(57) Abrégé/Abstract:
New 20-methyl-substituted vitamin D derivatives have general formula (I), in which R¹ is a hydrogen atom, a hydroxyl group or an alkanoyloxy group with 1 to 12 carbon atoms or a benzoyloxy group, R² is a hydrogen atom or an alkanoyl group with 1 to 12 carbon atoms or a benzoyl group, and R³ is saturated or unsaturated, straight-chain or branched-chain hydrocarbon residue with up to 18 C atoms, possibly interrupted and/or substituted by one or several carbocyclic structures (C₃-10-cycloalkyl or cycloalkenyl residues, the latter having up to 2 double bonds), possibly substituted by one or several hydroxyl, oxo, amino groups and/or by one or several halogen atoms, possibly having one or several oxygen, sulphur and/or nitrogen (as (a)) atoms as chaining members in the hydrocarbon residues. Also disclosed is a process for preparing the same. These new compounds have strongly improved induction of cell differentiation (HL-60), with respect to calcitriol, and are suitable for preparing medicaments.
ABSTRACT OF THE DISCLOSURE

New 20-methyl-substituted vitamin D derivatives have general formula (I), in which $R^1$ is a hydrogen atom, a hydroxyl group or an alkanoyloxyloxy group with 1 to 12 carbon atoms or a benzyloxyloxy group, $R^2$ is a hydrogen atom or an alkanoyl group with 1 to 12 carbon atoms or a benzoxy group; and $R^3$ is saturated or unsaturated, straight-chain or branched-chain hydrocarbon residue with up to 18 C atoms, possibly interrupted and/or substituted by one or several carbocyclic structures ($C_{3-10}$-cycloalkyl or cycloalkenyl residues, the latter having up to 2 double bonds), possibly substituted by one or several hydroxyl, oxo, amino groups and/or by one or several halogen atoms, possibly having one or several oxygen, sulphur and/or nitrogen (as (a)) atoms as chaining members in the hydrocarbon residue. Also disclosed is a process for preparing the same. These new compounds have strongly improved induction of cell differentiation (HL-60), with respect to calcitriol, and are suitable for preparing medicaments.
20-Methyl-Substituted Vitamin D Derivatives

This invention relates to 20-methyl-substituted vitamin D derivatives of general formula I

\[
\begin{align*}
R^1 \quad &
\end{align*}
\]

in which

\( R^1 \) means a hydrogen atom, a hydroxy group or an alkanoyloxy group with 1 to 12 carbon atoms or a benzoyloxy group,

\( R^2 \) means a hydrogen atom or an alkanoyl group with 1 to 12 carbon atoms or a benzoyl group and

\( R^3 \) means a saturated or unsaturated, straight-chain or branched hydrocarbon radical with up to 18 C atoms, which optionally is interrupted and/or substituted by one or more carbocyclic structure(s) (preferably C_3-C_{10} cycloalkyl or cycloalkenyl radical(s), the latter with up to 2 double bonds), which optionally is substituted with one or more hydroxy, oxo, amino group(s) and/or one or more halogen atom(s), and optionally exhibits one or more oxygen, sulfur and/or nitrogen atoms) (preferably as > NH) as bridging link(s) in the hydrocarbon radical,
a process for their production, pharmaceutical preparations that contain these compounds and their use for the production of pharmaceutical agents.

The alkanoyloxy or alkanoyl groups with 1 to 12 carbon atoms possible for radicals $R^1$ or $R^2$ are derived especially from saturated carboxylic acids. These radicals can be cyclic, acyclic, carbocyclic or heterocyclic and all optionally also unsaturated. The preferred radicals are derived form $C_1$- to $C_9$-, especially $C_2$- to $C_5$- alkanecarboxylic acids, such as, for example, acetyl(oxy)-, propionyl(oxy)-, butyryl(oxy)-.

