



US006774251B2

(12) **United States Patent**
DeLuca et al.

(10) **Patent No.:** **US 6,774,251 B2**
(45) **Date of Patent:** **Aug. 10, 2004**

(54) **METHOD OF SYNTHESIZING 1 α -HYDROXY-2-METHYLENE-19-NOR-HOMOPREGNACALCIFEROL**

5,972,917 A * 10/1999 Bishop et al. 514/167
6,277,837 B1 8/2001 DeLuca et al. 514/167
6,306,844 B1 10/2001 DeLuca et al. 514/167

(75) Inventors: **Hector F. DeLuca**, Deerfield, WI (US);
Sumithra Gowlugari, Fremont, WI (US); **Rafal R. Sicinski**, Warsaw (PL)

FOREIGN PATENT DOCUMENTS
WO WO 02/20021 3/2002

(73) Assignee: **Wisconsin Alumni Research Foundation**, Madison, WI (US)

OTHER PUBLICATIONS

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/397,135**

(22) Filed: **Mar. 26, 2003**

(65) **Prior Publication Data**

US 2003/0191095 A1 Oct. 9, 2003

Related U.S. Application Data

(60) Provisional application No. 60/369,159, filed on Mar. 29, 2002.

(51) **Int. Cl.⁷** **C07C 401/00**; A61K 31/59

(52) **U.S. Cl.** **552/653**; 514/167

(58) **Field of Search** 514/167; 552/653

Pearlman et al., 1 α , 25-dihydroxy-19-nor-vitamin D₃, A Novel Vitamin D-Related Compound with Potential Therapeutic Activity, Feb. 1, 1990, Pergamon Press, Tetrahedron Letters, vol. 31, No. 13, pp 1823-1824.*
Brown et al, "New Active Analogues of Vitamin D with Low-Calcemic Activity" Kidney International, vol. 38, Suppl. 29 (1990) pp. S-22-S-27.

Hareau et al, "Asymmetric Synthesis of 1 α ,25-Dihydroxyvitamin D₃ A-Ring Precursor Starting with 5-Tert-Butyldimethylsiloxy-2-Cyclohexenone" Tetrahedron Letters, 41 (2000) pp. 2385-2388.

Sicinski et al, "New 1 α ,25-Dihydroxy-19-Norvitamin D₃ Compounds of High Biological Activity: Synthesis and Biological Evaluation of 2-Hydroxymethyl, 2-Methyl, and 2-Methylene Analogues" J. Med. Chem., 41 (1998) pp. 4662-4674.

* cited by examiner

Primary Examiner—Sabiha Qazi

(74) *Attorney, Agent, or Firm*—Andrus, Scales, Starke & Sawall, LLP

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,666,634 A 5/1987 Miyamoto et al. 260/397.2
4,800,198 A 1/1989 DeLuca et al. 514/167
5,089,641 A 2/1992 DeLuca et al. 552/653
5,536,713 A 7/1996 DeLuca et al. 514/167
5,578,587 A 11/1996 DeLuca et al. 514/167
5,587,497 A 12/1996 DeLuca et al. 552/653
5,843,928 A * 12/1998 Deluca et al. 514/167
5,877,168 A 3/1999 Miyamoto et al. 514/167
5,936,105 A 8/1999 Paaren
5,936,133 A 8/1999 DeLuca et al. 568/828
5,945,410 A 8/1999 DeLuca et al. 514/167

(57) **ABSTRACT**

A method of making 1 α -hydroxy-2-methylene-19-nor-homopregnacalciferol. The method includes the steps of condensing a bicyclic ketone with an allylic phosphine oxide to produce a protected 19-nor-pregnacalciferol analog, thereafter cleaving the protecting group to form 22-alcohol, converting the alcohol to an ester, reducing the ester to 17 β -isopropyl-19-nor-vitamin D analog, and finally deprotecting the 17 β -isopropyl derivative to form the desired compound.

15 Claims, No Drawings

1

METHOD OF SYNTHESIZING 1 α -HYDROXY-2-METHYLENE-19-NOR-HOMOPREGNACALCIFEROL

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is based on and claims priority from provisional patent Application No. 60/369,159 filed on Mar. 29, 2002.

BACKGROUND OF THE INVENTION

The natural hormone, 1 α ,25-dihydroxyvitamin D₃ and its analog in the ergosterol series, i.e. 1 α ,25-dihydroxyvitamin D₂ are known to be highly potent regulators of calcium homeostasis in animals and humans, and more recently their activity in cellular differentiation has been established, Ostrem et al., Proc. Natl. Acad. Sci. USA, 84, 2610 (1987). Many structural analogs of these metabolites have been prepared and tested, including 1 α -hydroxyvitamin D₃, 1 α -hydroxyvitamin D₂, various side chain homologated vitamins and fluorinated analogs. Some of these compounds exhibit an interesting separation of activities in cell differentiation and calcium regulation. This difference in activity may be useful in the treatment of a variety of diseases such as renal osteodystrophy, vitamin D-resistant rickets, osteoporosis, psoriasis, and certain malignancies.

Recently, a new class of vitamin D analogs has been discovered, i.e. the so called 19-nor-vitamin D compounds, which are 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., 1 α ,25-dihydroxy-19-nor-vitamin D₃) revealed a selective activity profile with high potency in inducing cellular differentiation, and very low calcium mobilizing activity. Thus, these compounds are potentially useful as therapeutic agents for the treatment of malignancies, or the treatment of various skin disorders. Two different methods of synthesis of such 19-nor-vitamin D analogs have been described [Perlman et al., Tetrahedron Lett. 31, 1823 (1990); Perlman et al., Tetrahedron Lett. 32, 7663 (1991), and DeLuca et al., U.S. Pat. No. 5,086,191].

