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CA 2140382 C 2007/11/20

(11)(21) 2 140 382

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(22) Date de dépôt/Filing Date: 1995/01/17

(41) Mise à la disp. pub./Open to Public Insp.: 1995/07/21

(45) Date de délivrance/Issue Date: 2007/11/20

(30) Priorité/Priority: 1994/01/20 (EP94200131.4)

(51) Cl.Int./Int.Cl. *C07C 401/00* (2006.01),
A61K 31/59 (2006.01), *A61P 11/06* (2006.01),
A61P 17/00 (2006.01), *A61P 19/00* (2006.01),
A61P 35/00 (2006.01), *C07D 309/12* (2006.01),
C07D 317/20 (2006.01), *C07F 7/18* (2006.01)

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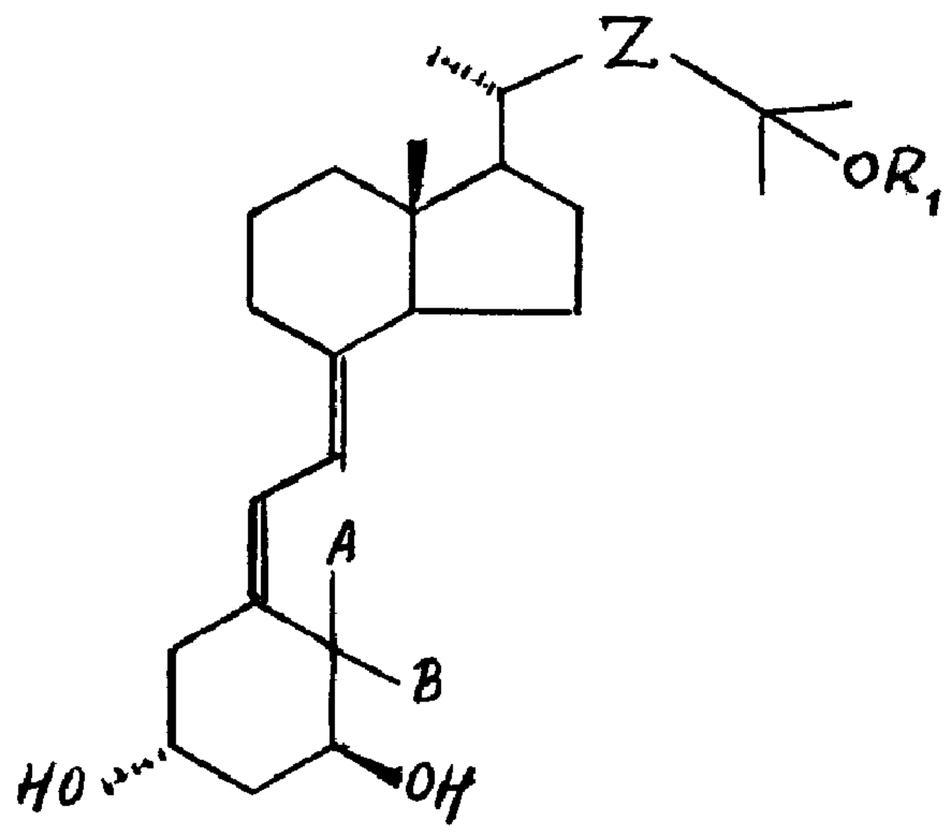
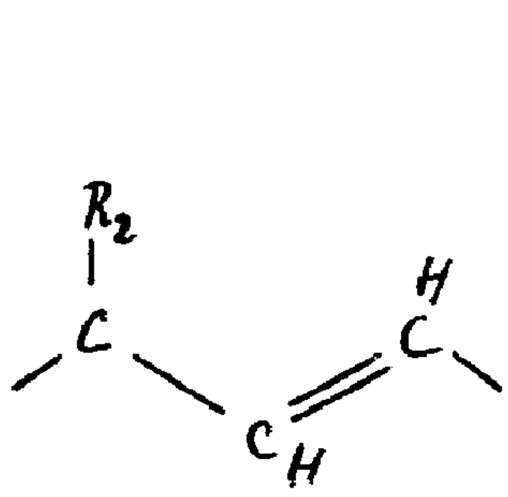
(54) Titre : COMPOSES DE TYPE VITAMINE D ET METHODE POUR LEUR PREPARATION
(54) Title: VITAMIN D COMPOUNDS AND METHOD OF PREPARING THESE COMPOUNDS



(I)



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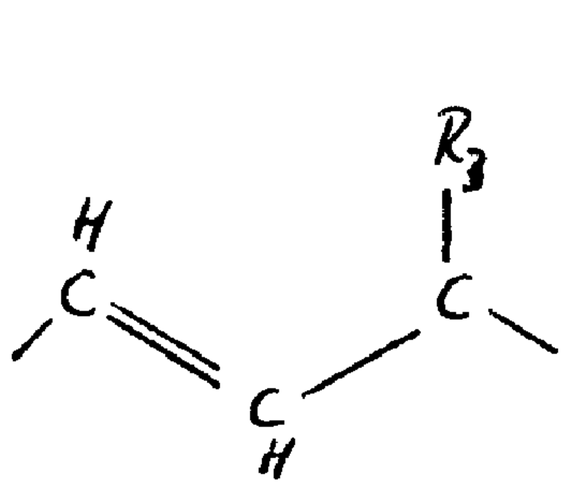

(III)

(57) Abrégé/Abstract:
The invention relates to a vitamin D compound of the general formula (see formula I) wherein: R_1 is a hydrogen atom or a hydroxy protecting group; Z is a group of the general formula (see formuila II) or (see formula III) wherein R_2 and R_3 are each individually

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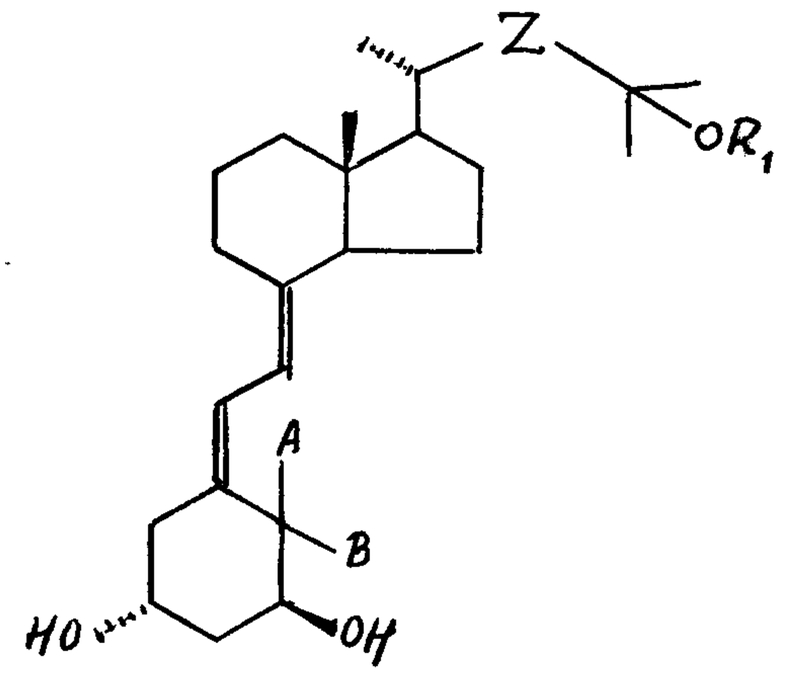
(57) Abrégé(suite)/Abstract(continued):
straight or branched, substituted or unsubstituted, (C_1-C_6)alkyl groups, (C_2-C_6)alkenyl groups, (C_3-C_6)cycloalkyl groups or phenyl groups; or wherein R_1 and R_3 together with the interconnecting oxadimethylene biradical form a 5-7 membered ring-closed (C_1-C_4)alkyl substituted hemiacetal; with the proviso, that R_2 and R_3 are not both or individually methyl groups; A and B are each individually hydrogen atoms or methyl groups, or A and B form together a methylene group. The invention also relates to a method of preparing these compounds and to their use in pharmacology. The invention further relates to valuable new intermediates.

Abstract

The invention relates to a vitamin D compound of the general formula

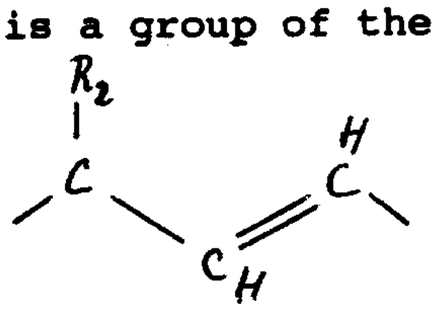


(I)

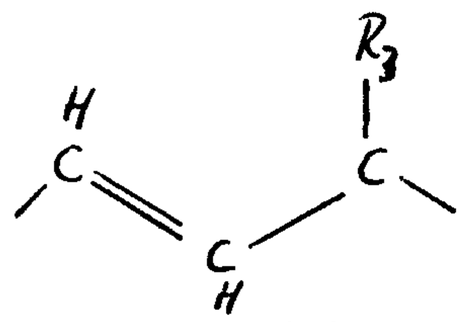
wherein:

R_1 is a hydrogen atom or a hydroxy protecting group;

Z is a group of the general formula



(II) or



(III)

wherein R_2 and R_3 are each individually straight or branched, substituted or unsubstituted, (C_1-C_6)alkyl groups, (C_2-C_6)alkenyl groups, (C_3-C_6)cycloalkyl groups or phenyl groups; or wherein R_1 and R_3 together with the interconnecting oxadimethylene biradical form a 5-7 membered ring-closed (C_1-C_4)alkyl substituted hemiacetal;

with the proviso, that R_2 and R_3 are not both or individually methyl groups;

A and B are each individually hydrogen atoms or methyl groups, or A and B form together a methylene group.

The invention also relates to a method of preparing these compounds and to their use in pharmacology. The invention further relates to valuable new intermediates.

27072-166

Vitamin D compounds and method of preparing these compounds.

The invention relates to new vitamin D compounds, to a method of preparing these compounds and to their use in pharmacology. The invention further relates to valuable new intermediates.

It is generally known, that vitamin D compounds or vitamin D related compounds ("vitamin D compounds") have a strong biological activity and may be used in all those cases in which problems with the calcium metabolism and bone metabolism play a part. A few years ago it was found that various active vitamin D compounds also have other pharmacotherapeutic activities and may be used successfully, for example, for the treatment of certain skin diseases, for cosmetic applications and for treating diseases which are related to cell differentiation, cell proliferation or imbalance in the immune system, including diabetes mellitus, hypertension and inflammatory diseases such as rheumatoid arthritis and asthma. In addition, these compounds may be used in various veterinary applications, and for diagnostic purposes.

It is therefore of the utmost importance to have the disposal of an arsenal of active vitamin D compounds for the above various application fields so as to be able to make the best possible choice of a vitamin D compound for the application in view.

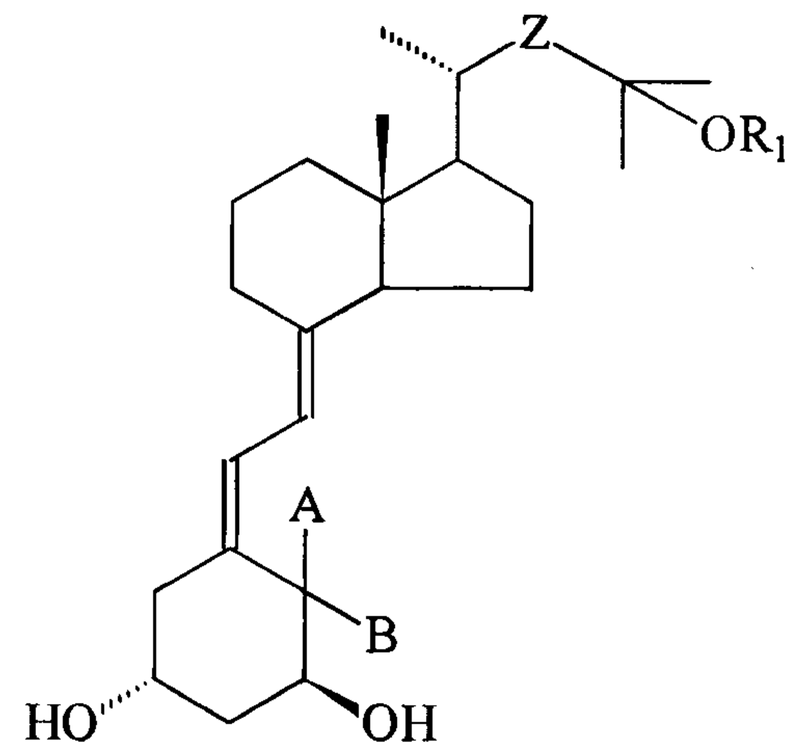
Vitamin D compounds which are of interest for the above applications are hydroxylated vitamin D compounds, in particular vitamin D compounds hydroxylated in the 1α-, 24- and/or 25-positions. Recent developments in the field of active vitamin D compounds are 19-nor-vitamin D compounds (EP-A-0387077), 25,25-di(cyclo)alkyl vitamin D compounds (US patent 5,449,668) and (C-18)-modified vitamin D compounds (EP-A-0521550), preferably also hydroxylated in the 1α-position and optionally in the (C-17)-side chain. Other modifications of the (C17)-side chain have been proposed, likewise to improve the intended activity and to suppress detrimental side-effects. Examples of modifications of the (C17)-side chain are chain elongations (homo compounds), 22-oxa modifications, fluor substitutions, epoxy groups (e.g. WO 92/21695), etc. Generally, however, the above (C17)-side chain

modified vitamin D compounds are still not completely satisfactory as regards their selective activity, i.e. the intended activity without detrimental side-effects, such as high calcemic and calciuric effects.

It is well-known in the art, that vitamin D_3 metabolizes in the living organism into a number of hydroxylated vitamin D_3 compounds, viz. 25-hydroxy-vitamin D_3 and 1α,25-dihydroxy-vitamin D_3. The metabolism of vitamin D_2 is thought to be related to that of vitamin D_3, also resulting in a number of hydroxylated vitamin D_2 metabolites. To investigate these hydroxylated vitamin D_2 metabolites, Sardina et al. (J. Org. Chem., Vol. 51, 1986, 1264-1269) have synthetized 25-hydroxyvitamin D_2, Granja et al. (J. Org. Chem., Vol. 58, 1993, 124-131) have recently synthetized 1α,25-dihydroxy-vitamin D_2, and Choudhry et al. (J. Org. Chem., Vol. 58, 1993, 1496-1500) have - also recently - succeeded in the synthesis of 1α,25,28-trihydroxy-vitamin D_2. Although during the last decade a great number of publications has been devoted to vitamin D_3 analogues and derivatives as well as to their biological activity, vitamin D_2 compounds have not been explored largely, apparently (also) due to their difficult synthetic accessibility.

The present invention provides a new class of vitamin D compounds, in particular vitamin D_2 compounds and related compounds, which is well accessible from readily available or accessible starting materials.

According to the present invention this can be achieved with a new vitamin D compound of the general formula

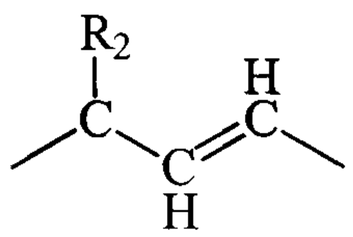


(I)

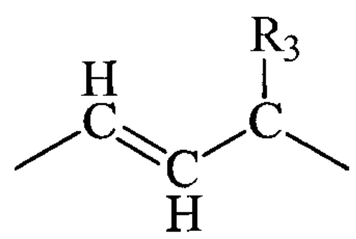
wherein:

R_1 is a hydrogen atom or a hydroxy protecting group;

Z is a group of the general formula



(II) or



(III)

wherein R_2 and R_3 are each individually straight or branched (C_1-C_6)alkyl groups or (C_2-C_6)alkenyl groups, optionally substituted with one or more substituents selected from hydroxy, (C_1-C_4)alkoxy, fluoro, (C_3-C_6)cycloalkyl and (C_2-C_3)alkylenedioxy; or with unsubstituted or substituted phenyl;

or (C_3-C_6)cycloalkyl groups, or unsubstituted or substituted phenyl groups;

or wherein R_1 and R_3 together with the interconnecting oxadimethylene biradical form a 5-7 membered ring-closed (C_1-C_4)alkyl substituted hemiacetal;

with the proviso, that R_2 and R_3 are not both or individually methyl groups;

A and B are each individually hydrogen atoms or methyl groups, or A and B form together a methylene group.

Compounds where R_3 is hydroxymethyl are disclosed by Batcho et al., Bioorg. & Med. Chem. Lett. 3, 1821-1824, 1993.