Preferred radicals $R^3$ are the chains mentioned below with respect to structural formula:

\[
\begin{align*}
\text{R} &= C_1-C_4\text{-alkyl, -hydroxyalkyl, -O-alkyl \text{ (-alkoxy).}}
\end{align*}
\]

In particular, the following compounds according to the invention can be mentioned:

1α,25-Dihydroxy-20,26,27-trimethyl-23-oxa-vitamin D₃,
1(S),3(R)-dihydroxy-20-(5-hydroxy-5-methyl-hexa-1E,3E-dien-1-yl)-20-methyl-9,10-secopregna-5Z,7E,10(19)-triene,
1α,25-dihydroxy-20-methyl-vitamin D₃,
1α,25-dihydroxy-20-methyl-24-homo-vitamin D₃,
1α,24(S)-dihydroxy-20-methyl-vitamin D₃,

1α,25-dihydroxy-20-methyl-23-oxa-vitamin D₃,

1α,24(R),25-trihydroxy-20-methyl-vitamin D₃,

1α,24(S),25-trihydroxy-20-methyl-vitamin D₃,

1α,25-dihydroxy-20-methyl-24-oxo-vitamin D₃,

(5Z,7E)-(1S,3R)-20-methyl-20-vinyl-9,10-seco-pregna-5,7,10(19)-triene-1,3-diol,

(5Z,7E)-(1S,3R)-20-ethyl-20-methyl-9,10-seco-pregna-5,7,10(19)-triene-1,3-diol,

(5Z,7E)-(1S,3R)-20-hydroxymethyl-20-methyl-9,10-seco-pregna-5,7,10(19)-triene-1,3-diol,

1α,25-dihydroxy-20-methyl-23-dehydro-vitamin D₃,

1α,25-dihydroxy-20,26,27-trimethyl-23-dehydro-vitamin D₃.

Natural vitamins D₂ and D₃ (cf. general formula VI) are biologically inactive per se and are converted only after hydroxylation in 25-position in the liver or in 1-position in the kidney to their biologically active metabolites. The action of vitamins D₂ and D₃ consists in the stabilization of the plasma-Ca²⁺ and plasma-phosphate levels; they counteract a decline of the plasma-Ca²⁺ level.
ergocalciferol: $R^a=R^b=H$, $R^c=CH_3$  
Vitamin D2

double bond C-22/23

cholecalciferol: $R^a=R^b=R^c=H$  
Vitamin D3

25-hydroxycholecalciferol: $R^a=R^c=H, R^b=OH$

$1\alpha$-hydroxycholecalciferol: $R^a=OH$, $R^b=R^c=H$

$1\alpha,25$-dihydroxycholecalciferol: $R^a=R^b=OH$, $R^c=H$

calcitriol


But in vitamin D use, it can result in symptoms of overdosage (hypercalcemia).
1α-Cholecalciferols hydroxylated in 24-position already follow from DE-AS-25 26 981; they have a lower toxicity than the corresponding non-hydroxylated 1α-cholecalciferol. The hydroxylated compounds show a selective activation of the intestinal calcium absorption and a weaker bone absorption effect than 1α-cholecalciferol.

The 24-hydroxy-vitamin D analogs described in international patent application WO 87/00834 can be used for treating disorders in humans and animals caused by abnormal cell proliferation and/or cell differentiation.

For various 1,25-dihydroxy-homo-vitamin D derivatives, a dissociation relative to the properties of bone absorption effect and HL-60 cell differentiation has already recently been mentioned by De Luca. In this case, the bone absorption effect in vitro is a direct measurement for the calcium mobilization in vivo.

The new vitamin D derivatives of general formula I are distinguished relative to the already known side chain-modified compounds with vitamin D activity by an additional methyl group on the carbon atom 20. In this way, the C-20 position loses the nature of a center of asymmetry.

