organic phases were dried (Na$_2$SO$_4$) and concentrated. The residue was purified by column chromatography on silica gel (10% ethyl acetate/hexane) to give cyanide **19** (0.242 g, 85% yield) as a colorless oil.

$[\alpha]_D$ +17.3 (*c* 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.04 (1H, d, J = 2.2 Hz), 2.44 (1H, dd, J = 16.7, 4.0 Hz), 2.38 (1H, dd, J = 16.7, 6.6 Hz), 1.06 (3H, d, J = 6.7 Hz), 0.94 (9H, t, J = 7.9 Hz), 0.91 (3H, s), 0.55 (6H, q, J = 7.9 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 118.90 (0), 69.07 (1), 54.96 (1), 52.74 (1), 41.91 (0), 40.23 (2), 34.29 (2), 31.79 (1), 27.01 (2), 24.00 (2), 22.68 (2), 19.58 (3), 17.53 (2), 13.81 (3), 6.90 (3), 4.88 (2); MS (EI) *m/z* 335 (3, M$^+$), 320 (1, M$^+$ - Me) 306 (76, M$^+$- Et), 292 (15), 271 (2), 225 (3), 202 (30), 161 (13), 103 (100), 75 (38); MS (ESI) *m/z* 336 (7, [M+H]$^+$), 358 (4, [M+Na]$^+$), 693 (100, [2M+Na]$^+$), 1028 (40, [3M+Na]$^+$); exact mass calculated for C$_{18}$H$_{32}$NOSi [M-Et]$^+$ 306.2253, found 306.2253.

(8S,20R)-Des-A,B-8-[(triethylsilyl)oxy]-20-(1'-methyl-1'-cyano-ethyl)-pregnane (20)

[0068]   n-Butyllithium (1.6 M in hexane, 2.4 mL, 3.8 mmol) was added to a solution of diisopropylamine (0.54 mL, 0.384 g, 3.8 mmol) in THF (2 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, then it was cooled to -78 °C and a solution of the

compound **19** (0.326 g, 0.973 mmol) in THF (2 mL) was added. The mixture was stirred at -78 °C for 30 min and then iodomethane (1.2 mL, 2.73 g, 19.2 mmol) was added. The reaction mixture was stirred at -78 °C 1 h and then at room temperature for 1 h. It was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate. Combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (5%, then 10% ethyl acetate/hexane) to give the product **20** (0.197 g, 56% yield).

$[\alpha]_D$ + 30.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (1H, d, J = 2.2 Hz), 1.30 (3H, s), 1.26 (3H, s), 0.97 (3H, d, J = 7.1 Hz), 0.95 (9H, t, J = 7.9 Hz), 0.84 (3H, s), 0.55 (6H, q, J = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.16 (0), 68.91 (1), 52.01 (1), 50.84 (1), 42.88 (0), 37.84 (1), 37.77 (2), 34.88 (2), 24.97 (3), 23.88 (3), 23.17 (2), 21.81 (2), 17.36 (2), 14.54 (3), 13.03 (3), 6.92 (3), 4.90 (2); MS (EI) *m/z* 363 (13, M$^+$), 334 (72, M$^+$-Et), 320 (12), 295 (4), 261 (4), 249 (15), 234 (29), 191 (100), 163 (72), 111 (81), 93 (28), 81 (39), 57 (49); MS (EI) *m/z* 363 (12, M$^+$), 334 (71), 320 (12), 295 (4), 234 (28), 191 (100), 163 (71), 135 (42), 111 (80); MS (ESI) *m/z* 364 (11, [M+H]$^+$), 749 (62, [2M+Na]$^+$), 1113 (100, [3M+Na+H]$^{2+}$); exact mass calculated for $C_{22}H_{42}ONSi$ [M+H]$^+$ 364.3031, found 364.3044.

(8S,20R)-Des-A,B-8-[(triethylsilyl)oxy]-20-(1'-methyl-1'-formyl-ethyl)-pregnane (21)

[0069]   Diisobutylaluminium hydride (1.0 M in dichloromethane, 3.1 mL, 3.1 mmol) was added to a solution of the compound **20** (0.197 g, 0.543 mmol) in dichloromethane (4 mL) at -10 °C. The reaction mixture was stirred at -10 °C for 1 hour, then it was quenched with a saturated aqueous sodium potassium tartrate solution (5 mL). The water phase was extracted with dichloromethane. Combined organic layers were washed with brine and dried (Na_2SO_4) and concentrated.   The residue was purified on Sep-Pak cartridge (5g). The cartridge was washed with hexane/ethyl acetate (9:1) to give the aldehyde **21** as colorless oil (0.15 g, 75% yield).

$[\alpha]_D$ +35.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (1H, s), 4.04 (1H, d, J = 2.2 Hz), 0.95 (6H, s), 0.94 (9H, t, J = 7.8 Hz), 0.85 (3H, d, J = 7.00 Hz), 0.85 (3H, s), 0.55 (6H, q, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.49 (1), 68.91 (1), 51.96 (1), 50.79 (1), 50.68 (0), 42.89 (0), 38.34 (2), 34.88 (2), 33.78 (1), 23.18 (2), 22.13 (2), 19.41 (3), 18.09 (3), 17.40 (2), 14.48 (3), 12.29 (3), 6.92 (3), 4.90 (2); MS (EI) *m/z* 366 (1, M$^+$), 337 (31, M$^+$-Et), 307 (37), 295 (12), 251 (13), 225 (30), 203 (22), 186 (9), 171 (14), 163 (74), 135 (43), 103

(100); MS (ESI) *m/z* 389 (29, [M+Na]$^+$), 755 (73, [2M+Na]$^+$), 1121 (15, [3M+Na]$^+$); exact mass (ESI) calculated for $C_{22}H_{42}O_2SiNa$ [M+Na]$^+$ 389.2847, found 389.2838.