The above new vitamin D compounds of the invention, presented by the general formula I, are valuable substances. The biological results indicate that these compounds are promising as biologically active substances and may be used in all above-mentioned pharmacotherapeutic indications, more in particular for the treatment of osteoporosis, renal osteodystrophy, osteomalacia, skin

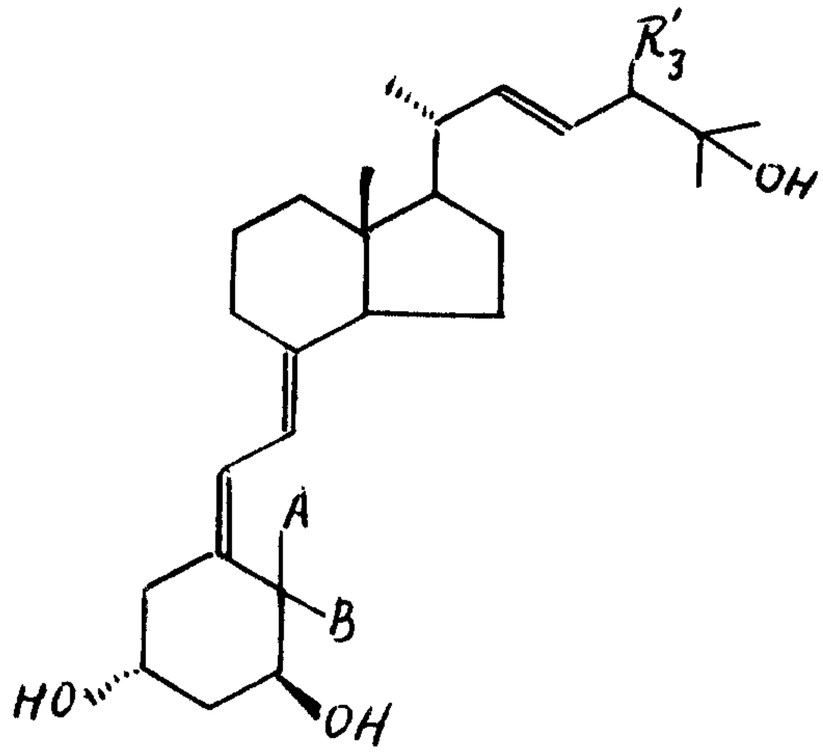
disorders such as psoriasis (and other hyperproliferative skin diseases), eczema and dermatitis, myopathy, leukemia, breast and colon cancer, osteosarcomas, squamous cell carcinomas, melanoma, certain immunological disorders, and transplant rejections.

Furthermore, the new vitamin D compounds of the invention may be used for wound healing and may be incorporated in cosmetic compositions, such as creams, lotions, ointments and the like, in order to preserve, condition and/or protect the skin and to improve various skin conditions, such as wrinkles, dry skin, skin slackness and insufficient sebum secretion. The new vitamin D compounds may also be used for

diagnostic purposes.

Suitable substituents of the above phenyl group are: (C_1-C_4)alkyl, (C_1-C_4)alkoxy, fluoro, trifluoromethyl and hydroxy.

Preferred is a vitamin D compound of the general formula



(IV)

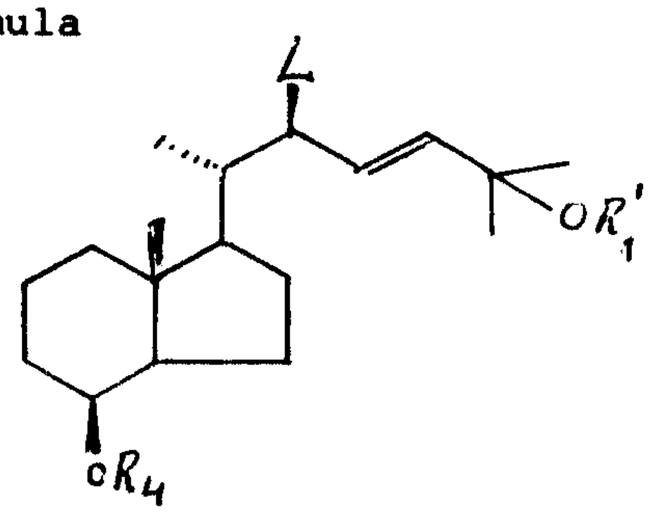
wherein:

A and B have the meanings given above, and

R_3' is a straight or branched (C_2-C_6)alkyl group, optionally substituted with hydroxy, (C_1-C_2)alkoxy or (C_2-C_3)alkylenedioxy, a cyclopropyl group or a phenyl group.

It is a merit of the present invention, that the desired C-24 stereoisomer can easily be obtained, as will be explained hereinafter. Therefore the present invention also relates to a vitamin D compound of the above general formula IV, wherein the C-24 atom, i.e. the carbon atom to which R_1' is attached, has either the **R** or the **S** configuration.

The invention also relates to a method of preparing a vitamin D compound of the above formula I as defined above, in that a hydrindane compound of the general formula



(V)

wherein:

L is a suitable leaving group, and

R_1' and R_4 are each individually hydroxy-protecting groups;

is reacted with a reagent of the general formula

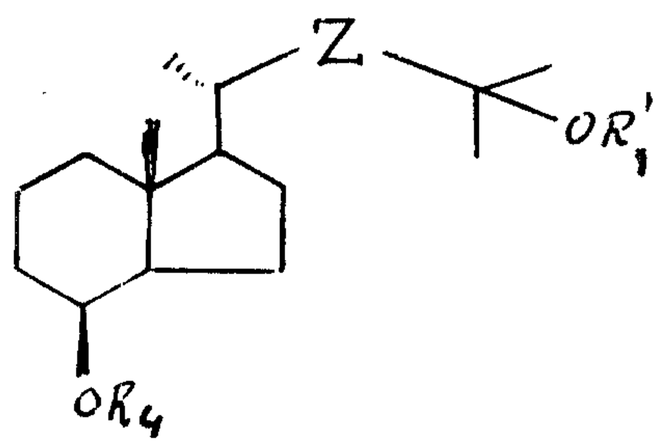
$$R_3\text{-MgX} \quad \text{or} \quad R_3\text{-Li}$$

wherein R_3 has the meaning given hereinbefore, and

X is a halogen atom,

in the presence of a Cu(I) compound;

after which the hydrindane intermediate obtained, having the general formula

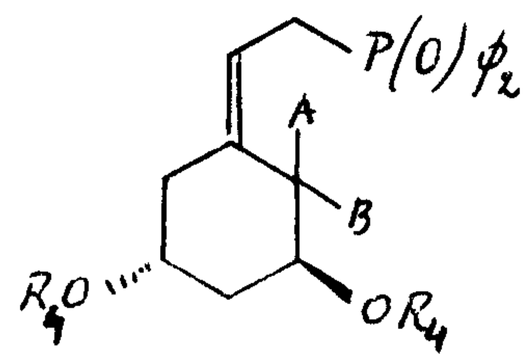


(VI)

wherein Z has the meaning given above,

is oxidized, after deprotection of OR_4, to the corresponding hydrindane-4-one compound, and is then converted, in a manner known per se for related compounds,

either (a) with a Wittig reagent of the general formula



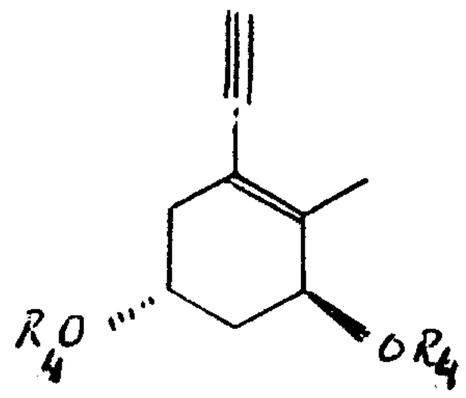
(VII)

wherein:

R_4 has the above meaning, and

A and B have the meanings given hereinbefore,

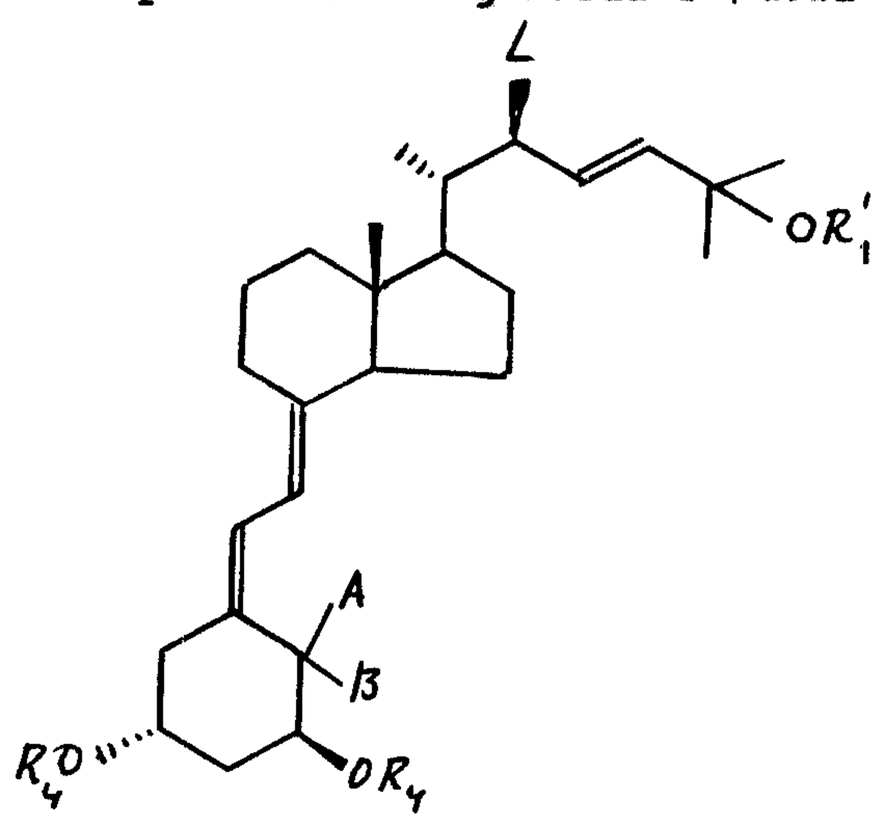
or (b), after enolization, with an enyne compound of the general formula



(VIII)

wherein R_4 has also the above meaning, followed by hydrogenation and isomerization, to produce a compound of the general formula I, wherein A and B form together a methylene group;
followed by deprotection.

Alternatively, the vitamin compound of the above formula I as defined above can be prepared with a method wherein a hydrindane compound of the general formula V as defined above is oxidized, after deprotection of OR_4, to the corresponding hydrindane-4-one compound, and is then converted, in a manner known per se for related compounds,
either (a) with a Wittig reagent of the general formula VII as defined above to produce a compound of the general formula



(XII)

wherein:

L is a suitable leaving group;

R_1' and R_4 are each individually hydroxy protecting groups; and

A and B are each individually hydrogen atoms or methyl groups, or A and B form together a methylene group

or (b) after enolization with an enyne compound of the general formula VIII as defined above, followed by hydrogenation and isomerization, to produce a compound of the general formula XII, wherein A and B form together a methylene group;
followed by reaction with a reagent of the general formula

$$R_3\text{-MgX or } R_3\text{-Li}$$

wherein:

R_3 has the meaning given hereinbefore, and

X is a halogen atom,

in the presence of a Cu(I) compound;

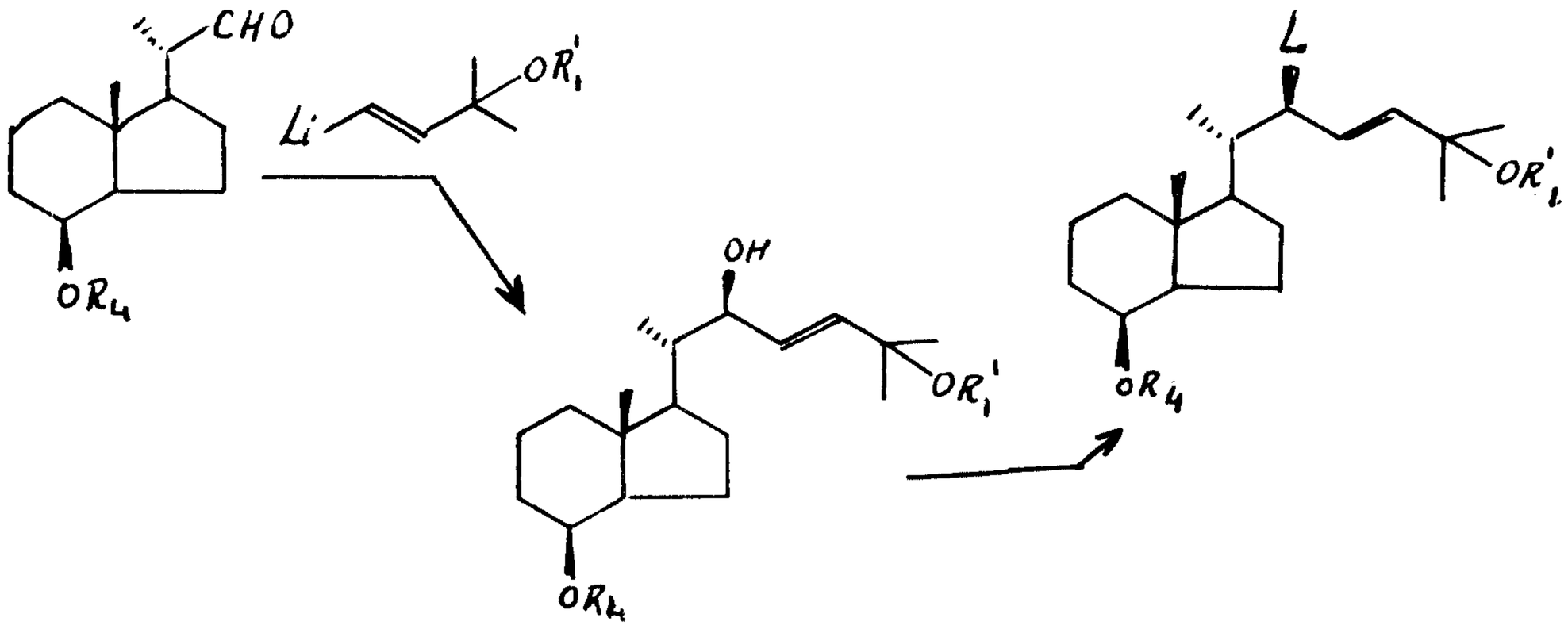
followed by deprotection.

Examples of suitable leaving groups L are: phosphate esters, sulphonates such as tosylate and mesylate, and N-arylcarbamates.

Hydroxy groups in the above intermediates or reactants may be protected by a reaction with a suitable etherification agent; for example, a methoxymethylating agent (such as methoxymethylchloride), a trialkylsilylimidazole, a trialkylsilylhalide, a trialkyl-silyltriflate (-trifluoromethanesulfonate), a diphenylalkylsilylhalide, or a diphenylalkylsilyltriflate, or a derivative thereof, the alkyl groups of which have 1 to 6 carbon atoms. Particularly suitable for this purpose are trimethylsilylchloride, tert.-butyldimethylsilylchloride, dimethyl-(1,1,2-trimethylpropyl)-silylchloride, tert.-butyldimethylsilyl triflate, or trimethylsilyl-imidazole, because these etherification agents readily react with the hydroxy group to be protected to form an ether function, which on the one hand is sufficiently stable under the conditions of the reaction or reactions in view, but on the other hand can easily be removed [deprotection] to recover the original hydroxy group; tert.-butyldimethylsilylchloride or triflate is to be preferred, because the tert.-butyldimethylsilyl group has been found to be excellently suitable as a protective group.

The enolic hydroxy group is preferably derivatized by a reaction with N-phenyltriflimide to produce a triflate.

The starting compounds of formula V can conveniently be prepared from readily available substances, e.g. as follows:



The second reaction step, i.e. the conversion of the hydroxy group in the intermediate allylic hydroxy compound to a leaving group L can be performed with the aid of various compounds, viz.:

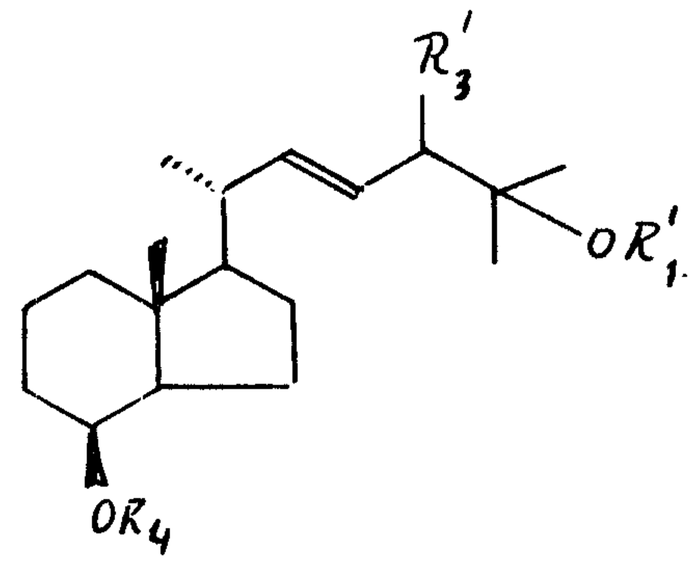
- sulphonating compounds, such as tosylchlorde and mesylchloride;
- phosphate-introducing compounds, such as $ClPO(O\text{-hydrocarbyl})_2$; and
- N-arylcarbamoyl-introducing compounds, such as phenylisocyanate.