Besides the thus caused simplifications in the case of synthesis and purification of intermediate and end products, new compounds result, which exhibit surprisingly high biological activity. Measured by the standard of calcitriol (1α,25-dihydroxy-vitamin D₃), the substances according to the invention
with comparable affinity to the calcitriol receptor show an induction of the cell differentiation (HL-60) improved by several powers of ten, achieve the object of the preparation of pharmaceutical agents, which are alternative cell proliferation inhibitors, and are therefore suitable in a special way for treating diseases that are characterized by hyperproliferation and impaired cell differentiation, such as, e.g., hyperproliferative diseases of the skin (psoriasis), malignant tumors (leukemia, colon cancer, breast cancer) and acne (J. Invest. Dermatol. Vol. 92 No. 3, 1989). In an especially preferred embodiment of the invention, calcitriol receptors are detected in the target organ before the treatment.

In addition, the new compounds can, of course, also be used in a way similar to the known vitamin D derivatives for treating disorders of the calcium metabolism, for immunomodulation and for retardation of the aging of the skin.
The vitamin D activity of the compounds according to the invention is determined by the calcitriol-receptor test. It is performed by using a specific receptor protein from the intestines of young swine. Receptor-containing binding protein is incubated with $^3$H-calcitriol ($5 \times 10^{-10}$ mol/l) in a reaction volume of 0.270 ml in the absence and in the presence of test substances for 2 hours at 4°C in a test tube. To separate free and receptor-bound calcitriol, a charcoal-dextran absorption is
performed. For this purpose, 250 µl of a charcoal-dextran suspension is fed to each test tube and incubated at 4°C for 20 minutes. Then, the samples are centrifuged at 10,000 x g for 5 minutes at 4°C. The supernatant is decanted and measured in a β-counter after 1 hour of equilibration in Picofluor 15 TM.

The competition curves obtained with various concentrations of the test substance as well as of the reference substance (unlabeled calcitriol) at constant concentration of the reference substance (³H-calcitriol) are placed in relation to one another and a competition factor (KF) is determined.

It is defined as a quotient from the concentrations of the respective test substance and the reference substance, which are necessary for 50% competition:

\[
KF = \frac{\text{Concentration of test substance at 50% competition}}{\text{Concentration of reference substance at 50% competition}}
\]

Accordingly, 1(S),3(R)-dihydroxy-20-(5-hydroxy-5-methyl-hexa-1E,3E-dien-1-yl)-20-methyl-9,10-secopregna-5Z,7E,10(19)-triene, 1α,25-dihydroxy-20,26,27-trimethyl-23-oxa-vitamin D₃ and 1α,25-dihydroxy-20-methyl-23,24-dehydro-vitamin D₃ have KF values of 3.4, 1.6 and 0.8, respectively.

The greatly improved induction of cell differentiation of the new compounds is produced from the test described below.

It is known in the literature (Mangelsdorf, D. J. et al., J. Cell. Biol. 92: 391-398 (1984)), that the treatment of human leukemia cells (promyelocyte cell line HL 60) in vitro with calcitriol induces the differentiation of cells to macrophages.
HL 60 cells are cultivated in tissue-culture medium (RPMI - 10% fetal calf serum) at 37°C in an atmosphere of 5% CO₂ in air.

For substance testing, the cells are centrifuged off and 2.8 x 10⁵ cells/ml in phenol red-free tissue-culture medium are taken up. The test substances are dissolved in ethanol and diluted with tissue-culture medium without phenol red to the desired concentration. The dilution stages are mixed with the cell suspension in a ratio of 1:10 and 100 µl each of this cell suspension mixed with substance is pipetted in an indentation of a 96-hole plate. For control, a cell suspension is mixed analogously with the solvent.

After incubation over 96 hours at 37°C in 5% CO₂ in air, 100 µl of an NBT–TPA solution (Nitro Blue Tetrazolium (NBT), end concentration in the batch of 1 mg/ml, tetradecanoylphorbolmyristate-13-acetate (TPA), end concentration in the batch of 2 x 10⁻⁷ mol/l) is pipetted in each indentation of the 96-hole plate to the cell suspension.

By incubation over 2 hours at 37°C and 5% CO₂ in air, NBT is reduced to insoluble formazan in the cells differentiated to macrophages because of the intracellular oxygen radical release (O₂²⁻), stimulated by TPA.