(8S,20R)-Des-A,B-8-[(triethylsilyl)oxy]-20-(1'-dimethyl-3'-ethyloxycarbonyl-2'-propenyl)-pregnane (22)

[0070]   n-Butyllithium (1.6 M in hexane, 5.2 mL, 8.3 mmol) was added to a solution of diisopropylamine (1.2 mL, 0.840 g, 8.3 mmol) in dry THF (2 mL) at 0 °C. After 30 min the mixture was cooled to -10 °C and triethylphosphonoacetate **8** (1.9 mL, 2.13 g, 9.5 mmol) was added. The reaction mixture was stirred at -10 °C for 30 min and a solution of the aldehyde **21** (0.15 g, 0.41 mmol) in anhydrous THF (5 mL + 3 mL) was added *via* cannula. The mixture was stirred under argon at -10 °C for 1 h, then it was heated to +37 °C for 3 h and later it was stirred at room temperature for 18 h. Dichloromethane was added and the organic phase was washed with water, dried (Na_2SO_4) and concentrated. The product was purified on Sep-Pak cartridge (5g). The cartridge was washed with hexane/ethyl acetate (2%, then 3% and 5%) to give the product **22** (99 mg, 55% yield) as a colorless oil. [α]$_D$ +18.1 (*c* 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.92 (1H, d, J = 15.9 Hz), 5.69 (1H, d, J = 15.9 Hz), 4.19 (2H, m), 4.03 (1H, d, J = 2.0 Hz), 1.29 (3H, t, J = 7.1 Hz), 0.98 (3H, s), 0.96 (3H, s), 0.94 (9H, t, J = 7.9 Hz), 0.81 (3H, d, J = 7.0 Hz), 0.80 (3H, s), 0.54 (6H, q, J = 7.9 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.19 (0), 159.65 (1), 117.69 (1), 69.04 (1), 60.07 (2), 52.08 (1), 50.18 (1), 42.83 (0), 41.16 (0), 38.53 (1), 38.19 (2), 35.00 (2), 24.64 (3), 23.30 (3), 22.14 (2), 17.49 (2), 14.50 (3), 14.29 (3), 13.02 (3), 6.94 (3), 4.93 (2); MS (EI) *m/z* 436 (0.3, M$^+$), 407 (3, M$^+$-Et), 334 (2), 286 (10), 257 (18), 229 (100), 206 (16), 191 (99), 163 (26), 142 (16); MS (ESI) *m/z* 459 (99, [M+Na]$^+$), 896 (100, [2M+Na+H]$^{2+}$), 1332 (47, [3M+Na+H]$^{2+}$), exact mass (ESI) calculated for $C_{26}H_{48}O_3SiNa$ [M+Na]$^+$ 459.3265, found 459.3259.

(8S,20R)-Des-A,B-20-(1'-dimethyl-3'-ethyloxycarbonyl-propyl)-pregnan-8-ol (23)

[0071]   A solution of the ester **22** (99 mg, 0.23 mmol) in methanol (5 mL) was hydrogenated in the presence of 10% palladium on powdered charcoal (10 mg) at room temperature for 20 h. The reaction mixture was filtered through a Waters silica Sep-Pak cartridge (2 g), which was further washed with methanol. After removal of the solvent the ester **23** (50.4 mg, 68%) was obtained as a colorless oil.

[α]$_D$ +15.3 (*c* 1.0, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.12 (2H, q, J = 7.1 Hz), 4.09 (1H, s), 2.25 (3H, m), 1.26 (3H, t, J = 7.1 Hz), 0.85 (3H, s), 0.80 (3H, s), 0.79 (3H, d, J = 7.6 Hz), 0.78 (3H, s); ^{13}C NMR (100 MHz, CDCl$_3$) δ 174.60 (0), 69.07 (1), 60.21 (2), 51.69 (1), 49.40

(1), 42.60 (0), 37.93 (2), 37.07 (1), 36.04 (0), 34.57 (2), 33.92 (2), 29.54 (2), 24.82 (3), 24.56 (3), 22.90 (2), 22.26 (2), 17.26 (2), 14.49 (3), 14.20 (3), 12.62 (3); MS (EI) m/z 324 (3, M^+), 278 (7), 261 (8), 224 (7), 210 (5), 181 (15), 163 (70), 143 (100), 129 (33), 111 (72), 97 (44), 69 (48); MS (ESI) m/z 342 (100, $[M+NH_4]^+$), 671 (11, $[2M+Na]^+$), exact mass calculated for $C_{20}H_{37}O_3$ $[M+H]^+$ 325.2738, found 325.2727.

(8S,20R)-Des-A,B-22-dimethyl-cholestan-8,25-diol (24)

[0072]   Methylmagnesium bromide (3.0 M solution in diethyl ether, 130 μL, 0.39 mmol) was added to a solution of the ester **23** (50 mg, 0.154 mmol) in anhydrous diethyl ether (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 18 h. It was quenched with a saturated aqueous NH₄Cl solution, extracted with ethyl acetate, dried (Na₂SO₄) and concentrated. The residue was applied to a Waters silica Sep-Pak cartridge (5 g). Elution with ethyl acetete/hexane (1:1) gave the diol **24** (48 mg, 100%) as colorless crystals. m.p. 122-124 °C (from ethyl acetate/hexane); $[\alpha]_D$ +21.2 (*c* 0.988, CHCl₃). ^{1}H NMR (400 MHz, CDCl₃) δ 4.10 (1H, d, J = 1.8 Hz), 1.21 (6H, s), 0.85 (3H, s), 0.81 (3H, s), 0.78 (3H, d, J = 7.3 Hz), 0.76 (3H, s); ^{13}C NMR (100 MHz, CDCl₃) δ 71.15 (0), 69.13 (1), 51.71 (1), 49.44 (1), 42.62 (0), 38.06 (2), 37.73 (2), 36.96 (1), 35.90 (0), 34.17 (2), 33.92 (2), 29.24 (3), 29.15 (3), 25.38 (3), 24.81 (3), 22.94 (2), 22.36 (2), 17.27 (2), 14.50 (3), 12.62 (3); MS (EI) m/z 292 (5, M^+-H₂O), 223 (3), 205 (9), 163 (43), 149 (9), 135 (21), 129 (41), 111 (100), 95 (25), 81 (20); MS (ESI) m/z 310 (84, $[M]^+$), 328 (88, $[M+NH_4]^+$), 643 (24, $[2M+Na]^+$), exact mass (ESI) calculated for na$C_{20}H_{38}O_2$Na $[M+Na]^+$ 333.2765, found 333.2764.

(20R)-Des-A,B-22-dimethyl-25-[(triethylsilyl)oxy]-cholestan-8-one (25)

[0073]   Molecular sieves A4 (100 mg) were added to a solution of 4-methylmorpholine oxide (90 mg, 0.77 mmol) in dichloromethane (400 μL). The mixture was stirred at room temperature for 15 min and tetrapropylammonium perruthenate (9.7 mg, 27.6 μmol) was added, followed by a solution of diol **24** (29.4 mg, 0.095 mmol) in dichloromethane (300 + 100 μL). The resulting suspension was stirred at room temperature for 1 h. The reaction mixture was filtered through a Waters silica Sep-Pak cartridge (2 g) that was further washed with ethyl acetate. After removal of the solvent the ketone (29.5 mg) was obtained as a colorless oil.