In U.S. Pat. No. 4,666,634, 2 β -hydroxy and alkoxy (e.g., ED-71) analogs of 1 α ,25-dihydroxyvitamin D₃ have been described and examined by Chugai group as potential drugs for osteoporosis and as antitumor agents. See also Okano et al., Biochem. Biophys. Res. Commun. 163, 1444 (1989). Other 2-substituted (with hydroxyalkyl, e.g., ED-120, and fluoroalkyl groups) A-ring analogs of 1 α ,25-dihydroxyvitamin D₃ have also been prepared and tested (Miyamoto et al., Chem. Pharm. Bull. 41, 1111 (1993); Nishii et al., Osteoporosis Int. Suppl. 1, 190 (1993); Posner et al., J. Org. Chem. 59, 7855 (1994), and J. Org. Chem. 60, 4617 (1995)]. Recently, similar analogs of 1 α ,25-dihydroxy-19-norvitamin D₃ have also been synthesized, i.e., compounds substituted at 2-position with hydroxy or alkoxy groups (DeLuca et al., U.S. Pat. No. 5,536,713), 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.

Recently analogs which are characterized by the transposition of the ring A exocyclic methylene group, present in the normal vitamin D skeleton, from carbon 10 (C-10) to carbon 2 (C-2), i.e., 2-methylene-19-nor-vitamin D compounds, were synthesized and tested. Molecular mechanics studies indicate that such molecular modification does not change substantially the conformation of the cyclohexanediol ring A. However, introduction of the 2-methylene group into 19-nor-vitamin D carbon skeleton changes the character of

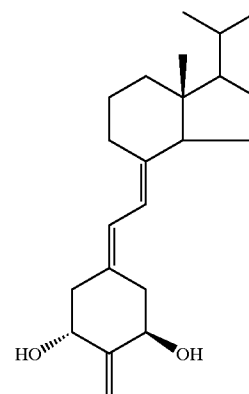
2

its (1 α - and 3 β -) A-ring hydroxyls. They are both now in the allylic positions, similarly, as 1 α -hydroxy group (crucial for biological activity) in the molecule of the natural hormone, 1 α ,25-(OH)₂D₃. These analogs have exhibited similar rate of binding to the receptor as 1 α ,25-dihydroxyvitamin D₃ and were also characterized by high cell differentiation activity. These compounds were characterized by little, if any intestinal calcium transport activity, as compared to that of 1 α ,25-dihydroxyvitamin D₃, while exhibiting relatively high activity, as compared to that of 1 α ,25-dihydroxyvitamin D₃ in their ability to mobilize calcium from bone.

More than ten years ago an interesting 1 α -hydroxyvitamin D analog was synthesized, namely, 1 α -hydroxy-20-methyl-pregnacalciferol (also sometimes referred to as 1 α -hydroxy-homopregnacalciferol) which was essentially devoid of calcemic activity, showed some HL-60 cell differentiation ability but unexpectedly exhibited comparable binding to the receptor as 1 α ,25-dihydroxyvitamin D₃ [Lau, W. F. (1986) Ph.D. Thesis, University of Wisconsin-Madison]. In a continuing effort to explore the 19-nor class of pharmacologically important vitamin D compounds, a 1 α -hydroxy-19-nor-vitamin D analog, which is characterized by the presence of methylene substituent at the carbon 2 (C-2) and 17 β -isopropyl side chain has now been synthesized and tested.

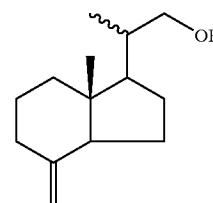
SUMMARY OF THE INVENTION

The present invention is directed toward a method of making 1 α -hydroxy-2-methylene-19-nor-homopregnacalciferol having the structure



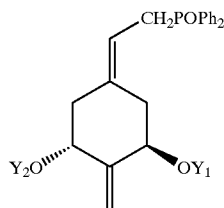
comprising the steps of:

condensing a bicyclic ketone having the structure

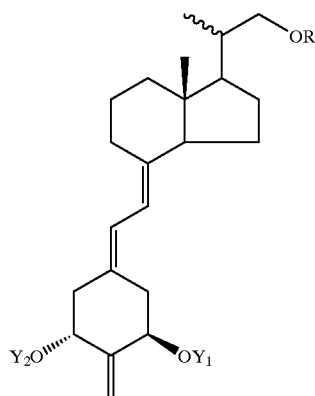


3

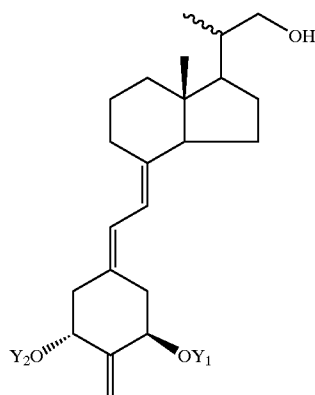
with an allylic phosphine oxide having the structure



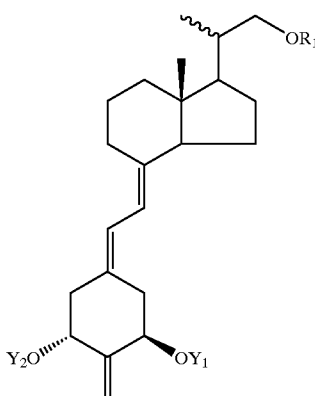
where Y_1 , Y_2 and R, which may be the same or different, are each a hydroxy-protecting group, to produce a protected 19-nor-vitamin D analog having the structure



thereafter cleaving the protecting group R to form an alcohol having the structure