The term hydrocarbyl includes: $(C_1\text{-}C_4)$alkyl, phenyl, phenyl$(C_1\text{-}C_2)$alkyl and cyclohexyl.

In this manner formula V compounds are prepared, wherein L is a hydrocarbyl sulphonate, a dihydrocarbyl phosphate or a N-arylcarbamate group, respectively.

The hydrindane intermediate of the above general formula VI is new. Therefore the present invention also relates to this intermediate, as well as to a method of preparing this compound.

A preferred hydrindane intermediate as defined above can be represented by the general formula



(IX)

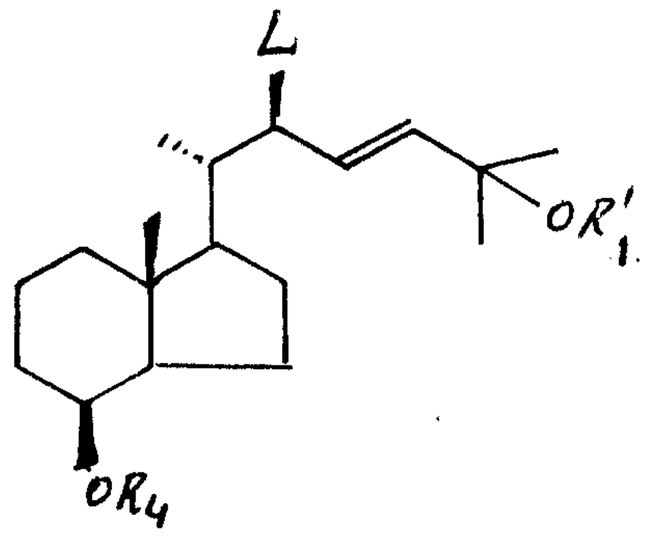
wherein:

R_1', R_3' and R_4 have the meanings given above.

Substantially pure C-24 enantiomeric vitamin D compounds can be obtained by using substantially pure hydrindane stereoisomers as intermediates. The present invention therefore also relates to a hydrindane intermediate of the above general formula IX, wherein the C-atom, to which substituent R_1' is attached, has either the **R** or the **S** configuration. As will be explained hereinafter, these isomers can be prepared stereospecifically in a convenient manner.

The hydrindane compound of the general formula VI, defined above, can be prepared conveniently by reacting a hydrindane compound of the general

formula



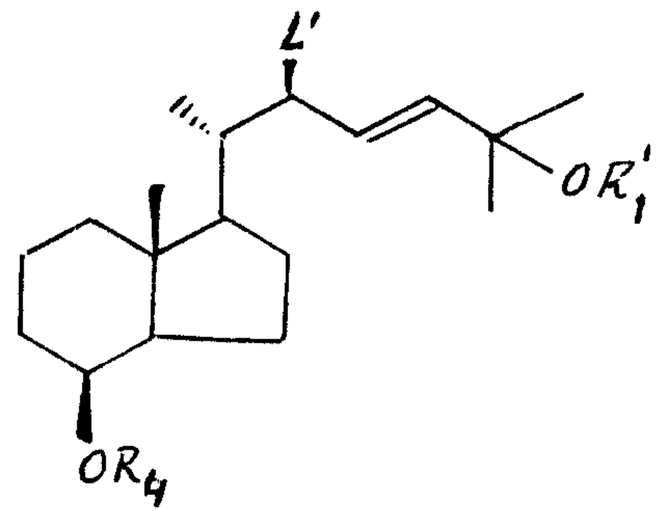
(V)

wherein L, R_1' and R_4 have the meanings given above,
with a reagent of the general formula

$$R_3\text{-MgX} \quad \text{or} \quad R_3\text{-Li}$$

wherein R_3 has the meaning given above and X is a halogen atom,
in the presence of a Cu(I) compound.
Examples of suitable reagents for the above reaction are:
R_3-MgBr, R_3-MgI, R_3-MgCl and R_3-Li, wherein R_3 is defined above; examples of suitable cupro compounds are CuCN, CuCl and CuI.

It has been found, that the above-mentioned hydrindane stereoisomers of the general formula IX, wherein the C-atom, to which substiuent R_3' is attached, has either the **R** or the **S** configuration, can be prepared selectively by using as the starting substance a hydrindane compound of the general formula V having a specific leaving group L.
So a hydrindane intermediate of formula IX, wherein said C-atom has the configuration as shown in formula IXA below, can be prepared selectively from a hydrindane compound of the general formula



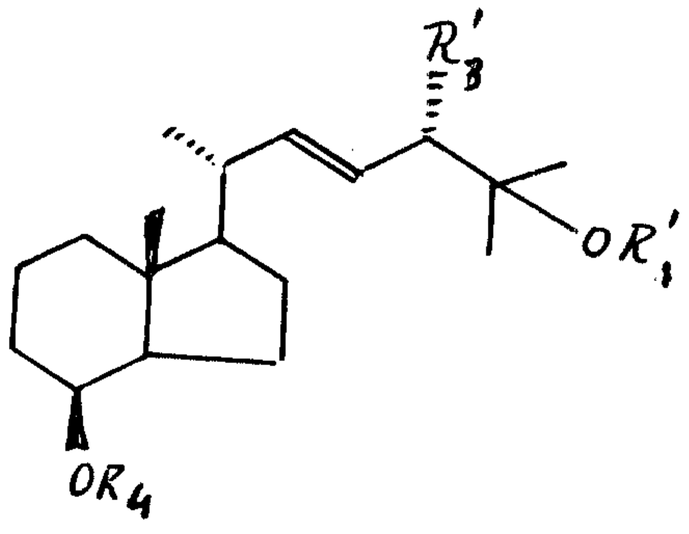
(X)

wherein:

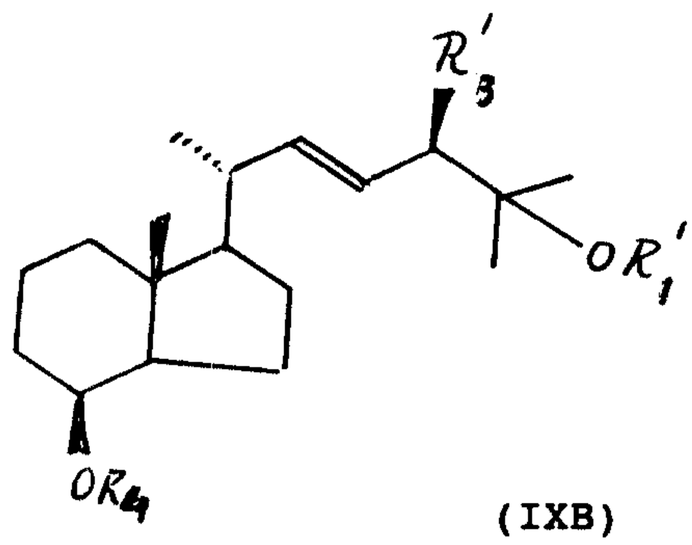
R_1' and R_4 have the meanings above, and

L' is a di(hydrocarbyl)phosphate leaving group.

If, however, a hydrindane intermediate of formula IX is desired, wherein said C-atom has the configuration as shown in formula IXB below, as the starting substance a hydrindane compound can excellently be used, wherein L' is a N-arylcarbamate leaving group.



(IXA)



(IXB)

To improve the applicability of the new vitamin D compounds of the invention for the above-described pharmacotherapeutic indications, the compounds are usually processed to pharmaceutical compositions, comprising an effective amount of said vitamin D compound as the active ingredient in addition to a pharmaceutically acceptable carrier and/or at least one pharmaceutically acceptable auxiliary substance. Such a composition may be delivered in a dosage unit form for oral, topical (dermal) or parenteral administration, comprising approx. 0.1 μg to approx. 0.1 mg active ingredient per dosage unit.

A composition for diagnostic purposes may comprise, in addition to the vitamin D compound of the present invention, a compatible, non-toxic carrier and/or at least one auxiliary substance.

A cosmetical composition may comprise, in addition to an effective amount (in the range of approx. 0.1 μg to approx. 0.1 mg per dosage unit in a dosage unit form) of the vitamin D compound of the present invention, a cosmetically acceptable, non-toxic carrier and/or at least one auxiliary substance.

Finally the invention relates to a method for the treatment and prophylaxis of a number of disease states including autoiummune diseases (including diabetes mellitus), acne, alopecia, skin aging (including photo-aging), imbalance in the immune system, inflammatory diseases such as rheumatoid arthritis and asthma, as well as diseases related to abnormal cell differentiation and/or proliferation, in a warm-blooded

living being, comprising administering to said being or treating said being with a pharmaceutical composition as defined above in a quantity effective for the intended purpose. Examples of such diseases are psoriasis and other hyperproliferative skin diseases. The present invention also relates to the use of the above pharmaceutical compositions for the treatment of solid, skin and blood cancers, in particular of blood cancers such as leukemia, of breast cancer, and of skin cancers such as melanoma and squamous cell carcinoma. The above-defined cosmetical compositions, in particular selected from the group consisting of creams, lotions, ointments, liposomes and gels, can be used for the treatment and prevention of a number of skin disorders, such as inadequate skin firmness or texture, insufficient skin hydration, wrinkles and insufficient sebum secretion.

In use aspects, the invention provides uses of the compounds or compositions of the invention for (i) preparing a medicament for the treatment or prevention of osteoporosis, renal osteodystrophy and osteomalacia, autoimmune diseases, acne, alopecia, skin aging, imbalance in the immune system, rheumatoid arthritis, asthma, diseases related to abnormal cell differentiation or proliferation, or solid, skin or blood cancers in a warm-blooded living being; or (ii) for the treatment or prevention of osteoporosis, renal osteodystrophy and osteomalacia, autoimmune diseases, acne, alopecia, skin aging, imbalance in the immune system, rheumatoid arthritis, asthma, diseases related to abnormal cell differentiation or proliferation, or solid, skin or blood cancers in a warm-blooded living being.

In a further aspect, the invention provides a commercial package comprising compounds or compositions of

the invention and associated therewith instructions for the use thereof in the treatment or prevention of osteoporosis, renal osteodystrophy and osteomalacia, autoimmune diseases, acne, alopecia, skin aging, imbalance in the immune system, rheumatoid arthritis, asthma, diseases related to abnormal cell differentiation or proliferation, or solid, skin or blood cancers in a warm-blooded living being.

The invention will now be described in greater detail with reference to the following specific Examples and in the accompanying Reaction Schemes A, B and C illustrating Examples I, II and III. The following abbreviations are used in the Examples:

THF = tetrahydrofuran

TBS = tert.-butyl dimethyl silyl

MOM = methoxymethyl

TBAF = tert.-butyl ammonium fluoride

PPTS = pyridinium p-toluene sulphonate

PDC = pyridinium dichromate

AIBN = azodiisobutyronitrile

DCM = dichloromethane.

Examples

Example I

Preparation of hydrindane compounds, intermediates for modified vitamin D_2 compounds.

The reaction equations are presented in the Reaction Scheme A appended.

(a). Preparation of compound 2.

Compound 1 is prepared as described by Sardina et al. in J. Or. Chem. 1986, 51, 1264.

A mixture of compound 1 (0.50 g, 3.90 mmol), n-Bu_3SnH (1.4 ml, 1.51 g, 5.20 mmol) and AIBN (20 mg) is irradiated with a tungsten lamp of 300 W for 15 min. and then heated at 95°C for 6 h. The reaction mixture is allowed to reach room temperature and is then chromatographed (silica gel; eluent: 0-7% EtOAc/hexane), producing compound 2 in a yield of 1.36 g, 83%, Rf=0.4 (10% EtOAc/hexane), liquid, b.p. 120°C/1 mm Hg.

^{1}H-NMR: 6.02 (2H, AB, J=19.5 Hz, HC=CH), 4.63 (2H, s, OCH_2O), 3.35 (3H, s, OCH_3), 1.47 (6H, m, $Sn(CH_2-)_3$), 1.30 (6H, s, $2CH_3$), 1.29 (6H, m, $Sn(CH_2\underline{CH}_2-)_3$), 0.91-0.85 (15H, m, $(-C\underline{H}_2C\underline{H}_3)_3$).

^{13}C-NMR: 153.26 (C=), 126.58 (C=), 91.97 (OCH_2O), 77.76 (<u>C</u>OMOM), 54.98 (OCH_3), 29.01 ($SnCH_2-)_3$), 27.12 ($Sn(CH_2\underline{C}H_2-)_3$), 26.75 ($(\underline{C}H_3)_2$), 13.55 ($(-CH_3)_3$), 9.42 ($(-\underline{C}H_2CH_3)_3$).

(b). Preparation of compound 6.

Compound 5 is prepared from compound 4 as described by Mascarenas et al. in J. Org. Chem. 1986, 51, 1269. Compound 6 is prepared from compound 5 as described by Fernandez et al. in J. Org. Chem. 1992, 57, 3173.

(c). Preparation of compound 7.

A solution of n-BuLi in hexane (2.38 M, 3 ml, 7.11 mmol) is added dropwise to a solution of compound 2 (2.98 g, 7.11 mmol, freshly distilled) in 19 ml Et_2O, cooled at -80°C. The mixture is stirred for 4 hours and then cooled to -85°C. During the reaction compound 3 is intermediately formed in situ. Thereupon a solution of compound 6 (1.49 g, 4.59 mmol) in 36 ml Et_2O, cooled at -85°C, is added in 15 minutes. After stirring for 2 h, a drop of MeOH is added. The reaction is allowed to reach room temperature, after which a saturated NaCl solution (50 ml) and HCl (10%, 2 ml) are added. Extraction with Et_2O (2x30 ml), drying, filtration and concentration yields a residue which is chromatographed over a silica gel column; eluent: 10% EtOAc/hexane. Products 7 [1.58 mg, 76%, Rf=0.61 (30% EtOAc/hexane); crystallizing upon cooling, m.p. 49°C] and 7a [0.24 mg, 11%, Rf=0.57 (30% EtOAc/hexane)] are obtained. Compound 7 is identified by ^{1}H-NMR and ^{13}C-NMR.

^{1}H-NMR: 5.66 (1H, d, J=16.1 Hz, H-24), 5.58 (1H, dd, J=16.1 and 3.5 Hz, H-23), 4.62 (2H, s, OCH_2O), 4.25 (1H, s, H-22), 3.98 (1H, s, H-8), 3.33 (3H, s, OCH_3), 1.31 (6H, s, CH_3-26 and 27), 0.90 (3H, s, CH_3-18), 0,86 (9H, s, $SiC(CH_3)_3$), 0.82 (3H, d, J=5.93 Hz, CH_3-21), -0.01 (3H, s, $SiCH_3$),

-0.03 (3H, s, $SiCH_3$).

^{13}C-NMR: 135.00 (C=), 132.58 (C=), 91.75 (OCH_2O), 75.88 (C-25), 73.35, 69.41, 54.95 (OCH_3), 53.13, 52.98, 41.95 (C-13), 40.81, 40.60 (CH_2), 34.35 (CH_2), 27.32 and 27.24 (C-26 and C-27), 26.81 (CH_2), 25.74 ($SiC(\underline{C}H_3)_3$), 22.93 (CH_2), 17.94 ($Si\underline{C}(CH_3)_3$), 17.58 (CH_2), 13.57, 11.78, -4.89 ($SiCH_3$).

(d). Preparation of compound 8.

A solution of n-BuLi in hexane (2.38 M, 1.26 ml, 3.0 mmol) is added to a solution of compound 7 (1.24 g, 2.71 mmol) in 25 ml Et_2O while stirring and cooling at -78°C. After 15 min, $ClPO(OEt)_2$ (0.43 ml, 0.52 g, 3.0 mmol, distilled over P_2O_5) is added. The mixture is stirred for 3 h, and then poured onto a mixture of saturated aqueous NaCl (100 ml) and ice (50 ml). The mixture is extracted with Et_2O (3x40 ml); the organic layer is dried, filtered, concentrated and chromatographed over a silica gel column (eluent: 15-30% EtOAc/hexane), to produce compound 8 in a yield of 1.50 g [93%, Rf=0.3 (30% EtOAc/hexane)].