[0074]   Triethylsilyl trifluoromethanesulfonate (30 μL, 35.1 mg, 0.133 mmol) was added dropwise to a solution of the ketone (29.2 mg, 0.095 mmol) and 2,6-lutidine (40 μL, 37

mg, 0.343 mmol) in dichloromethane (1.6 mL) at -50 °C. The reaction mixture was stirred at -40 °C for 15 min, then it was diluted with dichloromethane and washed with water. The organic layer was dried (Na$_2$SO$_4$) and concentrated. The residue was applied to a Waters silica Sep-Pak cartridge (5 g). Elution with hexane/ethyl acetate (1%, then 2%) gave the protected ketone **25** (34.4 mg, 86% yield).

[α]$_D$ -8.8 (*c* 1.0, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.44 (1H, dd, J = 11.5, 7.5 Hz), 1.20 (6H, s), 0.95 (9H, t, J = 7.9 Hz), 0.82 (3H, s), 0.79 (3H, d, J = 7.5 Hz), 0.78 (3H, s), 0.58 (3H, s), 0.57 (6H, q, J = 7.9 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 212.18 (0), 73.42 (0), 60.66 (1), 51.10 (0), 49.73 (1), 41.01 (2), 38.88 (2), 38.26 (1), 36.76 (2), 35.95 (0), 33.93 (2), 29.89 (3), 25.17 (3), 24.91 (3), 23.66 (2), 22.68 (2), 19.47 (2), 12.99 (3), 12.33 (3), 7.14 (3), 6.82 (2); MS (EI) *m/z* no M$^+$, 407 (33), 393 (68), 364 (54), 323 (11), 293 (25), 253 (42), 173 (82), 163 (70), 111 (78), 107 (100); MS (ESI) *m/z* 423 (27, [M+H]$^+$), 445 (47, [M+Na]$^+$), 867 (26, [2M+Na]$^+$), 1290 (8, [3M+Na+H]$^{2+}$), exact mass (ESI) calculated for C$_{26}$H$_{51}$O$_2$Si [M+H]$^+$ 423.3653, found 423.3649.

(20R)-2-Methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D$_3$ (27)

[0075]   Phenyllithium (1.70 M in di-n-buthylether, 105 μL, 0.178 mmol) was added to a stirred solution of the phosphine oxide **H** (73.6 mg, 0.126 mmol) in anhydrous THF (500 μL) at -30 °C. After 30 min the mixture was cooled to -78 °C and a precooled (-78 °C) solution of the ketone **25** (35 mg, 82.9 μmol) in anhydrous THF (400 + 300 μL) was added. The reaction mixture was stirred under argon at -78 °C for 4 hours and then at +4 °C for 19 h. Ethyl acetate was added and the organic phase was washed with brine, dried (Na$_2$SO$_4$) and concentrated. The residue was applied to a Waters silica Sep-Pak cartridge (5 g). The cartridge was washed with hexane and ethyl acetate/hexane (1:99) to give the crude product. The vitamin was further purified by straight phase HPLC [9.4 × 250 mm Zorbax Silica column, 4 mL/min, hexane/2-propanol (0.1%) solvent system, R$_t$ = 3.2 min.] to give the pure protected compound **26** (51.09 mg, 78% yield).

UV (in hexane) λ$_{max}$ 262.5, 252.5, 244.5 nm; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.22 (1H, d, J = 11.1 Hz, 6-H), 5.84 (1H, d, J = 11.1 Hz, 7-H), 4.97 (1H, s, =CH$_2$), 4.92 (1H, s, =CH$_2$), 4.42 (2H, m, 1β-H and 3α-H), 2.85 (1H, dd, J = 12.8, 3.6 Hz, 9β-H), 2.52 (1H, dd, J = 13.2, 6.0 Hz, 10α-H), 2.46 (1H, dd, J = 12.6, 4.3 Hz, 4α-H), 2.34 (1H, dd, J = 13.2, 2.7 Hz, 10β-H), 2.18 (1H, dd, J = 12.6, 8.4 Hz, 4β-H), 1.96 (1H, m), 1.19 (6H, s, 26-H$_3$, 27-H$_3$), 0.95 (9H, t, J = 7.9 Hz), 0.897 (9H, s, t-BuSi), 0.866 (9H, s, t-BuSi), 0.80 and 0.77 (each 3H, each s, 28-H$_3$, 30-H$_3$), 0.79 (3H, d, J = 8.2 Hz, 21-H$_3$), 0.57 (6H, q, J = 7.9 Hz), 0.46 (3H, s, 18-H$_3$), 0.080

(3H, s, SiMe), 0.069 (3H, s, SiMe), 0.049 (3H, s, SiMe), 0.029 (3H, s, SiMe); ^{13}C NMR (100

MHz, CDCl$_3$) δ 152.98 (0, C-2), 141.35 (0, C-8), 132.64 (0, C-5), 122.44 (1, C-6), 115.77 (1,

C-7), 106.24 (2, =CH$_2$), 73.51 (0, C-25), 72.50 and 71.64 (each 1, C-1, C-3), 55.06 (1), 49.61

(1), 47.59 (2), 46.71 (0, C-13), 38.92 (2), 38.55 (2), 38.29 (2), 38.09 (1), 35.96 (0, C-22) ,

34.08 (2), 29.93 and 29.88 (each 3, C-26, C-27), 28.93 (2), 25.84 (3), 25.77 (3), 25.25 (3),

25.02 (3), 23.05 (2), 22.68 (2), 22.63 (2), 18.26 (0), 18.17 (0), 12.81 (3), 12.44 (3), 7.16 (3),

6.84 (2), -4.86 (3), -4.91 (3), -5.08 (3); MS (ESI) *m/z* 809 (40, [M+Na]$^+$), exact mass (ESI)

calculated for C$_{47}$H$_{90}$O$_3$Si$_3$Na [M+Na]$^+$ 809.6091, found 809.6101.

[0076]   The protected compound **26** (50.94 mg, 64.8   mol) was dissolved in THF (5

mL) and acetonitrile (3 mL). A solution of aqueous 48% HF in acetonitrile (1:9 ratio, 4 mL)

was added at 0 °C and the resulting mixture was stirred at room temperature for 2 h.