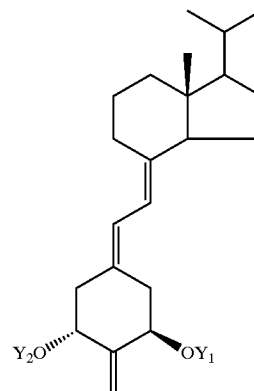
converting said alcohol to an ester having the structure



where R_1 is a tosyl group or a mesyl group;

4

reducing said ester to obtain 17 β -isopropyl vitamin D derivative having the structure

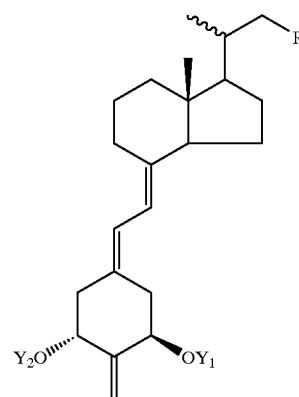


and deprotecting said 17 β -isopropyl vitamin D derivative to form 1 α -hydroxy-2-methylene-19-nor-homopregnalciferol.

DISCLOSURE OF THE INVENTION

A class of 1 α -hydroxylated vitamin D compounds not known heretofore are the vitamin D isomers in which the A-ring exocyclic methylene group, typical of all vitamin D system has been transposed to the carbon 2, i.e. 19-nor-vitamin D analogs, having a methylene group at the 2-position.

Structurally the novel analogs are characterized by the general formula I shown below:

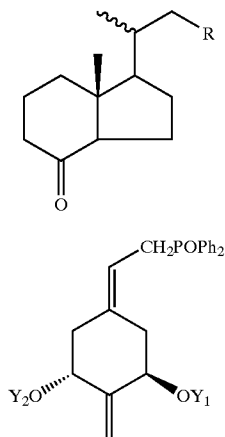


where Y_1 and Y_2 , which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, R may be selected from the group consisting of hydrogen, hydroxyl and protected hydroxyl.

5

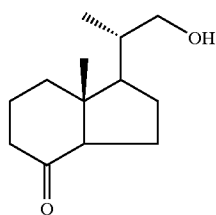
The wavy line to the methyl substituent at C-20 indicates that carbon 20 may have either the R or S configuration.

The preparation of 1 α -hydroxy-20-methyl-2-methylene-19-nor-pregnacalciferol compounds (also herein referred to as 1 α -hydroxy-2-methylene-19-nor-homopregnacalciferol compounds) having the basic structure I can be accomplished by a common general method, i.e. the condensation of a bicyclic Windaus-Grundmann type ketone II with the allylic phosphine oxide III:



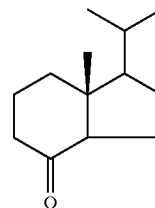
In the structures II and III, groups Y₁ and Y₂ and R represent groups defined above; Y₁ and Y₂ are preferably hydroxy-protecting groups, R is either hydrogen, hydroxyl or protected hydroxyl, it being also understood that any functionalities in R that might be sensitive, or that interfere with the condensation reaction, be suitably protected as is well known in the art. The process shown above represents an application of the convergent synthesis concept, which has been applied effectively for the preparation of vitamin D compounds [e.g. Lythgoe et al., J. Chem. Soc. Perkin Trans. I, 590 (1978); Lythgoe, Chem. Soc. Rev. 9, 449 (1983); Toh et al., J. Org. Chem. 48, 1414 (1983); Baggiolini et al., J. Org. Chem. 51, 3098 (1986); Sardina et al., J. Org. Chem. 51, 1264 (1986); J. Org. Chem. 51, 1269 (1986); DeLuca et al., U.S. Pat. No. 5,086,191; DeLuca et al., U.S. Pat. No. 5,536,713].

Hydrindanones of the general structure II are known, or can be prepared by known methods. Specific important examples of such known bicyclic ketones are Grundmann's ketone analogs (a & b) [Mincione et al., Synth. Commun. 19, 723, 1989; Peterson et al., J. Org. Chem. 51, 1948 (1986)].



6

-continued



b

2-Methylene phosphine oxide III can be prepared according to the procedure described by Sicinski et al., J. Med. Chem. 41, 4662 (1998), DeLuca et al., U.S. Pat. No. 5,843,928.

For the preparation of the required Grundmann's ketone analog of the general structure II, a new synthetic route has been developed starting from the diol 2, easily obtained from the commercial vitamin D₂ as described by Sardina et al., J. Org. Chem. 51, 1264 (1986). The overall process for the synthesis of the vitamin D analog 10 is summarized by the SCHEME 1. Thus the diol 2, obtained by the ozonolysis of vitamin D₂, was protected as mono triethyl silyl ether 3 and the secondary hydroxyl at C-8 was oxidized with PDC to get the Grundmann's ketone 4. Wittig-Homer coupling of the conjugate base of the phosphine oxide 5, produced upon deprotonation with phenyllithium, with the protected 22-hydroxy Grundmann's ketone afforded the expected protected 19-nor-vitamin D analog 6 in a high yield. The triethylsilyl protecting group of the compound 6 was cleaved using 8:8:1 mixture of AcOH:THF:H₂O to give 22-alcohol 7. This was then converted into its tosyl derivative 8 on reaction with p-toluenesulfonyl chloride in pyridine, which on reduction with LiAlH₄ gave the 20-methyl analog 9. The final step involved the unmasking of the silyl ethers with tetrabutylammonium fluoride to yield 1 α -hydroxy-20-methyl-2-methylene-19-nor-pregnacalciferol, i.e. 1 α -hydroxy-2-methylene-19-nor-homopregnacalciferol, 10. An alternative procedure for the synthesis of vitamin analog 10 involves the Wittig-Homer coupling of the Grundmann's ketone analog b with the 2-methylene phosphine oxide 5, followed by the deprotection of silyl ethers.