^{1}H-NMR: 5.71 (1H, d, J=15.95 Hz, H-24), 5.60 (1H, dd, J=15.95 and 5.0 Hz, H-23), 4.89 (1H, t, J=6.0 Hz, H-22), 4.64 (2H, s, OCH_2O), 4.14-3.97 (4H, m, J=7.2 Hz, $P(O\underline{C}H_2CH_3)_2$), 3.97 (1H, s, H-8), 3.34 (3H, s, OCH_3), 1.35-1.26 (6H, m, $P(OCH_2C\underline{H}_3)_2$), 1.32 (6H, s, CH_3-26 and 27), 0.91 (3H, d, J=6.33 Hz, CH_3-21), 0,90 (3H, s, CH_3-18), 0.87 (9H, s $SiC(CH_3)_3$), -0.01 (3H, s, $SiCH_3$), -0.02 (3H, s, $SiCH_3$).

^{13}C-NMR: 137.50, 128.04, 91.74 (OCH_2O), 81.16 (d, J=6.9 Hz, C-22), 75.50 (C-25), 69.23, 63.23 (c, J=2.8, $P(O\underline{C}H_2CH_3)_2$), 54.85 ($OCH_3$), 52.92, 52.53, 41.91 (C-13), 41.83, 40.49 (CH_2), 34.18 (CH_2), 27.06 (C-26 and 27), 26.75 (CH_2), 25,59 ($SiC(\underline{C}H_3)_3$), 22.84 (CH_2), 17.79 ($Si\underline{C}(CH_3)_3$), 17.41 (CH_2, 15.95 (c, J=3.5 Hz, $P(OCH_2\underline{C}H_3)_2$), 13.32, 12.16, -5.04 ($SiCH_3$), -5.40 ($SiCH_3$).

Example II

Preparation of compound 25 from compound 8.

The reaction equations are presented in the Reaction Scheme B appended.

(a). Preparation of compound 9.

A mixture of CuCN (0.90 g, 10 mmol) and LiCl (0.85 g, 20 mmol) in 28 ml THF is stirred at room temp. until a homogeneous solution is obtained.

After cooling to -78°C, a solution of n-BuMgCl in Et_2O (2M, 5 ml, 10 mmol) is added. The resulting reaction mixture is stirred for 5 min. A solution of phosphate 8 (0.96 g, 1.62 mmol, dried over P_2O_5) in 32 ml THF is added. The reaction mixture is stirred for 10 h, after which the mixture is allowed to reach room temperature without removing the cooling bath (12 h). After dropwise addition of a saturated solution of NH_4Cl (30 ml), the mixture is stirred for 10 min and then extracted with hexane (3x50 ml). The organic phase is dried, filtered and concentrated, yielding 784 mg of compound 9 [98%, Rf=0.8 (10% EtOAc/hexane].

^{1}H-NMR: 5.20 (1H, dd, J=15.2 and 8.5 Hz, H-22 or H-23), 5.03 (1H, dd, J=15.2 and 9.2 Hz, H-22 or H-23), 4.69 (2H, s, OCH_2O), 3.98 (1H, s, H-8), 3.36 (3H, s, OCH_3), 1.16 (3H, s, CH_3-26 or 27), 1.11 (3H, s, CH_3-26 or 27), 0.98 (3H, d, J=6.59 Hz, CH_3-21), 0.92 (3H, s, CH_3-18), 0.88 (12H, s and t, $SiC(CH_3)_3$ and $(CH_2)_3C\underline{H}_3$), 0.00 (3H, s, $SiCH_3$), -0.01 (3H, s, $SiCH_3$).

^{13}C-NMR: 139.75 (C=), 128.14 (C=), 90.91 (OCH_2O), 78.31 (C-25), 69.51, 56.56, 55.08, 53.17, 42.03 (C-13), 40.67 (CH_2), 39.98, 34.45 (CH_2), 30.17 (CH_2), 28.26 (CH_2), 27.86 (CH_2), 25.76 ($SiC(\underline{C}H_3)_3$), 25.52, 23.12 (CH_2), 23.06, 22.65 (CH_2), 20.69, 17.98 ($Si\underline{C}(CH_3)_3$), 17.64 (CH_2), 14.07, 13.88, -4.87 ($SiCH_3$), -5.24 ($SiCH_3$).

(b). Preparation of compound 13.

Compound 9 is added to a solution of TBAF in THF (1.1 M, 6 ml, 6.6 mmol). The reaction mixture is stirred for 24 h at 70°C and 48 h at room temperature. The reaction mixture is then poured into a saturated aqueous solution of $NaHCO_3$ (100 ml) and extracted with Et_2O (3x30 ml). The combined ether layers are dried, filtered and concentrated. The residue is chromatographed over silica gel (eluent: 9% EtOAc/hexane), yielding 471 mg of compound 13 [80%, Rf=0.4 (15% EtOAc/hexane)].

^{1}H-NMR: 5.18 (1H, dd, J=15.18 and 8.39 Hz, H-22 or H-23), 5.03 (1H, dd, J=15.18 and 9.10 Hz, H-23 or H-22), 4.67 (2H, s, OCH_2O), 4.04 (1H, s, H-8), 3.33 (3H, s, OCH_3), 1.14 (3H, s, CH_3-26 or 27), 1.09 (3H, s, CH_3-26 or 27), 0.97 (3H, d, J=6.61 Hz, CH_3-21), 0.92 (3H, s, CH_3-18), 0.84 (3H, t, J=6.92 Hz, $(CH_2)_3C\underline{H}_3$).

^{13}C-NMR: 139.46 (C=), 128.32 (C=), 90.87 (OCH_2O), 78.26 (C-25), 69.35, 56.38, 55.07, 53.12, 52.69, 41.71 (C-13), 40.30 (CH_2), 39.92, 33.57 (CH_2), 30.15 (CH_2), 28.19 (CH_2), 27.70 (CH_2), 25.49, 23.06, 22.61 (CH_2),

22.53 (CH_2), 20.61, 17.38 (CH_2), 14.05, 13.64.

(c). Preparation of compound 17.

To a solution of 196 mg (0.517 mmol) of compound **13** in 6 ml DCM are added 0.58 g (1.55 mmol) PDC and approx. 5-10 mg PPTS. After stirring at room temp. for 3.5 h, 20 ml Et_2O is added. Separation of the organic phase, filtration over silica gel and evaporation yields 0.18 g of a residue, which after flash chromatography (silica gel; eluent: EtOAc/hexane 1:20) gives the desired product **17** in a yield of 175.5 mg (90%).

(d). Preparation of protected vitamin D compound 21.

To a solution of the phosphine-oxide **45** (370 mg, 0.63 mmol) in 5 ml dry THF at -78°C is added a small amount of n-BuLi in THF (2.5 M, approx. 230 μl) until the reaction mixture colours red. Thereupon n-BuLi in THF (2.5 M, 254 μl, 0.63 mmol) is added dropwise. After stirring for 5 min, a solution of 80.1 mg (0.21 mmol) of compound **17** in 2 ml dry THF is added. The mixture is stirred for 0.5 h and allowed to reach room temperature. Purification by flash- chromatography yields 53.4 mg (34%) of the desired title compound **21**.

(e). Preparation of vitamin D compound 25.

Compound **21** is dissolved in a 0.83 M solution of TBAF (2.3 ml, 1.88 mmol, 20 eq.) in THF. The mixture is stirred overnight at ambient temperature. The solvent is evaporated and the residue is taken up with Et_2O and washed with brine. The organic phase is dried over $MgSO_4$ and the solvent evaporated. The residue is quickly chromatographed over silica (Et_2O) and the resulting product is dissolved in methanol (7 ml) and 1.15 g of Dowex^R resin (acidic resin) AG 50W-X4 (washed with MeOH (4x10 ml)) is added. After stirring overnight, filtration and washing with EtOAc (3x20 ml), the reaction mixture is evaporated. The desired vitamin D compound **25** is obtained in a yield of 20 mg as a white solid.

Example III

Preparation of compound 26 from compound 8.

The reaction equations are presented in the Reaction Scheme B appended.

Via a reaction sequence analogous to that described in Example II, Vitamin D compound **26** is prepared from compound **8**, via the intermediate compounds **10**, **14**, **18** and **22**.

Compound **10** is identified by ^{1}H-NMR and ^{13}C-NMR:
^{1}H-NMR: 5.25 (1H, dd, J=15.2 and 8.1 Hz, H-22 or H-23), 5.14 (1H, dd, J=15.2 and 7.9 Hz, H-23 or H-22), 4.73 (2H, s, OCH_2O), 3.99 (1H, s, H-8), 3.37 (3H, s, OCH_3), 1.25 (3H, s, CH_3-26 or 27), 1.24 (3H, s, CH_3-26 or 27), 0.98 (3H, d, J=6.58 Hz, CH_3-21), 0.92 (3H, s, CH_3-18), 0.88 (9H, s, $SiC(CH_3)_3$), 0.92-(-0.04) (5H, 5m, c-Pr), 0.00 (3H, s, $SiCH_3$), -0.01 (3H, s, $SiCH_3$).
^{13}C-NMR: 138.95 (C=), 126.64 (C=), 90.93 (OCH_2O), 78.86 (C-25), 69.94, 56.75, 56.48, 54.93, 53.19, 41.99 (C-13), 40.68 (CH_2), 40.00, 34.44 (CH_2), 27.85 (CH_2), 25.76 ($SiC(\underline{C}H_3)_3$), 24.88 (C-26 or C-27), 24.73 (C-26 or C-27), 23.14 (CH_2), 20.69, 17.94 ($Si\underline{C}CH_3)_3$), 17.64 (CH_2), 13.90, 11.14, 5.49 (CH_2(c-Pr)), 2.41 (CH_2(c-Pr)), -4.89 ($SiCH_3$), -5.26 ($SiCH_3$).

Compound **14** is identified by ^{1}H-NMR and ^{13}C-NMR:
^{1}H-NMR: 5.27 (1H, dd, J=15.22 and 8.42 Hz, H-22 or H-23), 5.14 (1H, dd, J=15.22 and 8.18 Hz, H-23 or H-22), 4.72 (2H, s, OCH_2O), 4.06 (1H, s, H-8), 3.36 (3H, s, OCH_3), 1.24 (6H, s, CH_3-26 and 27), 0.98 (3H, d, J=6.60 Hz, CH_3-21), 0.93 (3H, s, CH_3-18), 0.92-(-0.06) (5H, 5m, c-Pr).
^{13}C-NMR: 138.61 (C=), 126.79 (C=), 90.84 (OCH_2O), 74.84 (C-25), 69.20, 56.68, 56.26, 54.92, 52.67, 41.65 (C-13), 40.26 (CH_2), 39.87, 33.52 (CH_2), 27.58 (CH_2), 24.79 and 24.71 (C-26 and C-27), 22.50 (CH_2), 20.59, 17.34 (CH_2), 13.59, 11.09, 5.52 and 2.39 (CH_2CH_2(c-Pr)).

Compound **26** is identified by ^{1}H-NMR and ^{13}C-NMR:
^{1}H-NMR (δ, CD_2Cl_2): 6.23 (1H, d, J=11.2 Hz), 6.00 (1H, d, J=11.2 Hz), 5.30-5.27 (2H, m), 5.26 (1H, s), 4.94 (1H, s), 4.36 (1H, dd, J=4.4 and 6.5 Hz), 4.15 (1H, m), 2.82 (1H, d, J=12.5 Hz), 2.53 (1H, dd, J=2.66 and 13.3 Hz), 2.25 (1H, dd, J=6.5 and 13.3 Hz), 1.19 (3H, s), 1.16 (3H, s), 1.02 (3H, d, J=6.6 Hz), 0.73 (1H, m), 0.55 (3H, s), 0.53 (1H, m), 0.36 (1H, m), 0.22 (1H, m), 0.02 (1H, m).
^{13}C-NMR (δ, CD_2Cl_2): 148.41, 143.12, 140.28, 133.90, 127.22, 124.83, 117.49, 111.74, 73.29, 71.04, 67.06, 58.89, 56.72, 56.48, 46.11, 45.66, 43.28, 40.94, 40.72, 29.34, 28.24, 27.84, 27.41, 23.93, 22.63, 21.23,

12.33, 11.67, 6.11, 2.54.

Example IV

Preparation of compound **27a** from compound **8**.

The reaction equations are presented in the Reaction Scheme B appended. Vitamin D compound **27a** is prepared from compound **8**, via the intermediate compounds **11**, **15**, **19**, **23** and **27**, analogous to the reaction sequence described in Example II for the first 5 steps. During the fifth step (deprotection step) ring closure takes place between the deprotected aldehyde group of the 24-substituent and the free 25-OH group, forming compound **27**. Compound **27** can easily be converted to the corresponding alcohol **27a** by ring-opening and reduction of the aldehyde group.

Compound **11** is identified by ^{1}H-NMR and ^{13}C-NMR:

^{1}H-NMR: 5.22 (1H, dd, J=15.2 and 8.5 Hz, H-22 or H-23), 5.04 (1H, dd, J=15.2 and 9.2 Hz, H-23 or H-22), 4.83 (1H, t, J=4.5 Hz, OCHRO), 4.72 (2H, AB, J=7.4 Hz, OCH_2O), 3.96 (1H, s, H-8), 3.96-3.78 (4H, m, OCH_2CH_2O), 3.34 (3H, s, OCH_3), 1.16 (3H, s, CH_3-26 or 27), 1.11 (3H, s, CH_3-26 or 27), 0.96 (3H, d, J=6.57 Hz, CH_3-21), 0.90 (3H, s, CH_3-18), 0.87 (9H, s, $SiC(CH_3)_3$), -0.01 (3H, s, $SiCH_3$), -0.03 (3H, s, $SiCH_3$).

^{13}C-NMR: 140.33 (C=), 127.58 (C=), 104.91 (OCHRO), 90.89 (OCH_2O), 78.10 (C-25), 69.45, 64.78 ($O\underline{C}H_2CH_2O$), 64.73 ($OCH_2\underline{C}H_2O$), 56.41, 55.09, 53.25, 53.10, 41.99 (C-13), 40.62 (CH_2), 39.94, 34.39 (CH_2), 32.46 (CH_2), 27.93 (CH_2), 25.73 ($SiC(\underline{C}H_3)_3$), 25.47, 23.14 (CH_2), 23.03 (CH_2), 22.94, 20.56, 17.93 ($Si\underline{C}(CH_3)_3$), 17.60, (CH_2), 13.83, -4.91 ($SiCH_3$), -5.28 ($SiCH_3$).

Compound **27** is identified by ^{1}H-NMR and ^{13}C-NMR:

^{1}H-NMR (δ, CD_2Cl_2): 6.33 (1H, d, J=11.2 Hz), 5.99 (1H, d, J=11.2 Hz), 5.30-5.26 (1H, m), 5.27 (1H, s), 5.12 (1H, dd, J=15.3 Hz and 8.4 hz), 4.93 (1H, s), 4.60 (0.375 H, d, J=1.4 hz), 4.44 (0.625 H, dd, J=9.5 and 2.4 Hz), 4.35 (1H, m), 4.14 (1H, m), 3.34 (1.875 H, s), 3.32 (1.125 H, s), 2.82 (1H, d, J=12.4 Hz), 2.52 (1H, dd, J=13.4 and 3.5 Hz), 2.25 (1H, dd, J=13.4 and 6.6 hz), 1.17 (3H, s), 1.12 (1.125 H, s), 1.08 (1.875 H, s), 0.99 (3H, d, J=6.6 Hz), 0.53 (3H, s).

^{13}C-NMR (δ, CD_2Cl_2): 148.45, 143.01, 142.98, 138.77, 138.19, 134.02, 133.99, 129.05, 128.46, 124.76, 117.53, 111.70, 99.08, 98.41, 76.26, 75.47, 70.95, 67.03, 56.70, 56.65, 55.59, 55.14, 49.12, 48.68, 46.13,

45.63, 43.32, 40.77, 40.72, 40.69, 31.53, 30.40, 29.74, 29.70, 29.35, 28.05, 25.91, 23.92, 23.35, 22.58, 22.11, 20.99, 19.66, 12.34.

Example V

Preparation of compound **28** from compound **8**.

The reaction equations are presented in the Reaction Scheme B appended. Via a reaction sequence analogous to that described in Example II, Vitamin D compound **28** is prepared from compound **8**, via the intermediate compounds **12**, **16**, **20** and **24**.