Saturated aqueous NaHCO$_3$ solution was added and the reaction mixture was extracted with

dichloromethane. The combined organic phases were dried (Na$_2$SO$_4$) and concentrated under

reduced pressure. The residue was diluted with 2 mL of hexane/ethyl acetate (7:3) and

applied to a Waters silica Sep-Pak cartridge (5 g). An elution with hexane/ethyl acetate (7:3,

then 1:1) gave the crude product **20**. The vitamin **20** was further purified by straight phase

HPLC [9.4 × 250 mm Zorbax Silica column, 4 mL/min, hexane/2-propanol (85:15) solvent

system, R$_t$ = 7.4 min.] and reverse phase HPLC [9.4 × 250 mm Zorbax RX-C18 column, 3

mL/min, methanol/water (85:15) solvent system, R$_t$ = 13.3 min.] to give the pure compound

27 (22.71 mg, 79% yield).

m.p. 154 °C (from 2-propanol/hexane); UV (in EtOH) λ$_{max}$ 261.0, 252.0, 244.0 nm; ^{1}H NMR

(500 MHz, CDCl$_3$) δ 6.35 (1H, d, J = 11.2 Hz, 6-H), 5.88 (1H, d, J = 11.2 Hz, 7-H), 5.11 (1H,

s, =CH$_2$), 5.08 (1H, s, =CH$_2$), 4.48 (2H, m, 1β-H and 3α-H), 2.86 (1H, dd, J = 13.0, 4.7 Hz,

10β-H), 2.84 (1H, m, 9β-H), 2.56 (1H, dd, J = 13.3, 3.5 Hz, 4α-H), 2.33 (1H, dd, J = 13.3, 6.0

Hz, 4β-H), 2.28 (1H, dd, J = 13.0 Hz, 8.4 Hz, 10α-H), 1.96 (2H, m), 1.88 (1H, m), 1.21 (6H,

s, 26-H$_3$, 27-H$_3$), 0.83 and 0.78 (each 3H, each s, 28-H$_3$, 30-H$_3$), 0.79 (3H, d, J = 7.4 Hz, 21-

H$_3$), 0.48 (3H, 18-H$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) δ 151.98 (0, C-2), 143.27 (0, C-8),

130.51 (0, C-5), 124.09 (1, C-6), 115.02 (1, C-7), 107.66 (2, =CH$_2$), 71.74 and 70.51 (each 1,

C-1, C-3), 71.23 (0, C-25), 55.05 (1), 49.52 (1), 46.81 (0, C-13), 45.70 (2), 38.10 (2 × 2),

37.73 (1 and 2), 35.95 (0, C-22), 34.17 (2), 29.20 (3), 29.13 (3), 29.06 (2), 25.35 (3), 24.83

(3), 23.05 (2), 22.65 (2 × 2), 12.82 (3), 12.41 (3); MS (EI) *m/z* 444 (6, M$^+$), 426 (3, M$^+$- H$_2$O),

393 (2), 341 (2), 313 (6), 269 (5), 251 (6), 199 (6), 191 (15), 161 (10), 145 (19), 111 (43),

107 (100), 89 (80), 79 (78), 75 (43); MS (ESI) *m/z* 467 (100, [M+Na]$^+$), 911 (55, [2M+Na]$^+$),

1355 (15, [3M+Na]$^+$, exact mass (ESI) calculated for $C_{29}H_{48}O_3Na$ [M+Na]$^+$ 467.3496, found 467.3483.

Example 3: Biological Activity

Vitamin D Receptor Binding

Test Material

Protein Source

[0077]   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, 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 was bound to the receptor.

Study Drugs

[0078]   Unlabeled ligands were dissolved in ethanol and the concentrations determined using UV spectrophotometry (1,25(OH)$_2$D$_3$: 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)$_2$D$_3$, ~159 Ci/mmole) was added in ethanol at a final concentration of 1 nM.

Assay Conditions

[0079]   Radiolabeled and unlabeled ligands were added to 100 µL 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 µL of hydroxylapatite slurry (50%) was

added to each tube and mixed at 10-minute intervals for 30 minutes. The hydroxylapaptite was collected by centrifugation and then washed three times with Tris-EDTA buffer (50 mM Tris, 1.5 mM EDTA, pH 7.4) containing 0.5% Titron X-100. After the final wash, the pellets were transferred to scintillation vials containing 4 mL of Biosafe II scintillation cocktail, mixed and placed in a scintillation counter. Total binding was determined from the tubes containing only radiolabeled ligand.

HL-60 Differentiation

Test Material

Study Drugs

[0080]   The study drugs were dissolved in ethanol and the concentrations determined using UV spectrophotometry. Serial dilutions were prepared so that a range of drug concentrations could be tested without changing the final concentration of ethanol ($\leq 0.2\%$) present in the cell cultures.

Cells

[0081]   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

[0082]   HL60 cells were plated at 1.2×10^5 cells/mL. Eighteen hours after plating, cells in duplicate were treated with drug. Four days later, the cells were harvested and a nitro blue tetrazolium reduction assay was performed (Collins *et al.*, *J. Exp. Med.* (1979) 149:969-974). The percentage of differentiated cells was determined by counting a total of 200 cells and recording the number that contained intracellular black-blue formazan deposits. Verification of differentiation to monocytic cells was determined by measuring phagocytic activity (data not shown).

In Vitro Transcription Assay

[0083]   Transcription activity was measured in ROS 17/2.8 (bone) cells that were stably transfected with a 24-hydroxylase (24Ohase) gene promoter upstream of a luciferase reporter gene (Arbour *et al.*, *Analytical Biochem.* (1998) 255(1):148-154). Cells were given a range of doses. Sixteen hours after dosing the cells were harvested and luciferase activities were measured using a luminometer. RLU = relative luciferase units.

Intestinal Calcium Transport and Bone Calcium Mobilization

[0084]   Male, weanling Sprague-Dawley rats were placed on Diet 11 (0.47% Ca) diet + AEK oil for one week followed by Diet 11 (0.02% Ca) + AEK oil 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 intraperitoneal 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.