EXAMPLE 1

Preparation of 1 α -hydroxy-2-methylene-19-nor-homopregnacalciferol (Sometimes also Referred to as 1 α -hydroxy-20-methyl-2-methylene-19-nor-pregnacalciferol) 10

a) Ozonolysis of Vitamin D₂

A solution of vitamin D₂ (2.00 g, 5.05 mmol) in absolute methanol (175 mL) and pyridine (1.75 mL) was placed in an ozonation vessel provided with a magnetic stirring bar. The solution was cooled to -78° C. while purging with oxygen. Then a stream of ozone was passed until a deep blue color appeared (1 h). The ozone flow was discontinued, and the reaction mixture was purged with oxygen (-78° C.) until no ozone remained in solution. Then NaBH₄ (500 mg) was added in one portion, and the resulting solution was stirred at -78° C. for 20 min while a gentle flow of N₂ was maintained. The reaction was allowed to stir at room temperature overnight. An additional quantity of NaBH₄ (500 mg) was added at room temperature, and the resulting solution was stirred for 30 min. The resulting solution was rotary evaporated to a small volume, and the residue was extracted with ether. The ethereal layers were washed with 5% HCl and H₂O and then dried over Na₂SO₄. Filtration and concentration in vacuo afforded a residue that was flash chromatographed (75:25 mixture of hexane/ethyl acetate) to yield diol 2 (1.2 g, 82%): ¹H NMR (CDCl₃) δ 0.958 (3H, s, 18-CH₃), 1.03 (2H, d, J=6.6 Hz, 21-CH₃), 3.38 (1H, dd,

7

J=10.5, 6.7 Hz, 22-H), 3.64 (1H, dd, J=10.5, 3.5 Hz, 22-H), 4.09 (1H, m, 8 α -H).

b) Preparation of Silyl Ether 3

De-A,B-23,24-dinor-22-[(triethylsilyl)oxy]-cholan-8 β -ol (3). To a solution of the diol 2 (100 mg, 0.472 mmol) in anhydrous acetonitrile (250 μ L) and 2,6-lutidine (138 μ L, 1.17 mmol) was added triethylsilyl trifluoromethanesulfonate (118 μ L, 0.518 mmol). The reaction was then stirred at room temperature under argon for 2 h, then quenched with water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried (Na₂SO₄). The organic extracts were evaporated to get the crude product, which was purified by silica gel chromatography to yield the silyl ether 3 (120 mg, 80%): ¹H NMR (CDCl₃) δ 0.575 (6H, q, 3 \times SiCH₃), 0.947 (9H, t, 3 \times SiCH₂CH₃), 0.958 (3H, s, 18-CH₃), 1.03 (2H, d, J=6.6 Hz, 21-CH₃), 3.24 (1H, dd, J=9.6, 7.7 Hz, 22-H), 3.59 (1H, dd, J=3.5, 9.6 Hz, 22-H), 4.08 (1H, m, 8 α -H).

c) Oxidation of the 8 α -hydroxyl Group in Compound 3

De-A,B-23,24-dinor-22-[(triethylsilyl)oxy]-8-oxocholane (4). Pyridinium dichromate (87.6 mg, 0.232 mmol) was added to a solution of alcohol 3 (50 mg, 0.155 mmol) and pyridinium p-toluenesulfonate (10 mg) in CH₂Cl₂ (2 mL). The resulting orange suspension was stirred for 3 h at room temperature. Ether was added, and the resulting suspension was filtered through a short column of Celite. The filtrate was washed with a saturated aqueous solution of CuSO₄ and H₂O, dried (Na₂SO₄), and filtered. Removal of solvents under reduced pressure afforded the ketone, which was then purified by column chromatography. The compound was further purified by HPLC (250 \times 10 mm Zorbax-Sil column, 4 mL/min) using 90:10 mixture of hexane/ethyl acetate as eluent. Pure protected ketone 4 (38 mg, 79%), was eluted at R_V 17 mL: ¹H NMR (CDCl₃) δ 0.582 (6H, q, 3 \times SiCH₃), 0.643 (3H, s, 18-CH₃), 0.952 (9H, t, 3 \times SiCH₂CH₃), 1.036 (3H, d, J=6.1 Hz, 21-CH₃), 3.29 (1H, dd J=6.9, 9.6 Hz, one of 22-H), 3.58 (1H, dd, J=2.8, 9.6 Hz, one of 22-H).

d) Wittig-Horner Condensation of Phosphine Oxide 5 with Protected Grundmann's Ketone 4