Compound **12** is identified by ^{1}H-NMR and ^{13}C-NMR:

^{1}H-NMR: 5.23 (1H, dd, J=15.2 and 9.36 Hz, H-22 or H-23), 5.13 (1H, dd, J=15.2 and 8.3 Hz, H-22 or H-23), 4.68 (2H, s, OCH_2O), 3.99 (1H, s, H-8), 3.35 (3H, s, OCH_3), 1.17 (6H, s, CH_3-26 and 27), 0.99 (3H, d, J=6.55 Hz, CH_3-21), 0.93 (3H, s, CH_3-18), 0.88 (9H, s, $SiC(CH_3)_3$), 0.87 and 0.84 (6H, 2d, J=3.5 and 3.4 Hz, $CH(C\underline{H}_3)_2$), 0.00 (3H, s, $SiCH_3$), -0.01 (3H, s, $SiCH_3$).

^{13}C-NMR: 140.65 (C=), 124.53 (C=), 90.84 (OCH_2O), 78.69 (C-25), 69.49, 58.64, 56.48, 55.05, 53,20, 42.00 (C-13), 40.69 (CH_2), 40.35, 34.45 (CH_2), 28.38 (CH_2), 26.75, 26.15, 25,77 ($SiC(\underline{C}H_3)_3$), 24.48, 24.09, 23.19 (CH_2), 20.71, 18.96, 17.96 ($Si\underline{C}(CH_3)_3$), 17.64 (CH_2), 13.88, -4.89 ($SiCH_3$), -5.25 ($SiCH_3$).

Compound **28** is identified by ^{1}H-NMR and ^{13}C-NMR:

^{1}H-NMR (δ, CD_2Cl_2): 6.34 (1H, d, J=11.2 Hz), 6.00 (1H, d, J=11.2 Hz), 5.30-5.27 (2H, m), 5.26 (1H, s), 4.94 (1H, dd, J=1.2 and 1.8 hz), 4.36 (1H, m), 4.14 (1H, m), 2.82 (1H, d, J=12.3 Hz), 2.54 (1H, dd, J=3.5 and 13.4 Hz), 2.25 (1H, dd, J=6.6 and 13.4 Hz), 1.14 (3H, s), 1.04 (3H, d, J=6.6 Hz), 0.86 (6H, d, J=6.9 Hz), 0.56 (3H, s).

^{13}C-NMR (δ, CD_2Cl_2): 148.43, 1543.13, 142.30, 133.86, 124.85, 124.68, 117.48, 111.69, 72.95, 71.06, 67.08, 60.30, 56.74, 56.54, 46.13, 45.69, 43.32, 41.27, 40.74, 29.34, 28.75, 28.57, 28.38, 27.70, 24.39, 23.93, 22.67, 21.26, 19.00, 12.27.

Example VI

Preparation of compound **30** from compound **17**.

The reaction equations are presented in the Reaction Scheme B appended.

(a). The preparation of protected 19-nor-vitamin D compound 29.

To a solution of the phosphine-oxide **46** (360 mg, 0.63 mmol) in 5 ml dry THF at -78°C is added a small amount of n-BuLi in THF (2.5 M, approx. 230 μl) until the reaction mixture colours red. Thereupon n-BuLi in THF (2.5 M, 254 μl, 0.63 mmol) is added dropwise. After stirring for 5 min, a solution of 80.1 mg (0.21 mmol) of compound **17** in 2 ml dry THF is added. The mixture is stirred for 0.5 h and allowed to reach room temp. Purification by chromatography yields 106.7 mg (69%) of the desired title compound **29**.

(b). The preparation of 19-nor-vitamin D compound 30.

Compound **29** (103 mg, 0.139 mmol) is dissolved in a 0.83 M solution of TBAF (3.4 ml, 2.78 mmol, 20 eq.) in THF. The mixture is stirred overnight at ambient temperature. The solvent is evaporated and the residue is taken up with Et_2O and washed with brine. The organic phase is dried over $MgSO_4$ and the solvent evaporated. The residue is quickly chromatographed over silica (Et_2O) and the resulting product is dissolved in methanol (10 ml) and 1.75 g of Dowex^R resin (acidic resin) AG 50W-X4 (washed with MeOH (4x12 ml)) is added. After stirring overnight, filtration and washing with EtOAc (3x20 ml), the reaction mixture is evaporated. The desired 19-nor-vitamin D compound **30** is obtained in a yield of 30 mg as a white solid. The product is identified by ^{1}H-NMR and ^{13}C-NMR.

^{1}H-NMR (δ, $CDCl_3$): 0.36 (3H, s, 18-CH_3), 0.87 (3H, t, CH_3), 1.05 (3H, d, 21-CH_3), 1.12 (3H, s, 26-CH_3), 1.17 (3H, s, 27-CH_3), 2.48 (1H, dd), 2.71 (1H, dd,), 2.80 (1H, bd), 4.00-4.16 (2H, m), 5.10 (1H, dd, 22-H), 5.37 (dd, 23-H), 5.85 (1H, d, H-6), 6.31 (1H, d, H-7).

^{13}C-NMR: 12.32, 14.10, 21.20, 22.35, 22.55, 23.47, 26.80, 26.99, 28.07, 28.91, 29.19, 30.40, 37.20, 40.36, 40.67, 42.21, 44.71, 45.70, 54.85, 56.19, 56.35, 67.22, 67.43, 72.14, 115.37, 123.80, 128.00, 131,26, 141.49, 142.87.

Example VII

Preparation of compound 30 and 31 from compound 8.

The reaction equations are presented in the Reaction Scheme C appended.

A solution of phenylmagnesiumchloride in THF (2M, 15 ml, 30 mmol) is

added to a solution of CuCN (2.69 g, 30 mmol) and LiCl (2.54 g, 40 mmol) in 40 ml THF while stirring and cooling at -78°C. The reaction mixture is stirred for 5 min and a solution of phosphate **8** (897 mg, 1.518 mmol, dried over P_2O_5) in 15 ml THF is added. The reaction is stirred for 2 days under exclusion of light. To the reaction mixture is added a saturated solution of NH_4Cl (100 ml). After stirring for 10 min, the mixture is extracted at room temp with Et_2O (3x60 ml). The combined organic layers are dried, filtered and concentrated. The residue is separated by chromatograpy over silica gel (eluent: 0-1.5% EtOAc/hexane), yielding 173 mg of compound **30** [22%, Rf=0.52 (5% EtOAc/hexane), liquid], and 591 mg of compound **31** [76%, Rf=0.46 (5%EtOAc/hexane), m.p. 71-72°C]. The compounds **30** and **31** are identified by ^{1}H-NMR and ^{13}C-NMR.

Compound **30**: ^{1}H-NMR (δ): 7.26-7.17 (5H, m, Ar), 5.83 (1H, dd, J=15.3 and 8.8 Hz, H-23), 5.28 (1H, dd, J=15.3 and 8.4 Hz, H-22), 4.69 (2H, AB, J=7.4 Hz, OCH_2O), 3.96 (1H, s, H-8), 3.30 (3H, s, OCH_3), 3.20 (1H, d, J=8.8 Hz, H-24), 1.21 (3H, s, CH_3-26 or 27), 1.15 (3H, s, CH_3-26 or 27), 1.00 (3H, d, J=6.59 Hz, CH_3-21), 0.91 (3H, s, CH_3-18), 0.88 (9H, s, $SiC(CH_3)_3$), 0.00 (3H, s, $SiCH_3$), -0.02 (3H, s, $SiCH_3$).
^{13}C-NMR (δ): 142.65 (C), 139.25 (C=), 129.70 (C=), 127.60 (C=), 127.19 (C=), 125.95 (C=), 91.01 (OCH_2O), 78.08 (C-25), 69.44, 59.89, 56.66, 54.95, 53.04, 42.03 (C-13), 40.62 (CH_2), 39.77, 34.40 (CH_2), 27.58 (CH_2), 25.75 ($SiC(\underline{C}H_3)_3$), 25.02, 24,98, 23.01 (CH_2), 20.26, 17.93 ($Si\underline{C}(CH_3)_3$), 17.61 (CH_2), 13.83, -4.90 ($SiCH_3$), -5.27 ($SiCH_3$).

Compound **31**: ^{1}H-NMR (δ): 7.31-7.15 (5H, m, Ar), 5.92 (1H, dd, J=15.7 and 10.1 Hz, H-23), 5.60 (1H, d, J=15.7 Hz, H-24), 4.67 (2H, s, OCH_2O), 4.00 (1H, s, H-8), 3.51 (1H, d, J=10.1 Hz, H-22), 3.36 (3H, s, OCH_3), 1.39 (3H, s, CH_3-26 or 27), 1.37 (3H, s, CH_3-26 or 27), 0,94 (3H, s, CH_3-18), 0.89 (9H, s $SiC(CH_3)_3$), 0,76 (3H, d, J=6.76 Hz, CH_3-21), 0.01 (6H, s, $Si(CH_3)_2$).
^{13}C-NMR (δ): 145.22 (C), 138.09 (C=), 128.08 (C=), 127.92 (C=), 127.43 (C=), 125.64 (C=), 91.92 (OCH_2O), 76.24 (C-25), 69.44, 54.97, 53.10, 50.01, 48.54, 42.03, 40.71 (CH_2), 34.31 (CH_2), 27.91, 27.26 (CH_2), 27.22, 25.76 ($SiC(\underline{C}H_3)_3$), 23.04 (CH_2), 17.96 ($Si\underline{C}(CH_3)_3$), 17.55 (CH_2), 13.72, 13.29, -4.87 ($SiCH_3$), -5.25 ($SiCH_3$).

Example VIII

Preparation of compound 36 from compound 30.

The reaction equations are presented in the Reaction Scheme C appended.

Via a reaction sequence analogous to that described in Example II, Vitamin D compound **36** is prepared from compound **30**, via the intermediate compounds **33**, **34** and **35**.

Compound **36** is identified by ^{1}H-NMR and ^{13}C-NMR:

^{1}H-NMR (δ, CD_2Cl_2): 7.29-7.18 (5H, m), 6.33 (1H, d, J=11.2 Hz), 5.98 (1H, d, J=11.2 Hz), 5.82 (1H, dd, J=15.2 and 9.4 hz), 5.42 (1H, dd, J=15.2 and 8.5 Hz), 5.26 (1H, s), 4.92 (1H, dd, J=2.0 and 1.2 Hz), 4.34 (1H, m), 4.14 (1H, m), 3.18 (1H, d, J=9.5 Hz), 1.13 (3H, s), 1.10 (3H, s), 1.06 (3H, d, J=6.6 Hz), 0.53 (3H, s).

^{13}C-NMR (δ, CD_2Cl_2): 148.41, 142.99, 142.44, 140.46, 133.96, 129.58, 128.32, 127.19, 126.62, 124.78, 117.52, 111.784, 72.69, 71.00, 67.03, 60.72, 56.62, 46.17, 45.65, 43.29, 40.70, 40.66, 31.93, 29.33, 28.13, 27.99, 27.80, 23.91, 23.00, 22.56, 20.86, 14.23, 12.29.

Example IX

Preparation of compound 43 from compound 31.

The reaction equations are presented in the Reaction Scheme C appended.

Via a reaction sequence analogous to that described in Example II, Vitamin D compound **43** is prepared from compound **31**, via the intermediate compounds **37**, **39** and **41**.

Compound **43** is identified by ^{1}H-NMR and ^{13}C-NMR:

^{1}H-NMR (δ, CD_2Cl_2): 7.27-7.14 (5H, m), 6.35 (1H, d, J=11.2 Hz), 6.03 (1H, d, J=11.2 Hz), 5.89 (1H, dd, J=15.8 and 10.3 Hz), 5.55 (1H, d, J=15.8 Hz), 5.29 (1H, d, J=1.4 Hz), 4.96 (1H, s), 4.36 (1H, m), 4.15 (1H, m), 3.5 (1H, d, J=10.3 Hz), 2.80 (1H, d, J=12 Hz), 2.52 (1H, d, J=13 Hz), 2.25 (1H, dd, J=13 and 6.5 hz), 1.29 (3H, s), 1.27 (3H, s), 0.80 (3H, d, J=6.8 Hz), 0.57 (3H, s).

^{13}C-NMR (δ, CD_2Cl_2): 148.43, 145.66, 142.99, 138.69, 133.96, 128.33, 128.27, 127.51, 125.92, 124.84, 117.61, 111.76, 75.20, 71.08, 67.08, 56.74, 55.13, 50.67, 50.50, 46.14, 45.68, 43.34, 43.20, 40.90, 29.32,

27.97, 26.78, 25.77, 23.89, 22.64, 13.69, 12.11.

Example X

Preparation of compound 44 from compound 8.

The reaction equations are presented in the Reaction Scheme C appended.

(a). Preparation of compound 32.

A solution of vinylmagnesiumchloride in THF (15%, 5.08 ml, 8.6 mmol) is added to a solution of CuCN (770 mg, 8.6 mmol) and LiCl (729 mg, 17.2 mmol) in 20 ml THF while stirring and cooling at -78°C. The reaction mixture is stirred for 5 min and a solution of phosphate **8** (497 mg, 0.841 mmol, dried over P_2O_5) in 20 ml THF is added. The reaction is stirred for 3 days under exclusion of light. To the reaction mixture is added a satd. solution of NH_4Cl (25 ml). After stirring for 5 min, the mixture is extracted at room temp with Et_2O (3x20 ml). The combined organic layers are dried, filtered and concentrated. The residue is chromatographed over silica gel (eluent: 2-30% EtOAc/hexane), yielding 225 mg of compound **32** [58%, Rf=0.8 (10% EtOAc/hexane), crystallizing upon cooling, m.p. 30°C], whereas 61 mg of starting compound **8** is recovered. Compound **32** is identified by ^{1}H-NMR and ^{13}C-NMR.

^{1}H-NMR (δ): 5.83 (1H, ddd, J=17.3, 10.4 and 5.3 Hz, C$\underline{H}$=CH_2), 5.57-5.44 (2H, m, H-23 and H-24), 5.01 (1H, dt, J_{cis}=10.4 Hz, J_{gem}=1.8 Hz, C=CH$\underline{H}$), 4.91 (1H, dt, J_{trans}=17.3 Hz, J_{gem}=1.8 Hz, C=CH$\underline{H}$), 4.65 (2H, s, OCH_2O), 3.98 (1H, s, H-8), 3.35 (3H, s, OCH_3), 2.86 (1H, s, H-22), 1.34 (6H, s, CH_3-26 and 27), 0.92 (3H, s, CH_3-18), 0.88 (H, s, $SiC(CH_3)_3$), 0.84 (3H, d, J=6.81 Hz, CH_3-21), 0.00 (3H, s, $SiCH_3$), -0.01 (3H, s, $SiCH_3$).

^{13}C-NMR (δ): 142.31 (C=), 137.57 (C=), 127.93 (C=), 114.31 (=CH_2), 91.86 (OCH_2O), 76.20 (C-25), 69.43, 54.96, 54.73, 53.01, 48.54, 42.01 (C-13), 40.72 (CH_2), 40.35, 34.33 (CH_2), 27.82, 27.24, 26.90 (CH_2), 25.74 ($SiC(\underline{C}H_3)_3$), 23.00 (CH_2), 17.94 ($Si\underline{C}(CH_3)_3$), 17.56 (CH_2), 13.86, 13.69, -4.89 ($SiCH_3$), -5.27 ($SiCH_3$).