Biological Activity Results

[0085]   (20S)-2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D_3 (MET-1) is approximately equally effective as 1,25-$(OH)_2D_3$ in binding to the recombinant vitamin D receptor as shown in Fig. 1 (K_i of 4×10^{-11}M and 5×10^{-11} M respectively). However, MET-1 is 4 times more potent than 1,25-$(OH)_2D_3$ at inducing the differentiation of HL-60 cells in culture as shown in Fig. 2 (7×10^{-10}M and 3×10^{-9}M respectively). MET-1 is 10 times as potent in stimulating 24-OHase gene expression in bone cells than 1,25-$(OH)_2D$ as shown in Fig. 3 (3×10^{-11}M and 2×10^{-10}M respectively). By contrast, *in vivo* testing demonstrated that MET-1 is 20 times less active than 1,25-$(OH)_2D_3$ on bone calcium mobilization (Fig. 4), and noticeably less active than 1,25-$(OH)_2D_3$ in causing intestinal calcium transport (Fig. 5).
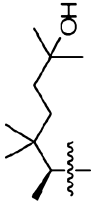
[0086]   (20R)-2-methylene-19-nor-22-dimethyl-1α,25-dihydroxyvitamin D_3 (MET-2) is equally effective as 1,25-$(OH)_2D_3$ in binding to the recombinant vitamin D receptor as shown in Fig. 6 (both display a K_i of 5×10^{-11}M). MET-2 is 3 times more potent than 1,25-

$(OH)_2D_3$ at inducing the differentiation of HL-60 cells in culture as shown in Fig. 7 ($7 \times 10^{-10}M$ and $3 \times 10^{-9}M$ respectively). However, MET-2 is about 3 times less potent in stimulating 24-OHase gene expression in bone cells than $1,25-(OH)_2D$ as shown in Fig. 8 ($3 \times 10^{-11}M$ and $2 \times 10^{-10}M$ respectively). *In vivo* testing demonstrated that MET-2 is 16 times less active than $1,25-(OH)_2D_3$ on bone calcium mobilization (Fig. 4), and noticeably less active than $1,25-(OH)_2D_3$ in causing intestinal calcium transport (Fig. 5).

[0087]   Comparative Example: Table 1 shows biological data for 2-methylene-19-nor-1α,25-dihydroxyvitamin D_3 and its 20R isomer in comparison to compounds from the present disclosure (MET-1 and MET-2). The former compounds differ from the latter in that they have two methyl groups attached to the position 21 carbon rather than two hydrogens. While binding of the vitamin D receptor and HL-50 differentiation is generally within an order of magnitude for each compound, the present compounds demonstrate surprising and unexpected effects on calcemic activity. Whereas the 2MD compounds show extremely potent net bone calcium mobilization activity ranging from 4.5 mg/dL in the 20R isomer to 9.3 mg/dL in the 20S isomer, the present MET compounds show virtually no calcemic activity. On the other hand, while the 2 MD compounds demonstrate intestinal calcemic activity lower than that of vehicle, but the present compounds show small but significant ratio of serosal to mucosal calcium, i.e., 1.2 to 2.3 for MET-2 and MET-1, respectively.

[0088]   These properties illustrate that both compounds should be very useful in the treatment of diseases where a rise in serum calcium is not desirable. Thus, these compounds should find utility in the treatment of secondary hyperparathyroidism of patients suffering from chronic kidney failure because it is undesirable to elevate serum calcium above normal in these patients for fear of calcification of heart, aorta and other vital organs while suppressing parathyroid gland proliferation and transcription of the preproparathyroid gene. Likewise, these compounds should be useful in the treatment of malignancy such as breast, colorectal and prostate cancers, or in the treatment of autoimmune diseases such as multiple sclerosis, lupus, rheumatoid arthritis, type 1 diabetes, and inflammatory bowel disease. They should also be useful in preventing transplant rejection.

Table 1

Example*	Where	Side chain	Competitive VDR Binding (K_i, nM)	HL-60 Differentiation (EC_{50}, nM)	24-OHase Transcription (EC_{50}, nM)	Net Bone Ca^{2+} Mobilization (mg/dL)[1]	Net Intestinal Ca^{2+} Transport (S/M)[2]
MET-1	Present		0.04	0.7	0.03	0.4	2.3
MET-2	Present		0.05	1	0.6	0.2	1.2
2MD[3] (20R)	US 5,843,928		0.12	4.2	-	4.5[4]	-0.6[4]
2MD[3] (20S)	US 5,843,928		0.10	0.15	-	9.3[4]	-0.9[4]

*All compounds are 2-methylene-19-nor compounds

[1] At 780 pM dosage, except where indicated

[2] S/M = serosal Ca^{2+}/mucosal Ca^{2+}; at 780 pM dosage, except where indicated

[3] data from US 5,843,928 and *J. Med. Chem.* 1998, 41, 4662

[4] At 260 pM dosage

[0089]   It is understood that the present technology 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

What is claimed is:

1.   A compound having the formula I:

I   ,
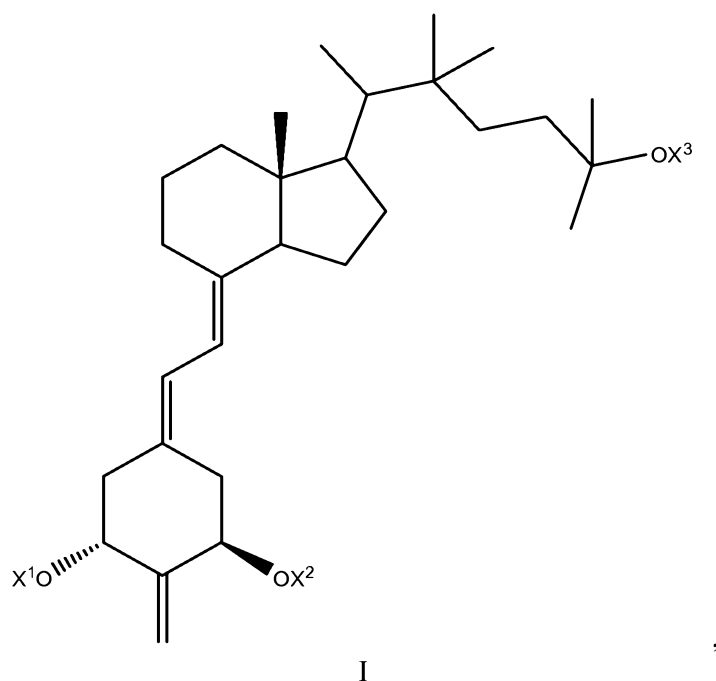
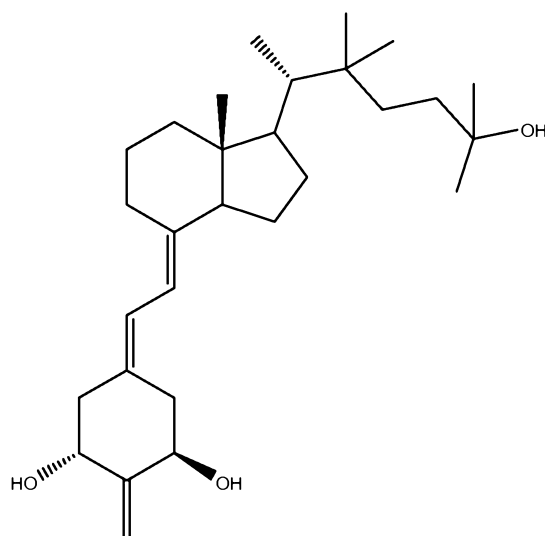wherein X^1, X^2 and X^3 are independently selected from H and hydroxy protecting groups.