For completion of the reaction, the indentations of the 96-hole plate are suctioned off and the adhering cells are fixed by adding methanol and dried after fixation.

To dissolve the formed intracellular formazan crystals, 100 µl of potassium hydroxide (2 mol/l) and 100 µl of dimethyl sulfoxide are pipetted in each indentation and treated
ultrasonically for 1 minute. The concentration of formazan is measured spectrophotometrically at 650 nm.

The concentration of formed formazan is regarded as a measurement for the differentiation induction of the HL 60 cells to macrophages. The relative effectiveness of the test substance follows from the quotient of ED$_{50}$ test substance/ED$_{50}$ calcitriol. In this case, the compounds according to the invention prove to be several powers of ten more effective than calcitriol.

The immunomodulatory effect of the compounds according to the invention is produced from the inhibition of the proliferation of stimulated human lymphocytes and their interleukin 2 (IL 2) production.

It has now been found that the compounds according to the invention are potent inhibitors of the proliferation and interleukin 2 (IL 2)-synthesis of human lymphocytes.

To determine the lymphocyte proliferation, mononuclear cells were obtained from citrated blood by density gradient centrifuging and 5 x 10$^4$ cells/200 µl were cultivated in microtiter plates in 200 µl of tissue-culture medium (RPMI 1640 by adding 10% fetal calf serum). In the dissemination, phytohemagglutinin (PHA) (5 µg) and various concentrations of the test substance or calcitriol (1,25-dihydroxycholecalciferol) were added as a standard, and the cells were incubated for 96 hours at 37°C in an atmosphere of 5% CO$_2$ in air. For the last 6 hours, 0.2 µCi/hole of $[^3]$H-thymidine was added to the cells.

Then, the cells were suctioned off through a glass-fiber filter and the radioactivity of the filters was measured as a
measurement for the incorporation of $[^3]H$-thymidine and thus for the cell proliferation in the $\beta$-counter.

To determine the IL 2 secretion, mononuclear cells were prepared from human blood as for the determination of the proliferation and $2 \times 10^6$ cells were cultivated in 1 ml of tissue-culture medium (RPMI 1640 by adding 2% fetal calf serum) in 24-hole plates. In the dissemination, PHA (20 $\mu$g) and various concentrations of the test substance or calcitriol were added as a standard. 24 hours after cultivation at 37°C in an atmosphere of 5% CO$_2$ in air, the tissue-culture supernatant was obtained by centrifuging, and in the supernatant, the IL 2 concentration was quantified with an ELISA.

The lymphocyte proliferation was inhibited around 50% by $1\alpha,25$-dihydroxy-20-methyl-23,24-dehydro-vitamin D$_3$ in a concentration of $1 \times 10^{-11}$, and by calcitriol in a concentration of $4 \times 10^{-10}$ around 50%.

The IL 2 secretion was inhibited by $1\alpha,25$-dihydroxy-20-methyl-23,24-dehydro-vitamin D$_3$ in the same range of concentration.

Because of the inhibition of the lymphocyte proliferation and IL 2 synthesis in low concentration, the compounds of general formula I according to the invention are suitable for treatment of diseases of the immunological system, e.g., diseases of the atopic type (atopic dermatitis, asthma), autoimmune diseases including diabetes mellitus, transplant rejection reactions and AIDS.
For calcitriol, it has been found that because of a receptor-mediated mechanism, it inhibits not only the IL 2 secretion, but also the production of other inflammatory-promoting cytokines. Since the compounds of general formula I, for example, bind just as well to the receptor as calcitriol, they are suitable for treating inflammatory diseases, such as arthritis, ulcerative colitis and Crohn’s disease.

In the treatment of autoimmune disease, transplant rejection reactions and AIDS, the new compounds of general formula I can advantageously be combined with other immunosuppressively effective substances such as cyclosporin A and FK 506.