1 α -[(tert-Butyldimethylsilyl)oxy]-(20S)-20-[(triethylsilyl)oxy]methyl-2-methylene-19-nor-pregnacalciferol tert-butyldimethylsilyl ether (6). To a solution of phosphine oxide 5 (13 mg, 0.0218 mmol) in anhydrous THF (130 μ L) at 0 $^{\circ}$ C. was slowly added PhLi (18 μ L, 0.0327 mmol) under argon with stirring. The solution turned deep orange. The mixture was cooled to -78 $^{\circ}$ C. and a precooled (-78 $^{\circ}$ C.) solution of protected hydroxy ketone 4 (8.5 mg, 0.0262 mmol) in anhydrous THF (170 μ L) was slowly added. The mixture was stirred at -78 $^{\circ}$ C. for 2 h 30 min and then at 0 $^{\circ}$ C. for 18 h. Ethyl acetate was added and the organic phase was washed with brine, dried (MgSO₄) and evaporated. The residue was dissolved in hexane, applied on a silica Sep-Pak cartridge, and washed with hexane/ethyl acetate (99.7:0.3, 20 mL) to give 19-nor-vitamin D derivative 6. The vitamin derivative was further purified by HPLC (250 \times 10 mm Zorbax-Sil column, 4 mL/min) using hexane/ethyl acetate (99.9:0.1) solvent system. Pure compound 6 was eluted at R_V 22 mL as a colorless oil: UV (in ethanol) λ_{max} 244, 252, 262 nm; ¹H NMR (CDCl₃) δ 0.026, 0.047, 0.065 and 0.079 (each 3H, each s, 4 \times SiCH₃), 0.559 (3H, s, 18-CH₃), 0.593 (6H, q, 3 \times SiCH₂), 0.864 and 0.894 (each 9H, each s, 2 \times Si-t-Bu), 0.966 (9H, t, 3 \times SiCH₂CH₃), 1.019 (3H, d, J=6.5 Hz, 21-CH₃), 3.25 (1H, dd, J=9.5, 7.9 Hz, 22-H), 3.62 (11H, dd, J=3.4, 9.6 Hz, 22-H), 4.42 (2H, m, 1 α -H, 3 β -H), 4.92 and 4.96 (each 1H, each s, =CH₂), 5.84 (1H, d, J=11.2 Hz, 7-H) and 6.21 (1H, d, J=11.2 Hz, 6-H); MS m/z (relative intensity): 688 (M⁺, 34), 659 (M⁺-CH₃), 557 (M⁺-OSi(CH₃)₂-t-Bu, 50).

e) Cleavage of Triethylsilyl Ether in the Vitamin Analog 6

1 α -[(tert-Butyldimethylsilyl)oxy]-(20S)-20-hydroxymethyl-2-methylene-19-nor-pregnacalciferol tert-

8

butyldimethylsilyl ether (7). To, a solution of the 19-nor-vitamin D derivative 6 (1.5 mg, 0.002 mmol) in 50 μ L benzene was added 200 μ L of 8:8:1 mixture of AcOH:THF:H₂O and stirred for 2 h. The reaction mixture was then quenched with aqueous solution of NaHCO₃ and extracted with ether. The combined ether layers were washed with brine, dried (Na₂SO₄) and the solvent evaporated to get the alcohol which was further purified by silica column chromatography with 95:5 mixture of hexane/ethyl acetate to yield pure 7 (1 mg, 80%): ¹H NMR (CDCl₃) δ 0.026, 0.047, 0.064 and 0.078 (each 3H, each s, 4 \times SiCH₃), 0.571 (3H, s, 18-CH₃), 0.864 and 0.895 (each 9H, each s, 2 \times Si-t-Bu), 1.065 (3H, d, J=6.6 Hz, 21-CH₃), 3.40 (1H, dd, J=10.4, 7.0 Hz, 22-H), 3.65 (1H, dd, J=3.3, 15.4 Hz, 22-H), 4.42 (2H, m, 1 α -H, 3 β -H), 4.92 and 4.97 (each 1H, each s, =CH₂), 5.84 (1H, d, J=11.3 Hz, 7-H) and 6.21 (1H, d, J=11.3 Hz, 6-H); MS m/z (relative intensity) 574 (M⁺, 17), 559 (M⁺-CH₃, <1), 442 (M⁺-OSi(CH₃)₂-t-Bu, 64).

f) Conversion of the Hydroxy Compound 7 into the Tosyl Derivative 8

1 α -[(tert-Butyldimethylsilyl)oxy]-(20S)-20-[(p-toluenesulfonyl)oxy]methyl-2-methylene-19-nor-pregnacalciferol tert-butyldimethylsilyl ether (8). A solution of the alcohol 7 (1 mg, 0.0017 mmol) and p-toluenesulfonyl chloride (498 μ g, 0.0026 mmol) in pyridine (34 μ L, 0.0043 mmol) was kept at 0 $^{\circ}$ C. for 3 h. Addition of ice resulted in a suspension that was extracted with ethyl acetate/hexane. The organic extracts were washed with 5% aqueous HCl, H₂O, and saturated aqueous NaHCO₃, and dried over Na₂SO₄. Removal of the solvents in vacuo afforded a residue that was crystallized from hexane to yield the tosylated product 8 (1 mg, 79%).

g) Reduction of Tosyl Ester 8.

1 α -[(tert-Butyldimethylsilyl)oxy]-20-methyl-2-methylene-19-nor-pregnacalciferol tert-butyldimethylsilyl ether (9). To the compound 8 (1 mg, 0.0013 mmol) in anhydrous ether (2 mL) was added lithium aluminum hydride (15 μ g, 0.0038 mmol). The reaction mixture was refluxed for 2 h, cooled and excess reagent was decomposed by saturated aqueous sodium chloride. The mixture was filtered and layers separated. The aqueous fraction was extracted with ether. Ether fractions were washed with water, saturated aqueous sodium chloride, dried (Na₂SO₄), evaporated to dryness and dried under vacuum to get the crude 17 β -isopropyl vitamin D derivative 9. The compound was purified on a silica Sep-Pak cartridge using 97:3 mixture of hexane/ethyl acetate. 9: ¹H NMR (CDCl₃) δ 0.025, 0.047, 0.065 and 0.078 (each 3H, each s, 4 \times SiCH₃), 0.540 (3H, s, 18-CH₃), 0.864 and 0.895 (each 9H, each s, 2 \times Si-t-Bu), 0.865 (3H, d, J=6.6 Hz, 22-CH₃), 0.946 (3H, d, J=6.5 Hz, 21-CH₃), 4.42 (2H, m, 1 α -H, 3 β -H), 4.92 and 4.97 (each 1H, each s, =CH₂), 5.84 (1 H, d, J=11.0 Hz, 7-H) and 6.22 (1 H, d, J=11.0 Hz, 6-H).