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

3.   The compound of claim 2, wherein X^1 and X^2 are both t-butyldimethylsilyl groups and X^3 is a triethylsilyl group.

4.   A compound having the formula II:
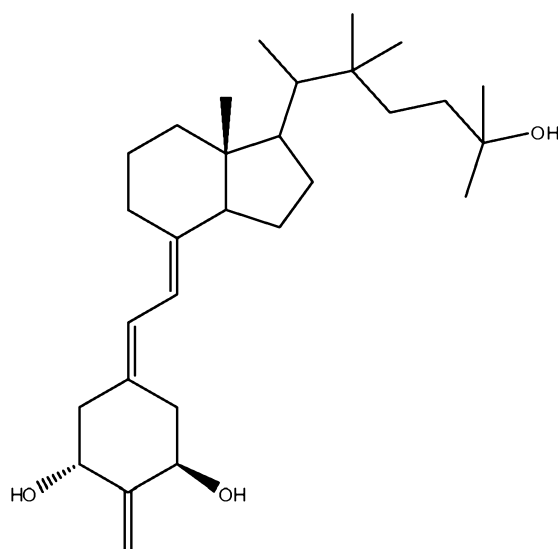
II

5.   The compound of claim 4 having the formula IIA:

IIA

6.   The compound of claim 4 having the formula IIB:
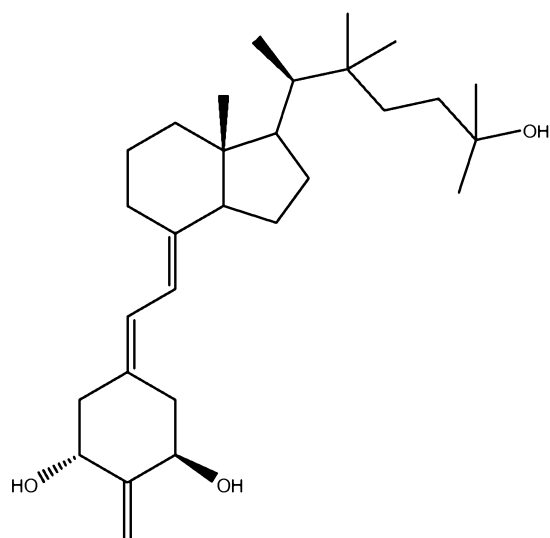
IIB

7.   The compound of claim 4, having the formula IIC or IID
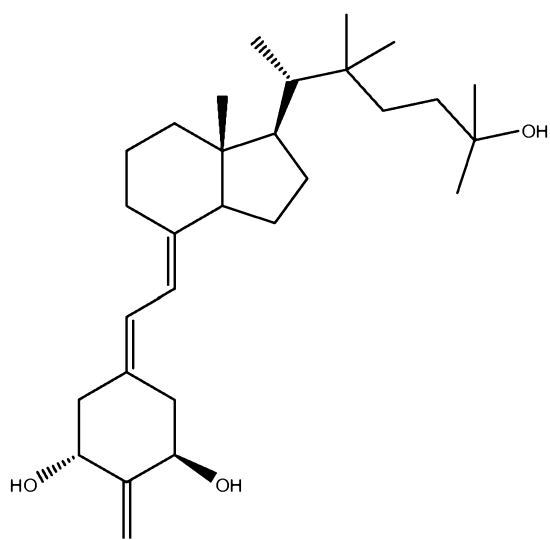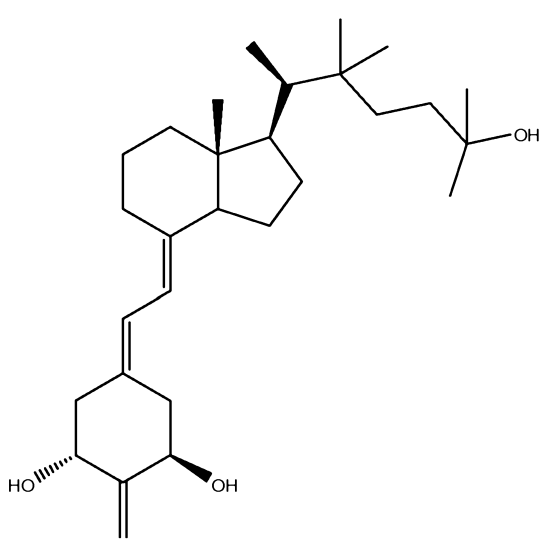
IIC   IID

8.   A pharmaceutical composition, comprising an effective amount of the compound of any one of claims 4-7 and a pharmaceutically acceptable carrier.

9.   The pharmaceutical composition of claim 8 wherein the effective amount comprises from about 0.01 µg to about 1 mg of the compound per gram of the composition.

10.   The pharmaceutical composition of claim 8 wherein the effective amount comprises from about 0.1 µg to about 500 µg of the compound per gram of the composition.

11.   A method of treating a subject suffering from a biological condition, comprising administering an effective amount of the compound of any one of claims 4-7 to the subject, wherein the biological condition is 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, 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; or osteoporosis.

12.   The method of claim 11, wherein the biological condition is psoriasis.

13.   The method of claim 11, wherein the biological condition is selected from leukemia, colon cancer, breast cancer, or prostate cancer.

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

15.   The method of claim 11, wherein the biological condition is selected from rheumatoid arthritis, asthma, or inflammatory bowel diseases selected from celiac disease, ulcerative colitis and Crohn's disease.

16.   The method of claim 11, wherein the biological condition is selected from wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration, or insufficient sebum secretion.