This invention thus also relates to pharmaceutical preparations that contain at least one compound according to general formula I together with a pharmaceutically compatible vehicle. The compounds can be formulated as solutions in pharmaceutically compatible solvents or as emulsions, suspensions or dispersions in suitable pharmaceutical solvents or vehicles, or as pills, tablets or capsules, which contain solid vehicles in a way known in the art. For a topical use, the compounds are advantageously formulated as creams or ointments or in a similar form of pharmaceutical agent suitable for topical use. Each such formulation can also contain other pharmaceutically compatible and nontoxic adjuvants, such as, e.g., stabilizers, antioxidants, binders, dyes, emulsifiers or flavoring substances. The compounds are advantageously administered by injection or intravenous infusion of suitable sterile solutions or as oral dosage through the alimentary tract or topically in the form of
creams, ointments, lotions or suitable transdermal plasters, as is described in EP-A-0 387 077.

The daily dose is

0.1 µg/patient/day -- 1000 µg (1 mg)/patient/day

preferably

0.1 µg/patient/day -- 500 µg/patient/day.

Furthermore, the invention relates to the use of the compounds according to formula I for the production of pharmaceutical agents.

The production of compounds of general formula I takes place according to the invention in that a compound of general formula II
in which

R' means a hydrogen atom or a protected hydroxy group and
R' means an alkali-stable hydroxy protective group and
R' has the same meaning as R' in the ultimately desired
compound of general formula I, in which optionally present
hydroxy groups are protected, is converted by cleavage of the
present hydroxy protective groups and optionally by partial or
complete esterification of the hydroxy group(s) to a compound of
general formula I.

In the alkali-stable hydroxy protective groups, which in
general are also used to protect the hydroxy groups in 1-position
and/or in side chain R', preferably the tert-butyldimethylsilyl
group, the tert-butyldiphenylsilyl group or other tertiary silyl
groups are involved. The cleavage of the tertiary silyl groups
is possible, e.g., by using tetra-n-butyl-ammonium fluoride.
After the cleavage of the protective groups, free hydroxy groups can optionally be esterified. The esterification of the various free hydroxy groups takes place according to conventional processes partially or completely with the corresponding carboxylic acid halide (halide = chloride, bromide) or carboxylic acid anhydride.

The production of the initial compounds of general formula II according to the invention starts from the known aldehydes of general formula III.
in which \( R' \) and \( R'' \) have the meaning indicated in general formula II (M. J. Calverley, Tetrahedron 43, 4609, 1987; G. Neef et al., Tetrahedron Lett. 1991, 5073).

Their \( \alpha \)-alkylation in the usual way produces the dimethylated aldehydes of general formula IV, which then are converted in an also known way by triplet-sensitized photoisomerization to the central intermediate compounds of general formula V
The methylation is performed, e.g., with iodomethane or dimethyl sulfate in the presence of a base (e.g., alkali metal hydroxides, -hydrides, -amides) in an aprotic solvent such as tetrahydrofuran, diethyl ether, hexane, ethylene glycol dimethyl ether or toluene, optionally by adding a tetraalkylammonium salt as a phase transfer catalyst.

By irradiation with ultraviolet light in the presence of a so-called "triplet sensitizer" (anthracene is used for this purpose in the scope of this invention), the compounds of general formula IV can be converted to the compounds of general formula V. By cleavage of the pi-bond of the 5,6-double bond, rotation of the A-ring by 180° around the 5,6-single bond and reestablishing the 5,6-double bond, the stereoisomerism on the 5,6-double bond is reversed.

Then, radical R₃ must also be introduced by coupling an aldehyde of general formula V with a precursor of R₃ suitable for coupling. This takes place analogously to known processes; the experimental performance of this process is found, for example, in M. J. Calverley, Tetrahedron 43, 4609, 1987; G. Neef and A. Steinmeyer, Tetrahedron Lett. 1991, 5073; international patent application WO 91/00855, DE-A 39 33 034 and DE-A 40 11 682. As examples, there can be mentioned: reaction of the aldehyde of general formula V with a Wittig reagent or reduction of the aldehyde to alcohol and its chain lengthening by reaction with a corresponding ω-halogen compound.