h) Deprotection of TBDMS Ethers of the Vitamin Analog 9

1 α -Hydroxy-20-methyl-2-methylene-19-nor-pregnacalciferol (10). Protected vitamin 9 (750 μ g, 0.0013 mmol) was dissolved in anhydrous THF (150 μ L), then tetrabutylammonium fluoride (1 M solution in THF, 4 μ L, 0.004 mmol) was added and the mixture was stirred at room temperature for 2 h under argon. The reaction was then quenched with water and extracted with ether, washed with brine, dried (Na₂SO₄), and evaporated. The residue was purified by HPLC (250 \times 6.2 mm Zorbax-ODS reversed phase column, 2 mL/min) using methanol/water (95:5) solvent system. Pure vitamin derivative 10 was eluted at R_V 9.4 mL (375 μ g, 85%): UV (in ethanol) λ_{max} 243.5, 251.5, 262.0 nm; ¹H NMR (CDCl₃) δ 0.547 (3H, s, 18-CH₃), 0.865 (3H, d, J=6.6 Hz, 22-CH₃), 0.944 (3H, d, J=6.5 Hz, 21-CH₃), 4.48 (2H, m, 1 α -H, 3 β -H), 5.09 and 5.10 (each 1H, each s, =CH₂), 5.88 (1H, d, J=11.4 Hz, 7-H) and 6.36 (1H, d, J=11.4 Hz, 6-H); MS m/z (relative intensity) 330 (M⁺, 100), 312 (M⁺-H₂O), 287 (M⁺-C₃H₇, 22).

9

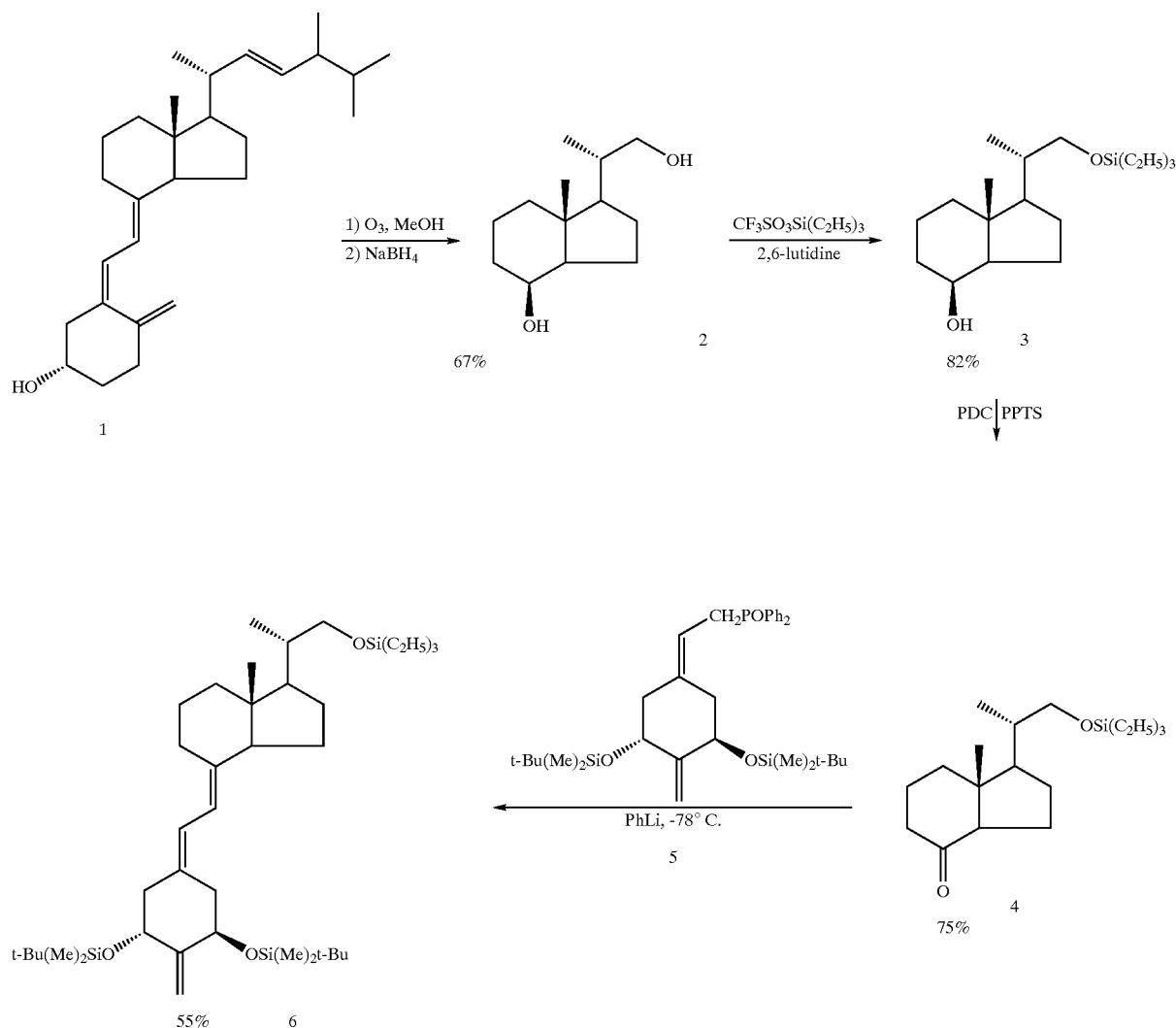
As used in the description and in the claims, the term “hydroxy-protecting group” signifies any group commonly used for the temporary protection of hydroxy functions, such as for example, alkoxy carbonyl, acyl, alkylsilyl or alkylarylsilyl groups (hereinafter referred to simply as “silyl” groups), and alkoxyalkyl groups. Alkoxy carbonyl protecting groups are alkyl-O-CO-groupings such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl or allyloxycarbonyl. The term “acyl” signifies an alkanoyl group of 1 to 6 carbons, in all of its isomeric forms, or a carboxyalkanoyl group of 1 to 6 carbons, such as an oxalyl, malonyl, succinyl, glutaryl group, or an aromatic acyl group such as benzoyl, or a halo, nitro or alkyl substituted benzoyl group. The word “alkyl” as used in the description or the claims, denotes a straight-chain or branched alkyl radical of 1 to 10 carbons, in all its