17.   The method of claim 11, wherein the compound is administered orally to the subject.

18.   The method of claim 11, wherein the compound is administered parenterally to the subject.

19.   The method of claim 11, wherein the compound is administered transdermally or topically to the subject.

20.   The method of claim 11, wherein the compound is administered in a dosage of from 0.01 μg per day to 1 mg per day.
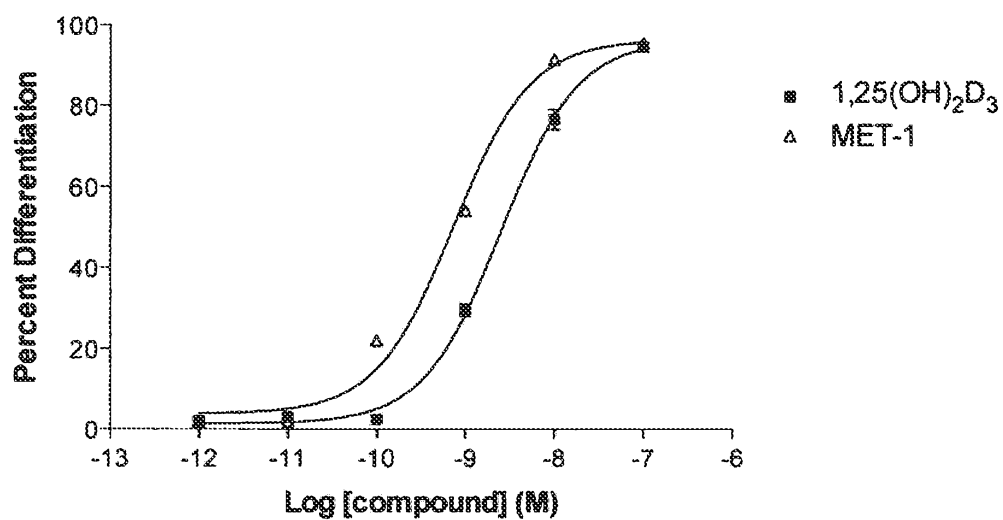
FIG. 1

Competitive VDR Binding
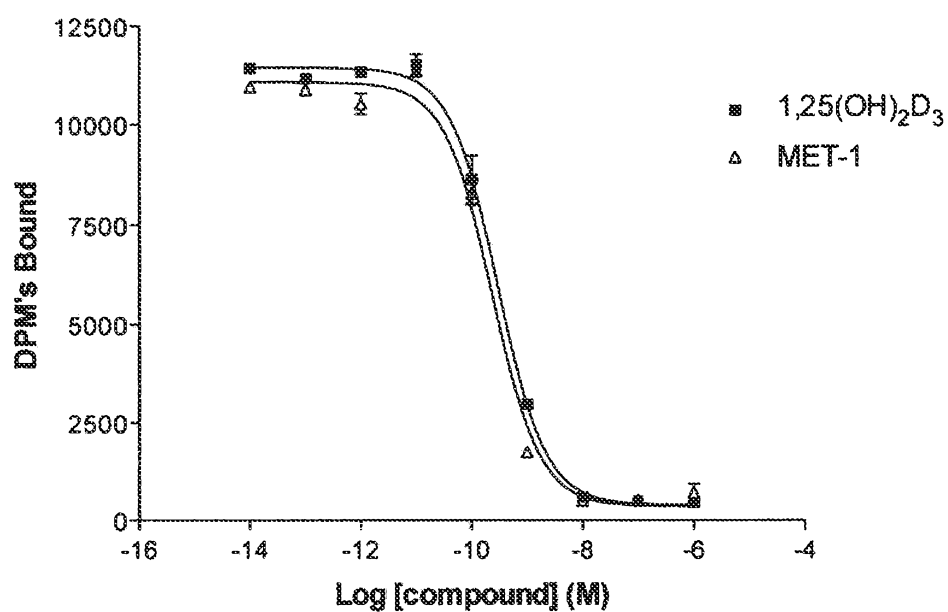
K_i: $1,25(OH)_2D_3 = 5 \times 10^{-11}$ M