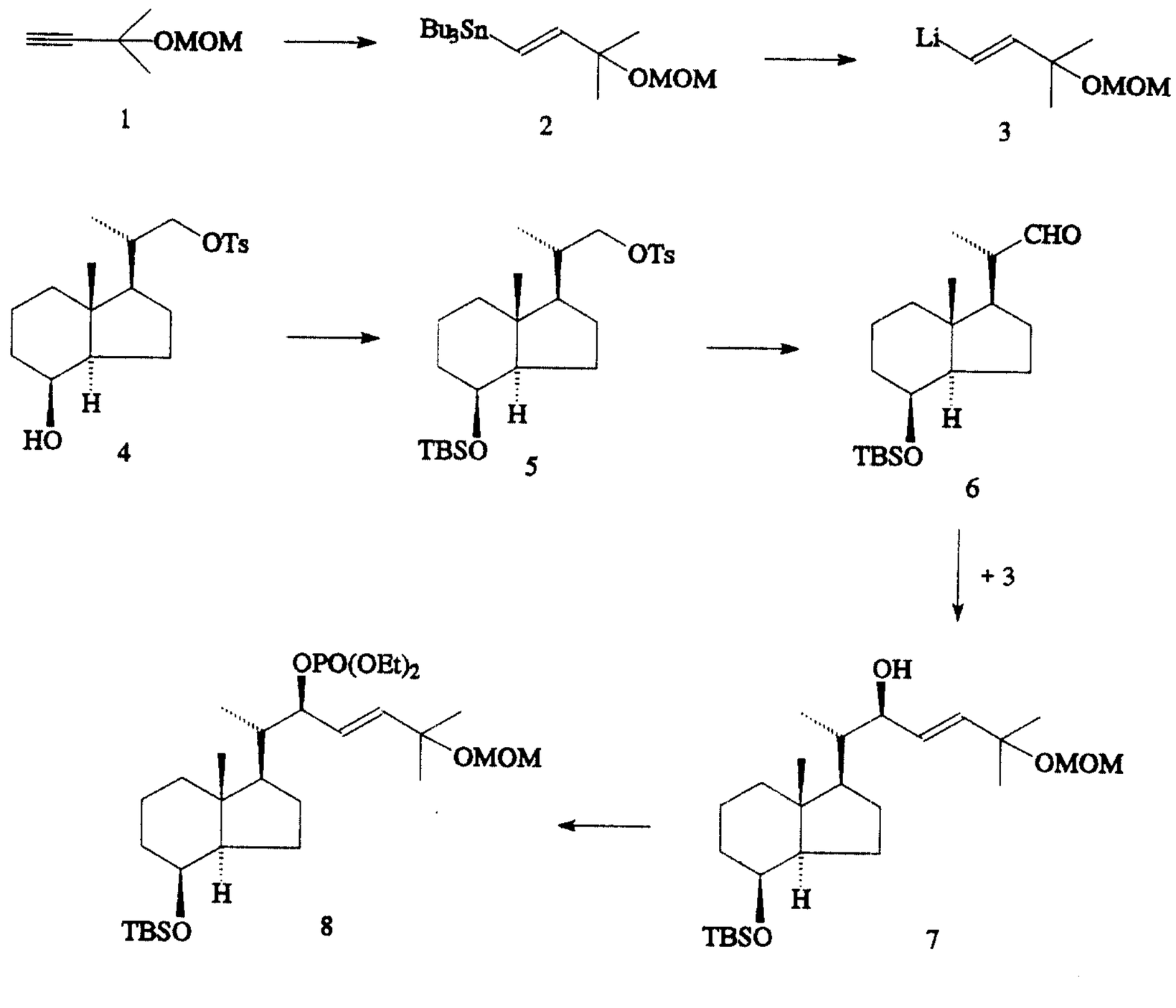
Via a reaction sequence analogous to that described in Example II, Vitamin D compound **44** is prepared from compound **32**, via the intermediate compounds **38**, **40** and **42**.

Compound **44** is identified by ^{1}H-NMR and ^{13}C-NMR:

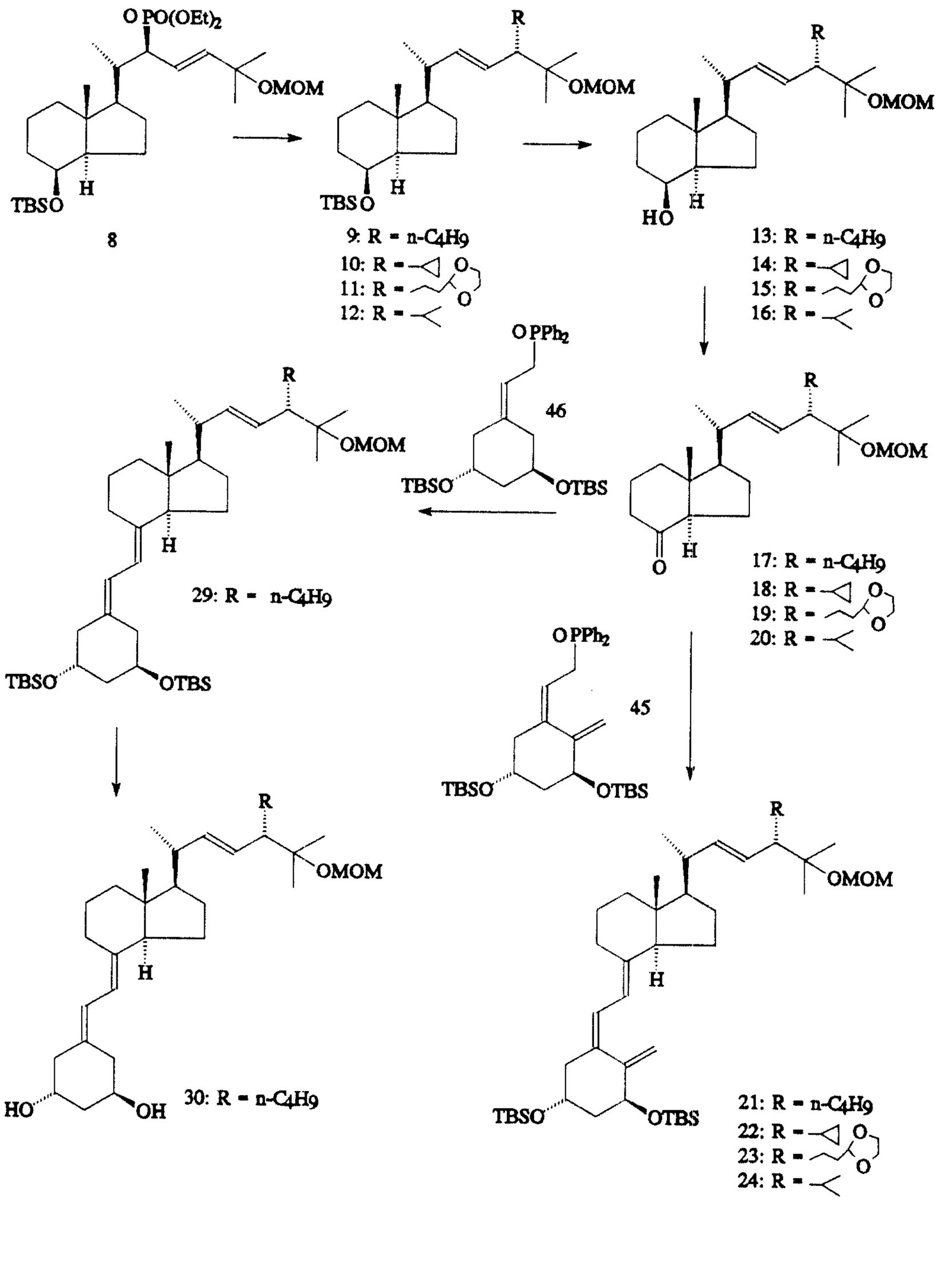
^{1}H-NMR (δ, CD_2Cl_2): 6.33 (1H, d, J=11.2 Hz), 6.00 (1H, d, J=11.2 Hz), 5.85 (1H, ddd, J=17.2, 10.4 and 5.7 Hz), 5.48 (1H, dd, J=15.9 and 8.4 Hz), 5.42 (1H, d, J=15.9 Hz), 5.28 (1H, t, J=1.6 Hz), 5.00 (1H, dt, J=10.4 and 1.8 Hz), 4.94 (1H, s), 4.93, (1H, dt, J=17.2 and 1.8 Hz), 4.35 (1H, m), 4.14 (1H, m), 2.85 (1H, m), 2.82 (1H, d, J=12 Hz), 2.53 (1H, dd, J=13 and 2.6 Hz), 2.25 (1H, dd, J=13.2 and 6.6 Hz), 1.24 (3H, s), 1.33 (3H, s), 0.87 (3H, d, J=6.8 Hz), 0.55 (3H, s).

^{13}C-NMR (δ, CD_2Cl_2): 148.41, 143.06, 142.83, 138.19, 133.90, 127.95, 124.85, 117.54, 114.32, 111.77, 75.16, 71.09, 67.07, 56.63, 54.88, 50.39, 49.19, 46.08, 45.69, 43.33, 41.54, 40.89, 29.33, 27.63, 26.64, 25.84, 23.91, 22.60, 14.26, 12.08.