The following examples are used for a more detailed explanation of this invention.
Example 1

1α,25-Dihydroxy-20,26,27-trimethyl-23-oxa-vitamin D₃

a. With ice water cooling, a solution of 4.5 g of 1(S)-(tert-butyldimethylsilyloxy)-3(R)-(tert-butyldiphenylsilyloxy)-20(S)-formyl-9,10-secopregna-5E,7E,10(19)-triene in 40 ml of absolute THF is instilled in a suspension of 213 mg of sodium hydride (80% in oil) in 42 ml of absolute THF. After adding 1.18 ml of iodomethane, it is stirred for 2 hours at room temperature, then poured in water and extracted with ethyl acetate.

The crude product obtained after concentration by evaporation is taken up in 400 ml of toluene and, after adding 432 mg of anthracene and 0.2 ml of triethylamine, it is irradiated for 20 minutes at room temperature in a smoke apparatus (pyrex glass) with a high-pressure mercury vapor lamp (Philips HPK 125). After the concentration by evaporation of the reaction solution, the residue is chromatographed on silica gel with hexane/ethyl acetate and 2.38 g of 1(S)-(tert-butyldimethylsilyloxy)-3(R)-(tert-butyldiphenylsilyloxy)-20-formyl-20-methyl-9,10-secopregna-5Z,7E,10(19)triene is obtained as colorless oil.

¹H-NMR (CDCl₃, 300 MHz): δ = 0.52 ppm (s,3H,H-18); 4.23 (m,1H,H-3); 4.46 (m,1H,H-1); 4.85 and 5.21 (m; 1H,H-19 each); 6.04 and 6.11 (d, J=11Hz; 1H,H-6 and H-7 each); 9.66 (s,1H,CHO).

b) To dissolve 2.35 g of the aldehyde, obtained under a., in 25 ml of THF and 25 ml of methanol, a solution of 1.41 g of CeCl₃ (heptahydrate) in 25 ml of methanol is first instilled. After adding 91 mg of sodium borohydride, it is stirred for 90
minutes at 25°C, then poured in water and extracted with ethyl acetate. Chromatography on silica gel with hexane/ethyl acetate produces 1.86 g of 1(S)-(tert-butyldimethylsilyloxy)-3(R)(tert-butyldiphenylsilyloxy)-20-hydroxymethyl-20-methyl-9,10-secopregna-5Z,7E,10(19)-triene as colorless oil.

c. A two-phase system, consisting of 10.1 ml of 25% NaOH, 2.74 ml of bromoacetic acid-tert-butylester, 1.67 g of the alcohol, obtained under b., in 25 ml of toluene and 48 mg of tetrabutylammonium hydrogen sulfate is stirred for 6 hours at 50-60°C. After the cooling, it is diluted with toluene, the toluene phase is separated, the latter is washed with water, dried on Na₂SO₄ and concentrated by evaporation. After chromatography on silica gel with hexane/ethyl acetate, 830 mg of 1(S)-(tert-butyldimethylsilyloxy)-3(R)-(tert-butyldiphenylsilyloxy)-20-(tert-butoxycarbonylmethoxymethyl)-20-methyl-9,10-secopregna-5Z,7E,10(19)-triene is obtained as yellowish oil.

d. The magnesium-organic compound is produced in the usual way from 490 mg of magnesium (chips) and 1.5 ml of bromoethane in 13 ml of absolute THF. After adding 810 mg of the tert-butylester, obtained under c., drop by drop, it is stirred for 3 hours at room temperature. For working up, the reaction solution is poured in NH₄Cl solution and extracted with ethyl acetate.

e. The oily crude product obtained after concentration by evaporation is dissolved in 15 ml of THF and, after adding 1.3 g of tetrabutylammonium fluoride, stirred for 2 hours at 50°C. After the usual working up, it is chromatographed on neutral aluminum oxide with hexane/ethyl acetate. By crystallizing the
main fraction from diisopropyl ether/ethyl acetate, 145 mg of the

title compound of melting point 146-148°C is obtained.