MET-1 $= 4 \times 10^{-11}$ M

FIG. 2

HL-60 Cell Differentiation

EC$_{50}$: 1,25(OH)$_2$D$_3$ = 3 x 10^{-9} M

MET-1 = 7 x 10^{-10} M

FIG. 3

24-OHase Transcription

EC$_{50}$:   1,25(OH)$_2$D$_3$ = 2 x 10^{-10} M
            MET-1 = 3 x 10^{-11} M

FIG. 4

Bone Calcium Mobilization

FIG. 5

Intestinal Calcium Transport

5/8

FIG. 6

Competitive VDR Binding
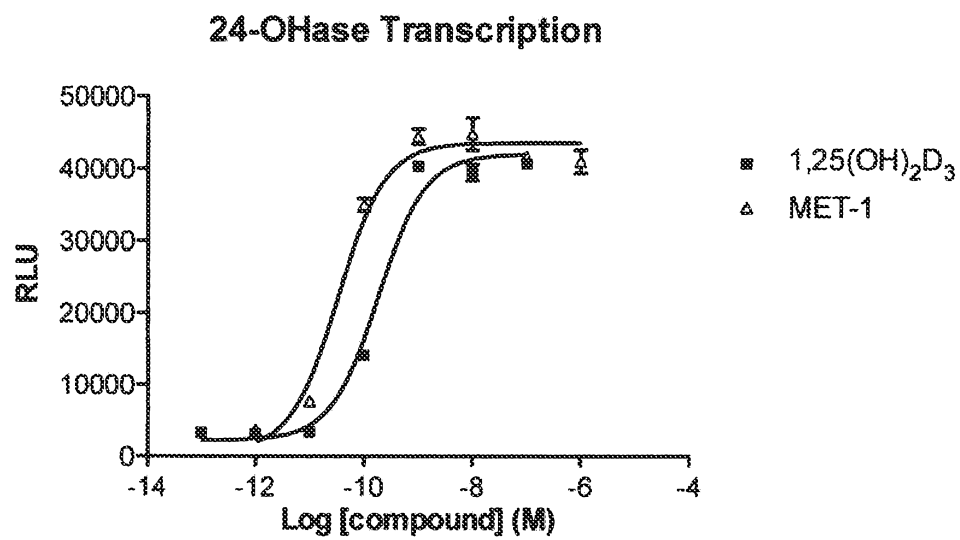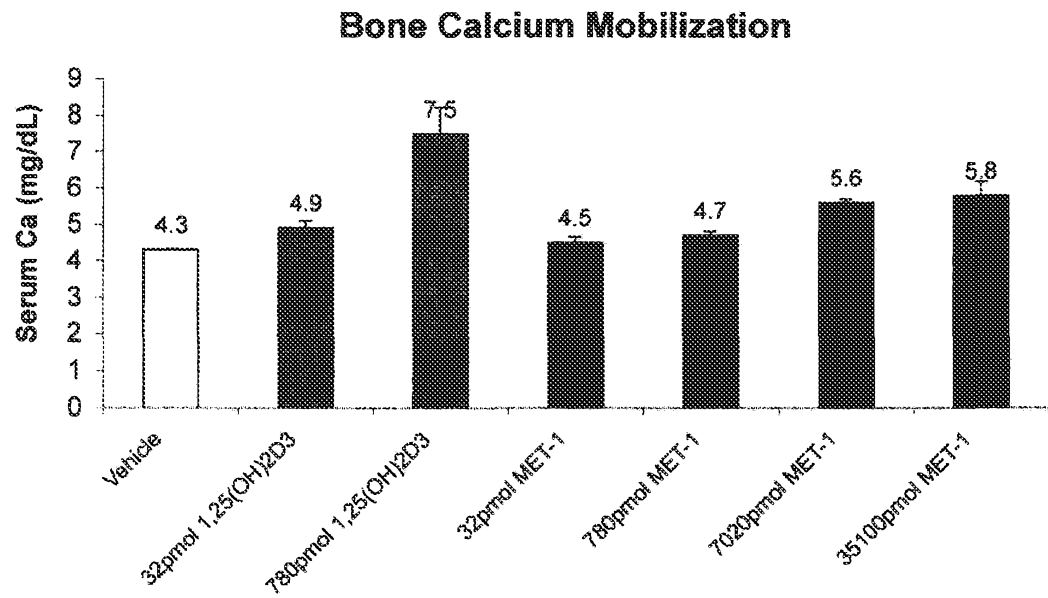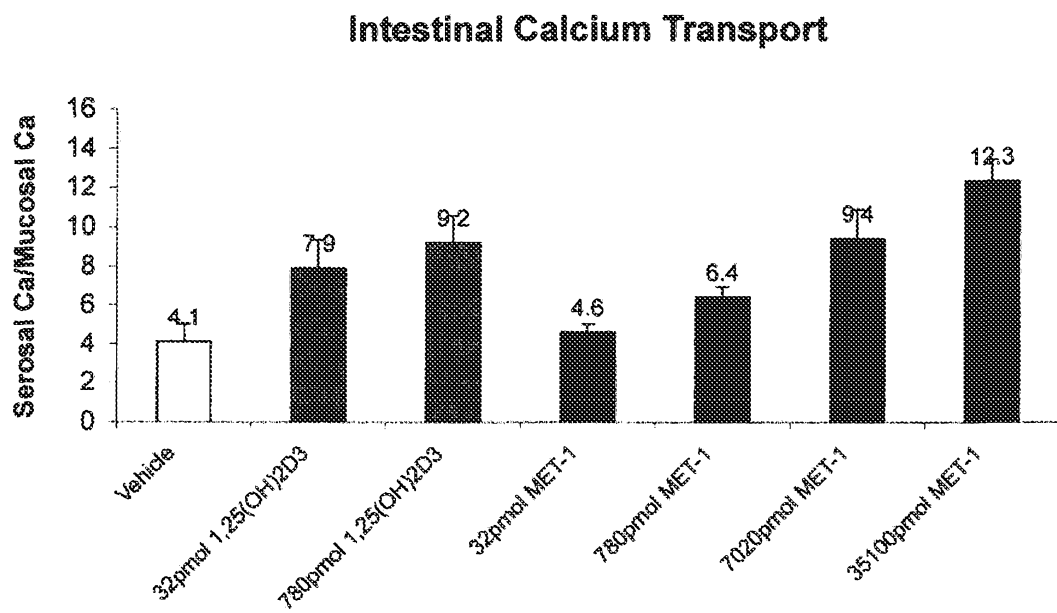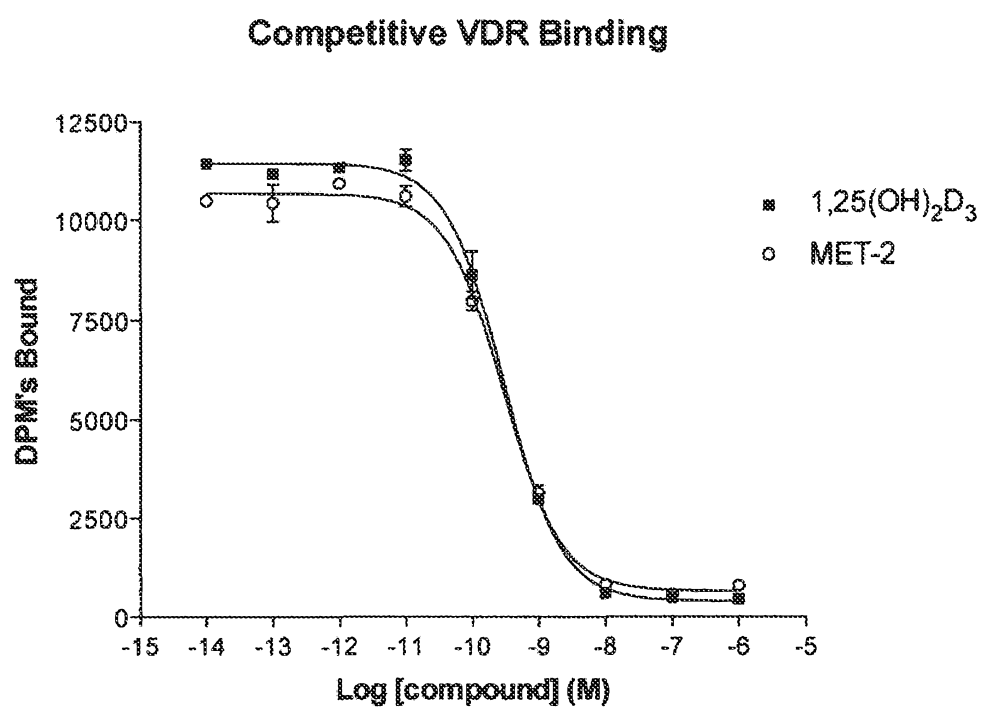
K_i: $1,25(OH)_2D_3 = 5 \times 10^{-11}$ M
MET-2 $= 5 \times 10^{-11}$ M

FIG. 7

HL-60 Cell Differentiation

EC$_{50}$: 1,25(OH)$_2$D$_3$ = 3 x 10^{-9} M

MET-2 = 1 x 10^{-9} M

FIG. 8

24-OHase Transcription

EC$_{50}$:   1,25(OH)$_2$D$_3$ = 2 x 10^{-10} M

MET-2 = 6 x 10^{-10} M

FIG. 9

Bone Calcium Mobilization

FIG. 10

Intestinal Calcium Transport