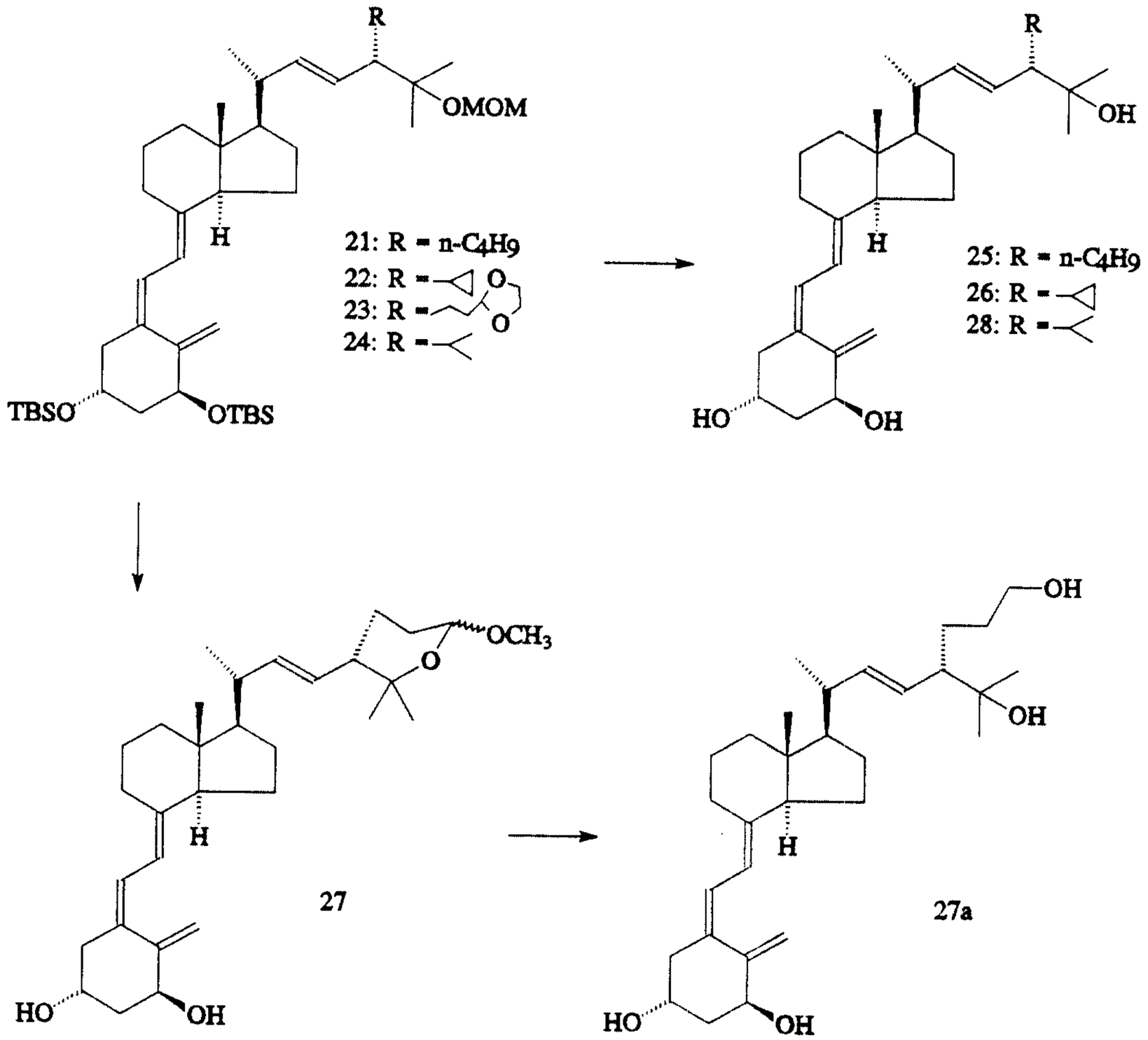
Reaction Scheme A



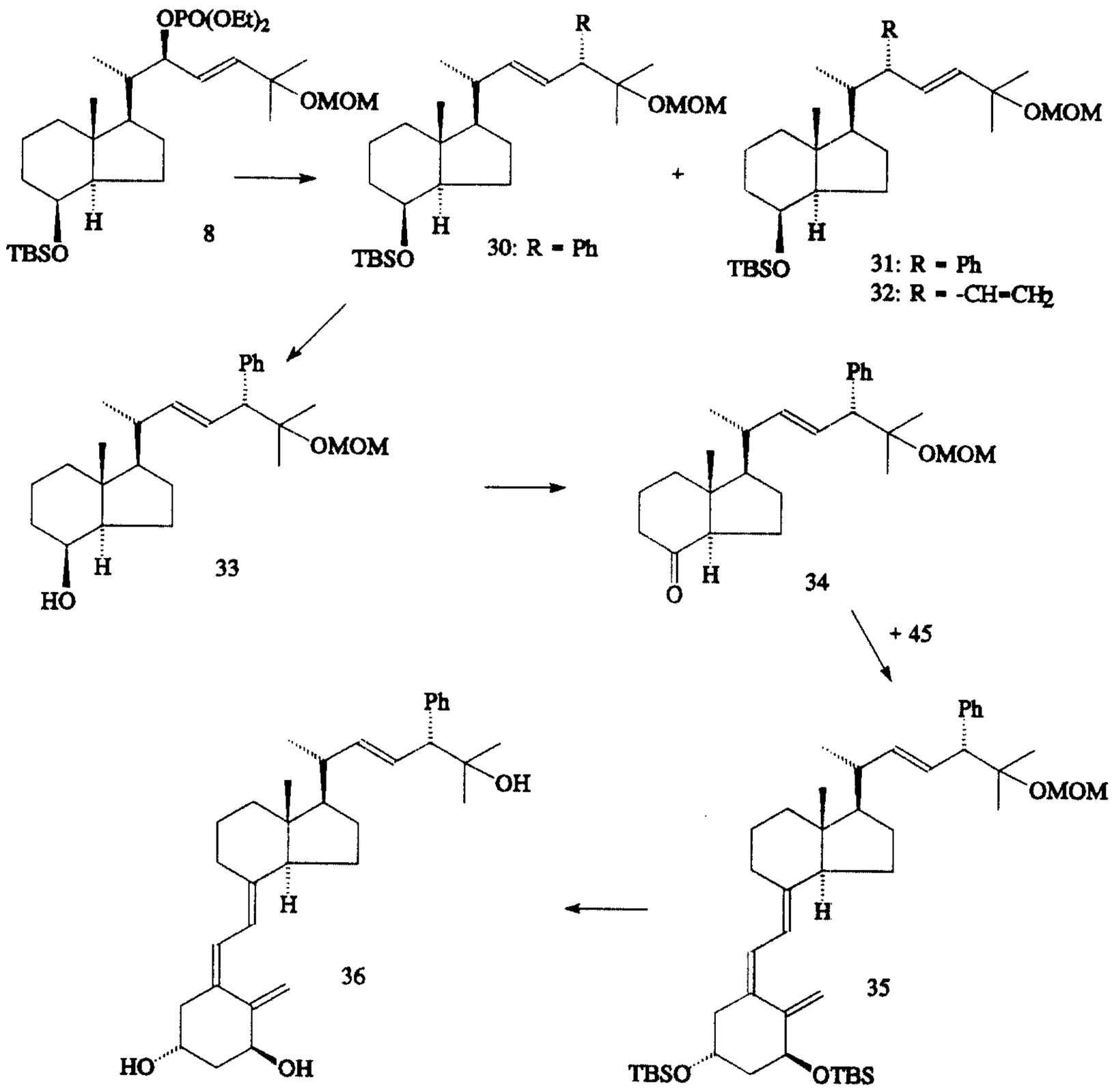
Reaction Scheme B1



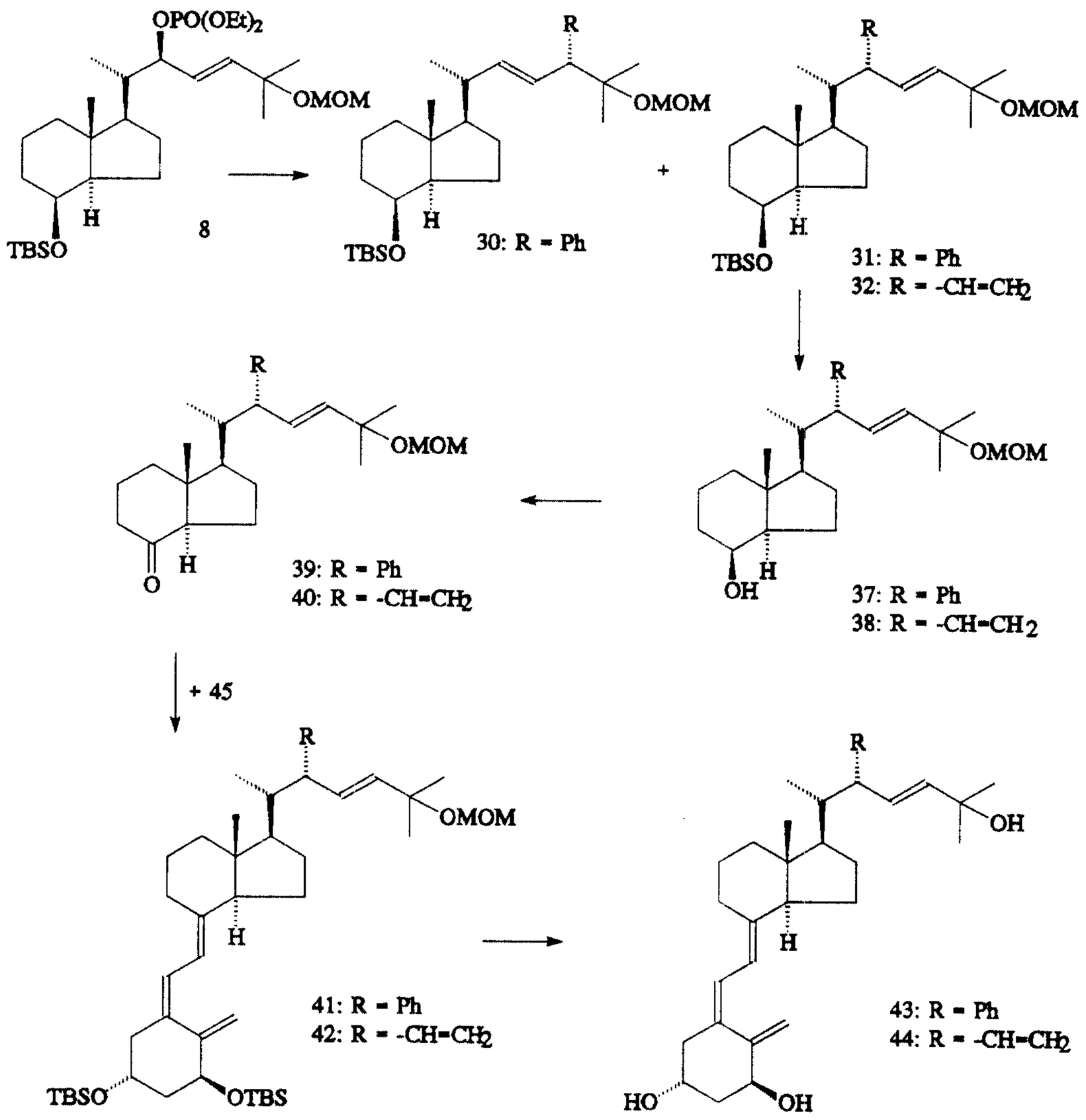
Reaction Scheme B2



Reaction Scheme C1



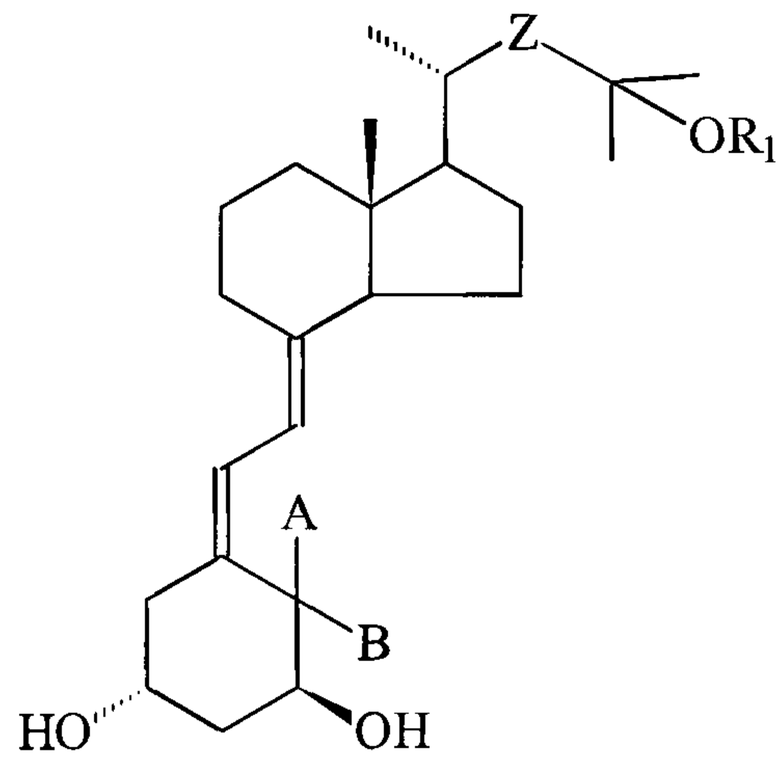
Reaction Scheme C2



27072-166

CLAIMS:

1. A vitamin D compound of the general formula (I):

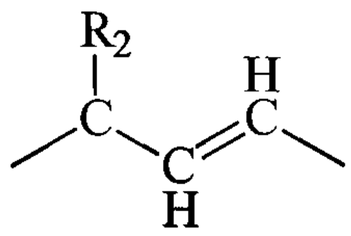


(I)

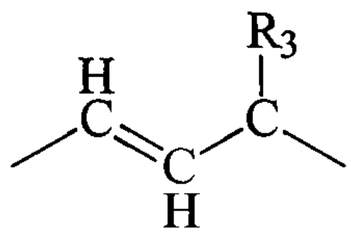
wherein:

R_1 is a hydrogen atom or a hydroxy protecting group;

Z is a group of the general formula:



(II) or



(III)

wherein R_2 and R_3:

(i) are each individually straight or branched (C_1-C_6)alkyl groups or (C_2-C_6)alkenyl groups, optionally substituted with: (a) one or more substituents selected from the group consisting of hydroxy, (C_1-C_4)alkoxy, fluoro, (C_3-C_6)cycloalkyl and (C_2-C_3)alkylenedioxy, or (b) phenyl optionally substituted with a substituent selected from the group consisting of (C_1-C_4)alkyl, (C_1-C_4)alkoxy, fluoro, trifluoromethyl and hydroxy; or

(ii) (C_3-C_6)cycloalkyl groups or phenyl groups optionally substituted with a substituent selected from the group consisting of (C_1-C_4)alkyl, (C_1-C_4)alkoxy, fluoro, trifluoromethyl and hydroxy; or

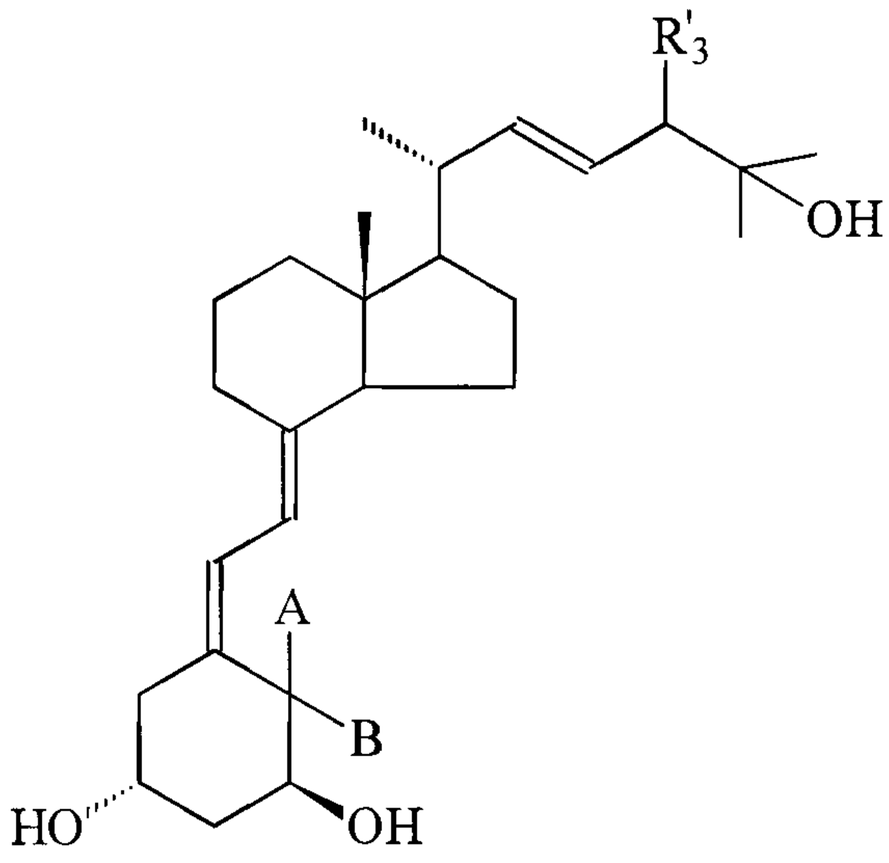
wherein R_1 and R_3 together with the interconnecting oxadimethylene biradical form a 5-7 membered ring-closed (C_1-C_4)alkyl substituted hemiacetal;

with the proviso that R_2 and R_3 are not methyl groups and R_3 is not hydroxymethyl; and

A and B are each individually hydrogen atoms or methyl groups; or

A and B form together a methylene group.

2. A vitamin D compound as claimed in claim 1, having the general formula (IV):



(IV)

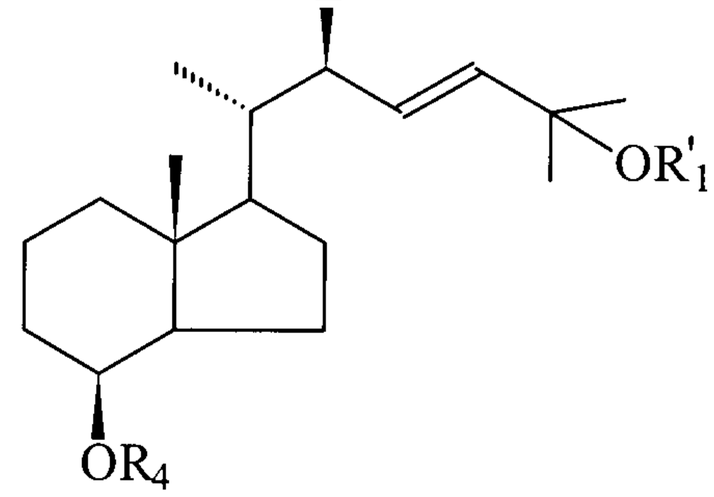
wherein:

A and B are as defined in claim 1; and

R'_3 is a straight or branched (C_2-C_6)alkyl group, a cyclopropyl group or a phenyl group, wherein the straight or branched (C_2-C_6)alkyl group is optionally substituted with hydroxy, (C_1-C_2)alkoxy or (C_2-C_3)alkylenedioxy.

3. A vitamin D compound as claimed in claim 2, wherein the C-24, to which substituent R'_3 is attached, has either the R or the S configuration.

4. A method of preparing a vitamin D compound as claimed in claim 1, comprising reacting a hydrindane compound of the general formula (V):



(V)

wherein:

L is a leaving group; and

R'_1 and R_4 are each individually hydroxy-protecting groups,

with a reagent of the general formula:

R_3-MgX or R_3-Li

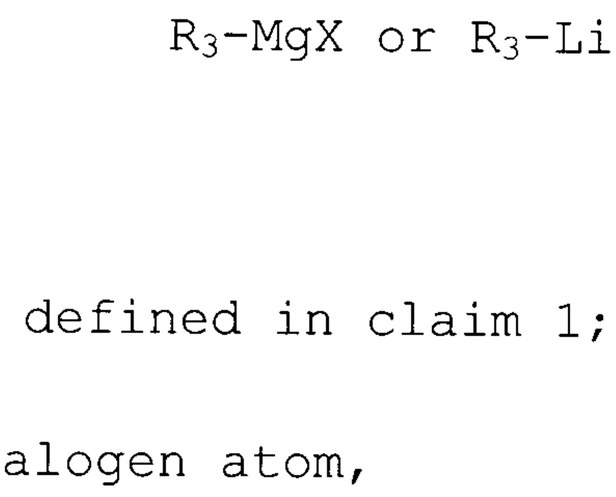
wherein:

R_3 is as defined in claim 1; and

X is a halogen atom,

in the presence of a Cu(I) compound;

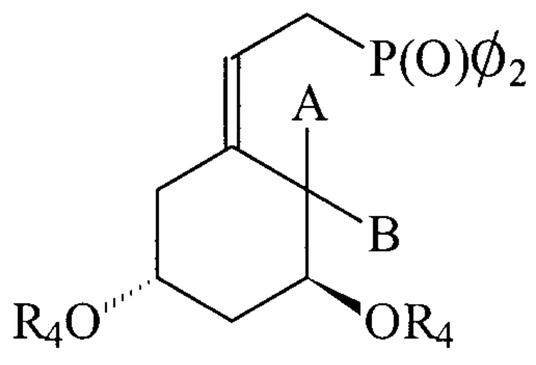
after which the hydrindane intermediate obtained, having the general formula (VI):



(VI)

wherein Z is as defined in claim 1, and R'_1 and R_4 are as defined above, is oxidized, after deprotection of OR_4, to the corresponding hydrindane-4-one compound, and is then converted, for related compounds,

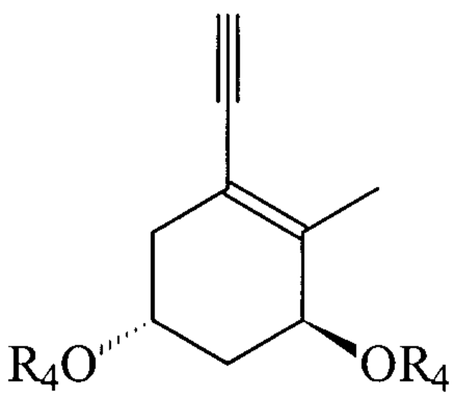
either (a) with a Wittig reagent of the general formula (VII):



(VII)

wherein R_4 is as defined above, and A and B are as defined in claim 1; or

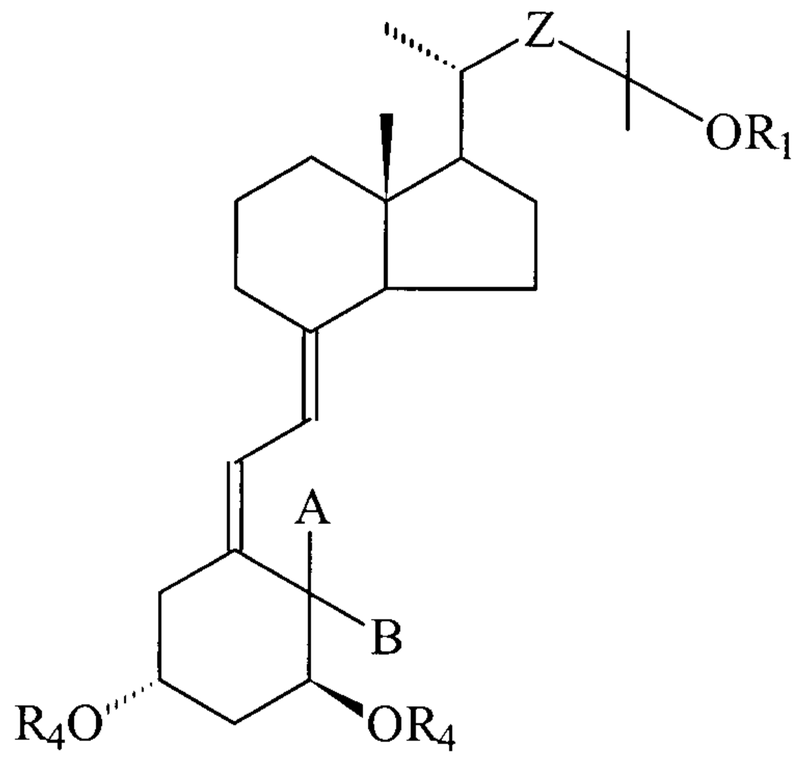
(b), after enolization, with an enyne compound of the general formula (VIII):



(VIII)

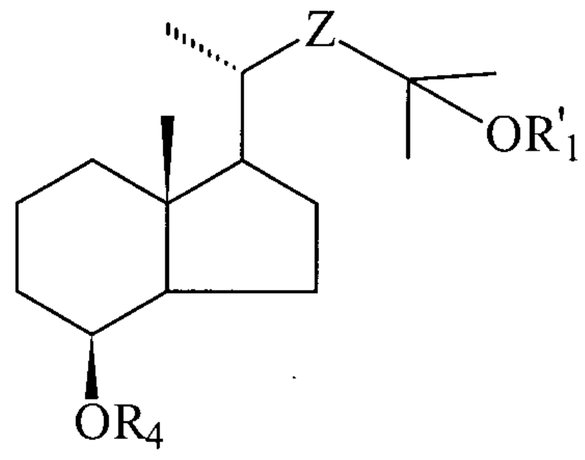
wherein R_4 is as defined above, followed by hydrogenation and isomerization, to produce a compound of the general formula I, wherein A and B form together a methylene group; followed by deprotection.

5. A method of preparing a vitamin D compound as claimed in claim 1, wherein a compound of the general formula:



wherein R_1, Z, A and B are as defined in claim 1, and R_4 is as defined in claim 4, is subjected to deprotection.