$^1$H-NMR (CDCl$_3$, 300 MHz); $\delta$ = 0.63 ppm (s,3H); 0.92 (s,3H);
1.00 (s,3H); 3.16 (s,2H); 3.23 (AB-$q,J=9$ and $7$ Hz,2H); 4.23
(m,1H); 4.43 (m,1H); 4.98 (m,1H); 5.32 (m,1H); 5.90
(d,J=11Hz,1H); 6.38 (d,J=11Hz,1H).

Example 2

1(S),3(R)-Dihydroxy-20-(5-hydroxy-5-methyl-hexa-1E,3E-dien-1-yl)-
20-methyl-9,10-secopregna-5Z,7E,10(19)-triene

The reaction sequence described in PCT application WO
91/00855 was performed with 2.12 g of the aldehyde obtained under
example 1a. After Wittig reaction with methoxycarbonyl-
triphenylphosphorane, reduction with diisobutylaluminum hydride,
oxidation with pyridinium dichromate, renewed Wittig olefination
with methoxycarbonyl-triphenylphosphorane, reaction of the
obtained ester with methylthiium and protective group cleavage
with tetrabutylammonium fluoride, 600 mg of the title compound
was obtained as colorless oil.

[α]$_b$-65.5°(CDCl$_3$, c = 0.525).

$^1$H-NMR (CDCl$_3$, 300 MHz); $\delta$ = 0.57 ppm (s,3H); 1.04 (s,3H);
1.09 (s,3H); 1.34 (s,6H); 4.23 (m,1H); 4.43 (m,1H); 4.98 (m,1H);
5.32 (m,1H); 5.72 (d,J=15Hz,1H); 5.87 (d,J=10Hz,1H); 5.88
(dd,J=15 and $10$ Hz,1H); 6.00 (d,J=11Hz,1H); 6.19 (dd,J= 15 and $10$
Hz,1H); 6.37 (d,J=11Hz,1H).
Example 3

\((5Z,7E)-(1S,3R)-20-Hydroxymethyl-20-methyl-9,10-seco-pregna-5,7,10(19)-triene-1,3-diol\)

By silyl ether cleavage of the alcohol, obtained under example 1b., under the conditions of example 1e., the title compound of melting point 183-185°C is obtained.

\(^1\text{H-NMR (CDCl}_3 + \text{DMSO-d}_6, 300 \text{ MHz);} \delta = 0.22, 0.46 \text{ and 0.58 ppm (3 x s; 3H, H-18 and 20-methyl each); 3.73 (m, 1H, H-3); 3.95 (m, 1H, H-1); 4.49 and 4.90 (2 x s; 1H, H-19 each); 5.62 and 5.87 (2 x d, J=11Hz; 1H, H-6 and H-7 each).}\

Example 4

\((5Z,7E)-(1S,3R)-20-Methyl-20-vinyl-9,10-seco-pregna-5,7,10(19)-triene-1,3-diol\)

By reaction of the aldehyde, described under example 1a., with methylene triphenylphosphorane and subsequent silyl ether cleavage according to example 1e., the title compound of melting point 139-142°C is obtained, \([\alpha]_D -23.9° \text{ (CHCl}_3, \text{ c = 0.255).}\

\(^1\text{H-NMR (CDCl}_3, 300 \text{ MHz);} \delta = 0.57 \text{ ppm (s, 3H, H-18); 1.03 and 1.08 (2 x s; 3H, 20-methyl each); 4.22 (m, 1H, H-3); 4.43 (m, 1H, H-1); 4.82-4.93 (m, 2H, vinyl-CH}_2); 4.99 \text{ and 5.32 (2 x s; 1H, H-19 each); 5.93 - 6.05 (m, 2H, H-6 and vinyl-CH); 6.37 (d, J=11Hz, 1H, H-7).}\