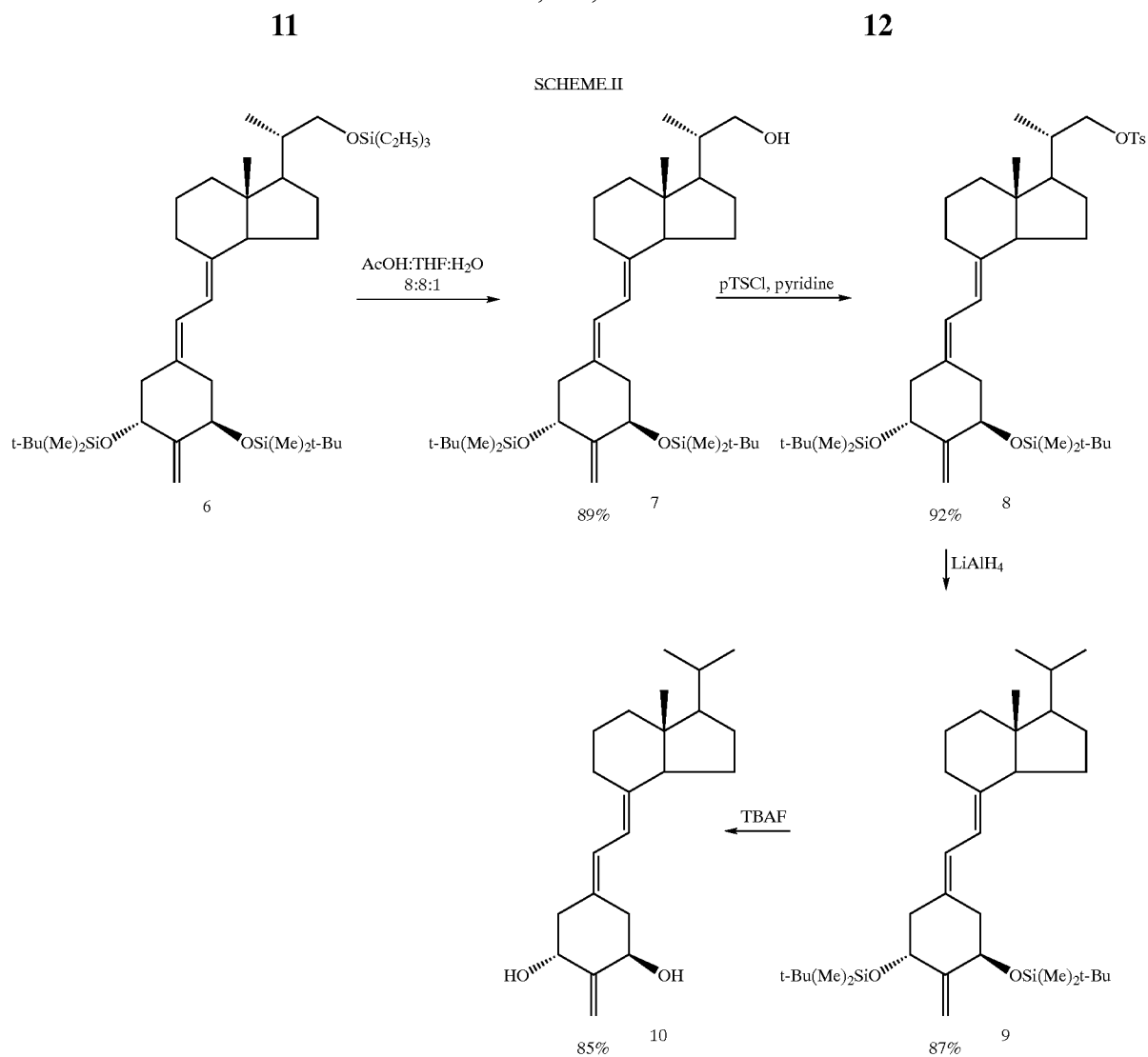
10

isomeric forms. Alkoxyalkyl protecting groups are groupings such as methoxymethyl, ethoxymethyl, methoxyethoxymethyl, or tetrahydrofuranyl and tetrahydropyranyl. Preferred silyl-protecting groups are trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, dibutylmethylsilyl, diphenylmethylsilyl, phenyldimethylsilyl, diphenyl-t-butylysilyl and analogous alkylated silyl radicals. The term “aryl” specifies a phenyl-, or an alkyl-, nitro- or halo-substituted phenyl group.

A “protected hydroxy” group is a hydroxy group derivatised or protected by any of the above groups commonly used for the temporary or permanent protection of hydroxy functions, e.g. the silyl, alkoxyalkyl, acyl or alkoxy carbonyl groups, as previously defined. The terms “hydroxyalkyl”, “deuteroalkyl” and “fluoroalkyl” refer to an alkyl radical substituted by one or more hydroxy, deuterium or fluoro groups respectively.