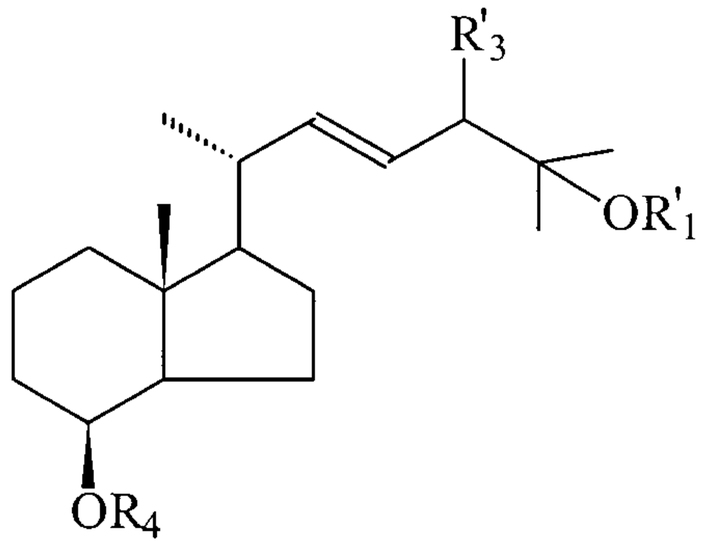
6. A hydrindane intermediate of the general formula (VI):



(VI)

wherein Z is as defined in claim 1, and R'_1 and R_4 are as defined in claim 4.

7. A hydrindane intermediate as claimed in claim 6, having the general formula (IX):

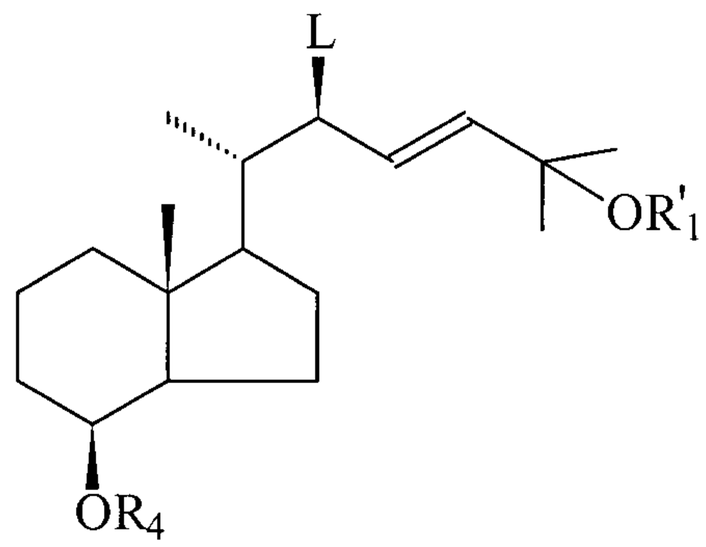


(IX)

wherein R'_3 is as defined in claim 2, and R'_1 and R_4 are as defined in claim 4.

8. A hydrindane intermediate as claimed in claim 7, wherein the C-atom, to which substituent R'_3 is attached, has either the R or the S configuration.

9. A method of preparing a hydrindane intermediate of the general formula (VI) as defined in claim 6, comprising reacting a hydrindane compound of the general formula (V):



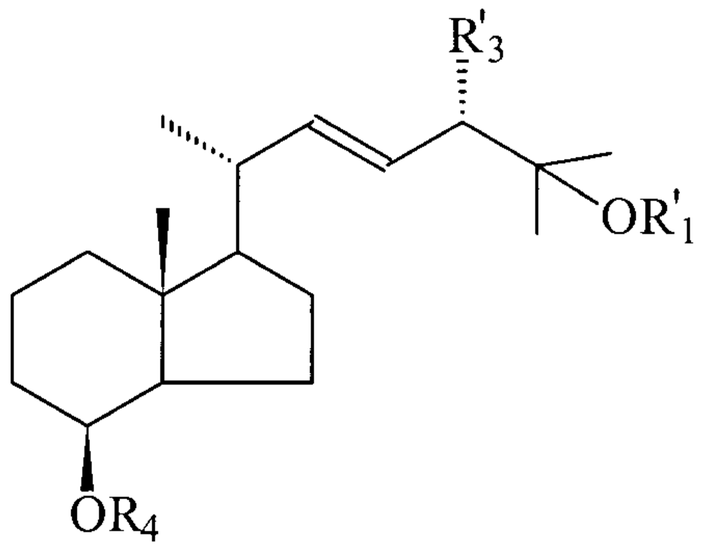
(V)

wherein L, R'_1 and R_4 are as defined in claim 4, with a reagent of the general formula:

$$R_3\text{-MgX or } R_3\text{-Li}$$

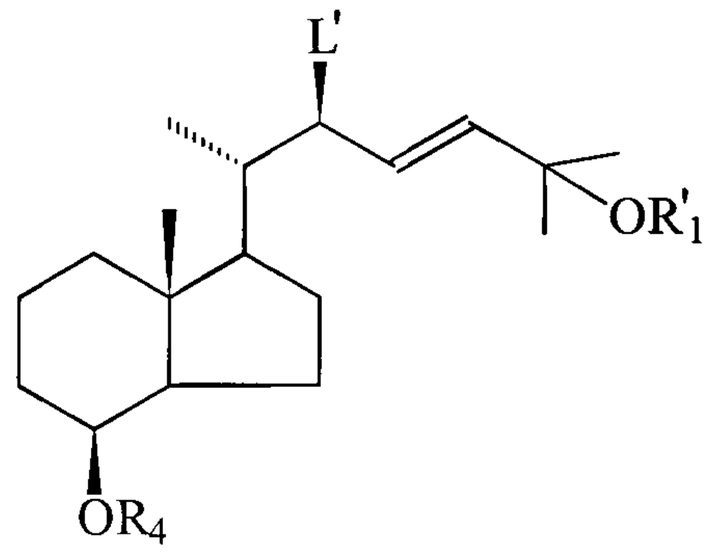
wherein R_3 is as defined in claim 1, and X is as defined in claim 4, in the presence of a Cu(I) compound.

10. A method as claimed in claim 9, wherein a compound of the general formula (IX) as defined in claim 7 is prepared, wherein the C-atom, to which substituent R'_3 is attached, has the configuration of formula (IXA):



(IXA)

wherein R'_1, R'_3 and R_4 are as defined in claim 7, by reacting a hydrindane compound of the general formula (X):



(X)

wherein R'_1 and R_4 are as defined in claim 4; and

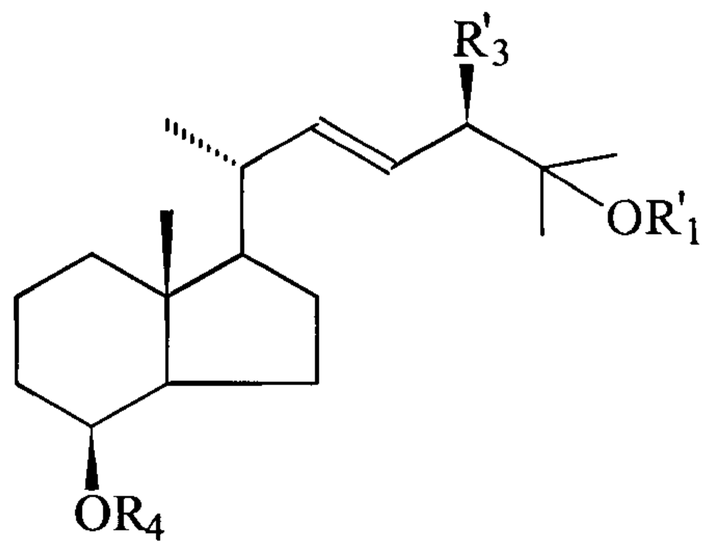
L' is a di(hydrocarbyl)phosphate leaving group,

with a reagent of the general formula:

R'_3-MgX or R'_3-Li

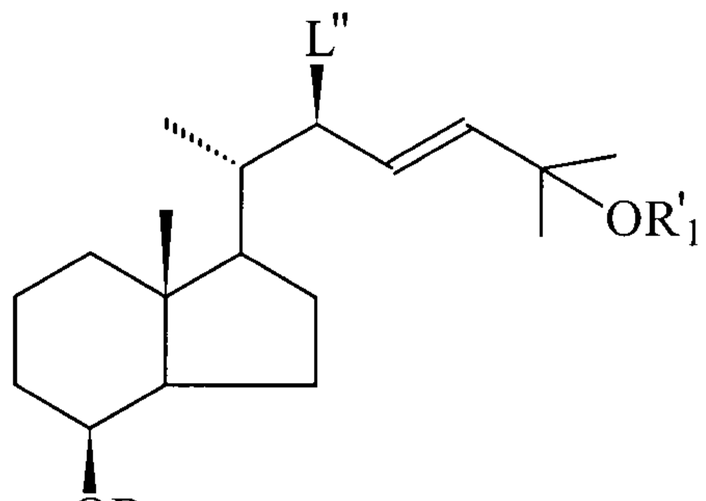
wherein R'_3 is as defined in claim 2, and X is a halogen atom, in the presence of a Cu(I) compound.

11. A method as claimed in claim 9, wherein a compound of the general formula (IX) as defined in claim 7 is prepared, wherein the C-atom, to which substituent R'_3 is attached, has the configuration of formula (IXB):



(IXB)

wherein R'_1, R'_3 and R_4 are as defined in claim 7, by reacting a hydrindane compound of the general formula (XI):



(XI)

wherein:

R'_1 and R_4 are as defined in claim 4; and

L" is a N-arylcarbamate leaving group,

with a reagent of the general formula:

R'_3-MgX or R'_3-Li

wherein R'_3 is as defined in claim 2, and X is a halogen atom, in the presence of a Cu(I) compound.

12. A pharmaceutical composition comprising, in addition to a pharmaceutically acceptable carrier, at least one pharmaceutically acceptable auxiliary substance or a mixture thereof, as the active ingredient at least one compound as defined in claim 1, 2 or 3.

13. Use of a compound as defined in claim 1, 2 or 3, or a composition as defined in claim 12, for preparing a medicament for the treatment or prevention of osteoporosis, renal osteodystrophy and osteomalacia, autoimmune diseases, acne, alopecia, skin aging, imbalance in the immune system, rheumatoid arthritis, asthma, diseases related to abnormal cell differentiation or proliferation, or solid, skin or blood cancers in a warm-blooded living being.

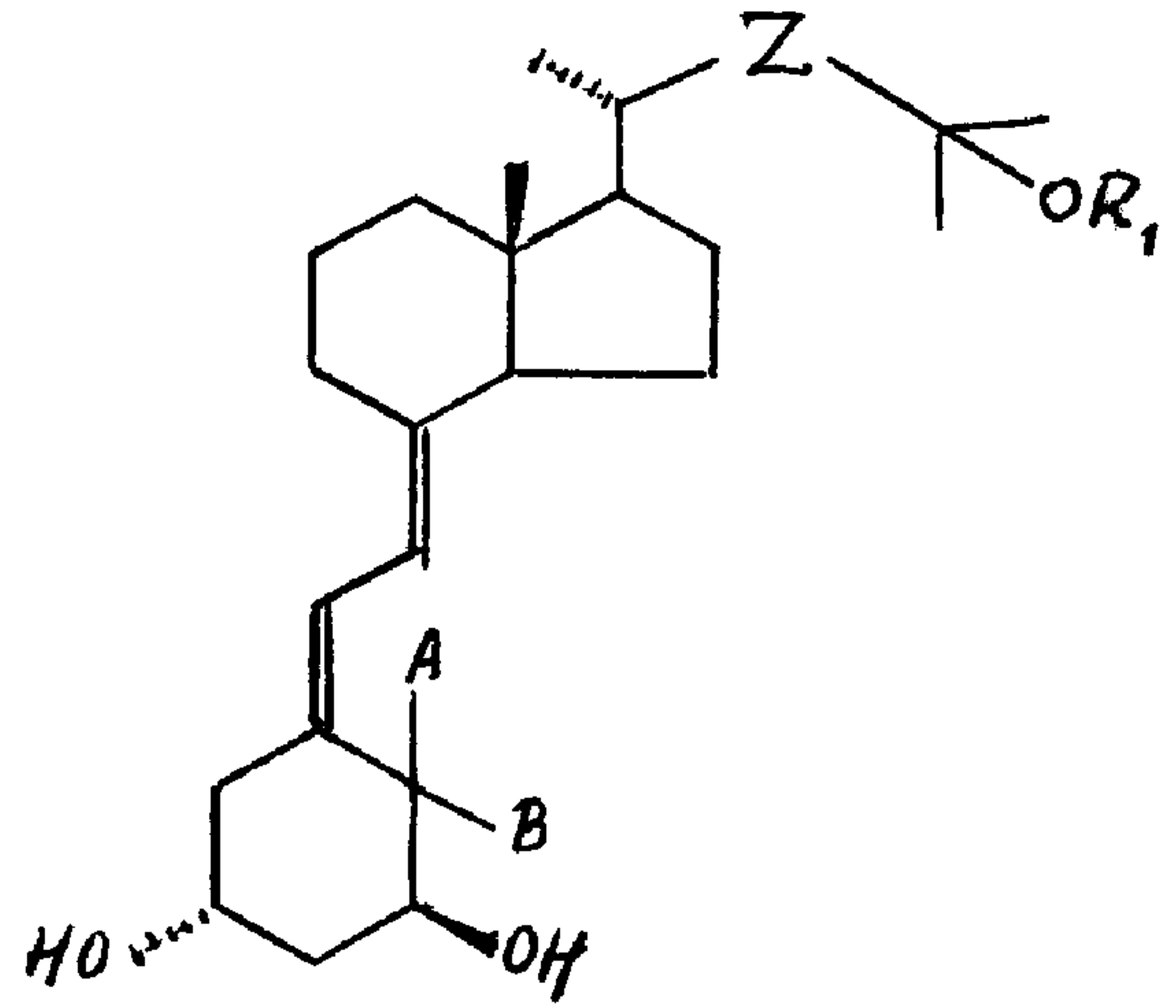
14. Use of a compound as defined in claim 1, 2 or 3, or a composition as defined in claim 12, for the treatment or prevention of osteoporosis, renal osteodystrophy and osteomalacia, autoimmune diseases, acne, alopecia, skin aging, imbalance in the immune system, rheumatoid arthritis, asthma, diseases related to abnormal cell differentiation or proliferation, or solid, skin or blood cancers in a warm-blooded living being.

15. A commercial package comprising a compound as defined in claim 1, 2 or 3, or a composition as defined in claim 12, and associated therewith instructions for the use thereof in the treatment or prevention of osteoporosis, renal osteodystrophy and osteomalacia, autoimmune diseases, acne, alopecia, skin aging, imbalance in the immune system, rheumatoid arthritis, asthma, diseases related to abnormal cell differentiation or proliferation, or solid, skin or blood cancers in a warm-blooded living being.

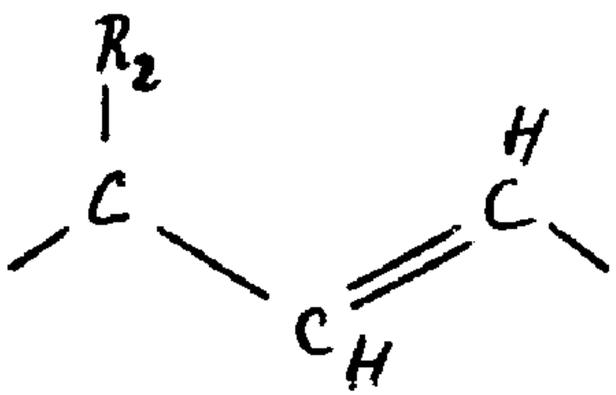
FETHERSTONHAUGH & CO.

OTTAWA, CANADA

PATENT AGENTS



(I)



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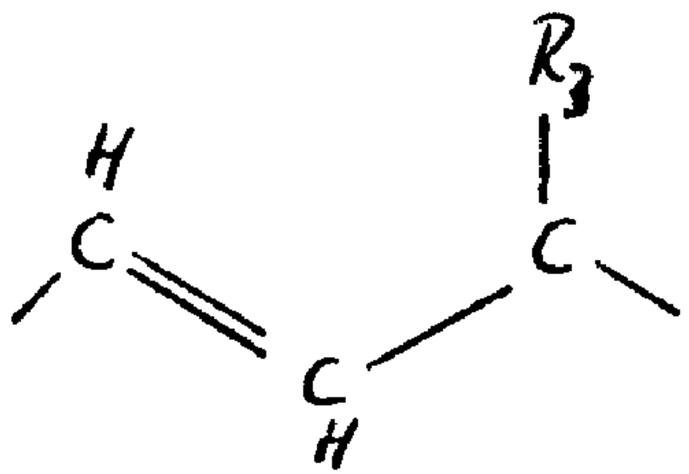

(III)