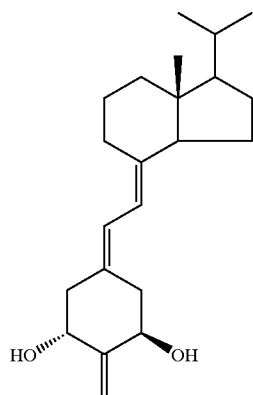
SCHEME I



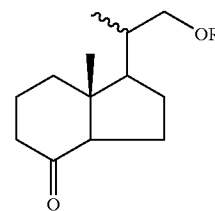


What is claimed is:

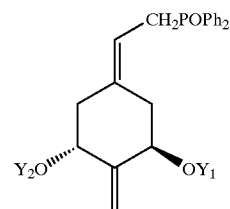
1. A method of making 1 α -hydroxy-2-methylene-19-nor-homopregnaciferol having the structure



condensing a bicyclic ketone having the structure



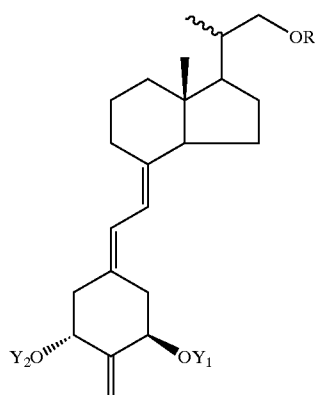
with an allylic phosphine oxide having the structure



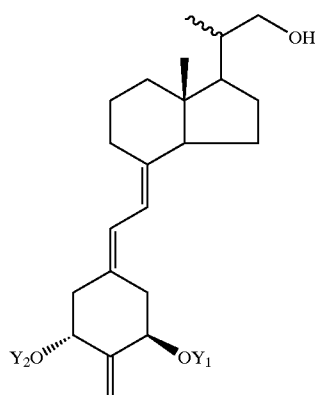
comprising the steps of:

13

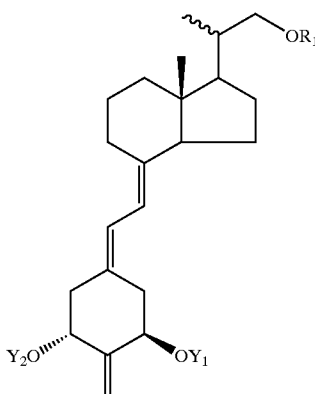
where Y_1 , Y_2 and R, which may be the same or different, are each a hydroxy-protecting group, to produce a protected 19-nor-pregnacalciferol analog having the structure



thereafter cleaving the protecting group R to form 22-alcohol having the structure

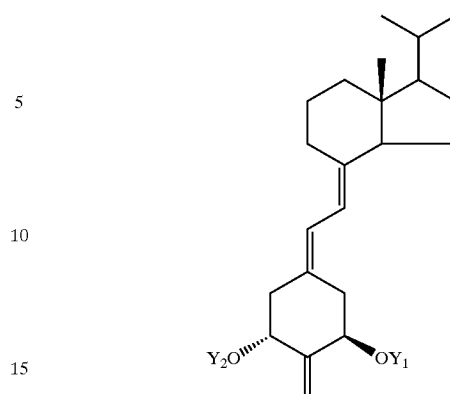


converting said 22-alcohol to an ester having the structure



where R_1 is a tosyl group or a mesyl group;

reducing said ester to obtain 17 β -isopropyl-19-nor-vitamin D analog having the structure

14

and deprotecting said 17 β -isopropyl vitamin D derivative to form 1 α -hydroxy-2-methylene-19-nor-homopregnacalciferol.

2. The method of claim 1 wherein the condensing step takes place in the presence of phenyllithium.

3. The method of claim 1 wherein the cleaving step comprises hydrolysis.

4. The method of claim 3 wherein said hydrolysis is acid hydrolysis.

5. The method of claim 3 wherein said hydrolysis is alkaline hydrolysis.

6. The method of claim 1 wherein the converting step comprises tosylation.

7. The method of claim 1 wherein the converting step comprises mesylation.

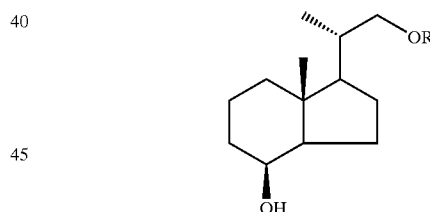
8. The method of claim 1 wherein the reducing step takes place in the presence of lithium aluminum hydride.

9. The method of claim 1 wherein the deprotecting step takes place in the presence of tetrabutylammonium fluoride.

10. The method of claim 1 wherein R is a triethylsilyl group.

11. The method of claim 1 wherein Y_1 and Y_2 are both a t-butyl-dimethylsilyl group.

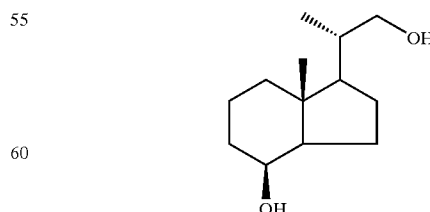
12. The method of claim 1, further including the step of oxidizing an 8 β -hydroxyl group in an alcohol having the structure



to form said bicyclic ketone.

13. The method of claim 12 wherein the step of oxidizing takes place in the presence of pyridinium dichromate and pyridinium p-toluenesulfonate.

14. The method of claim 12 further including the step of selectively protecting only the side chain hydroxyl group of a diol having the structure



to form said alcohol having said 8 β -hydroxyl group.

15. The method of claim 14 further including the step of ozonating vitamin D₂ to obtain said diol.

* * * * *