Example 5

(5Z,7E)-(1S,3R)-20-Ethyl-20-methyl-9,10-seco-pregna-5,7,10(19)-triene-1,3-diol

By homologation of the aldehyde, obtained under 1a. (e.g., according to M. J. Calverley, Synlett 1990, 155), subsequent reduction according to example 1b., conversion of the thus obtained alcohol to the corresponding iodide (e.g., according to G. L. Lange and C. Gottardo, Synth. Commun. 1990, 20, 1473), reduction of the iodide with LiAlH₄ in THF and subsequent silyl ether cleavage, the title compound is obtained.

¹H-NMR (CDCl₃, 300 MHz): δ = 0.64 ppm (s,3H,H-18); 0.87 and 0.93 (2 x s; 3H,20-methyl each); 4.23 (m,1H,H-3); 4.42 (m,1H,H-1); 5.01 and 5.34 (2 x s; 1H,H-19 each); 6.01 and 6.39 (2 x d, J=11Hz; 1H,H-6 and H-7 each).

Example 6

1α,25-Dihydroxy-20-methyl-23-dehydro-vitamin D₃

By homologation of the aldehyde described under 1a. (e.g., according to Synlett 1990, 155), Wittig-Horner olefination of the thus obtained homologous aldehyde with dimethyl phosphonoacetic acid methyl ester (NaH, THF), reaction of the thus obtained unsaturated ester with methylmagnesium bromide in THF and silyl ether cleavage, the title compound is obtained as colorless oil.

¹H-NMR (CDCl₃, 300 MHz): δ = 0.64 ppm (s,3H,H-18); 0.89 and 0.95 (2 x s; 3H,20-methyl each); 1.33 (s,6H,25-methyl); 4.23 (m,1H,H-3); 4.43 (m,1H,H-1); 5.00 and 5.33 (2 x s; 1H,H-19 each);
5.55-5.72 (m, 2H, H-23 and H-24); 6.00 and 6.38 (2 x d, J=11Hz; 1H,H-6 and H-7 each).

Example 7

1α,25-Dihydroxy-20-methyl-24-oxo-vitamin D₃

By homologation of the aldehyde described under 1a. (e.g., Synlett 1990, 155), Wittig-Horner olefination with diethylphosphono-ethoxyacetic acid ethyl ester (according to W. Grell and H. Machleidt, Liebig's Ann. Chem. 699, 53, 1966), addition of methylmagnesium bromide, enol ether cleavage (70% acetic acid) and removal of silyl ether protective groups, the title compound of melting point 141-144°C is obtained, [α]₀ +14.7° (CHCl₃, c = 0.505).

¹H-NMR (CDCl₃, 300 MHz); δ = 0.65 ppm (s, 3H, H-18); 0.90 and 0.98 (2 x s; 3H, 20-methyl each); 1.40 (s, 6H, 25-methyl); 4.23 (m, 1H, H-3); 4.44 (m, 1H, H-1); 5.00 and 5.33 (2 x broad s; 1H, H-19 each); 6.01 and 6.38 (2 x d, J=11Hz; 1H, H-6 and H-7 each).
The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A 20-methyl-substituted vitamin D compound of Formula I:

![Chemical Structure](image)

wherein

$R^1$ is a hydrogen atom, a hydroxy group, a $C_1$-$C_{12}$-alkanoyloxy group, or a benzoyloxy group;

$R^2$ is a hydrogen atom, a $C_1$-$C_{12}$-alkanoyl group, or a benzoyl group; and

$R^3$ is a saturated or unsaturated, straight-chain or branched $C_1$-$C_{18}$-hydrocarbon group, wherein said hydrocarbon group is optionally interrupted and/or is substituted with a $C_3$-$C_{10}$-cycloalkyl or -cycloalkenyl moiety; said hydrocarbon group is optionally substituted with at least one of hydroxy, oxo, amino, or halogen; and at least one carbon
atom of said hydrocarbon group is optionally replaced by an oxygen, sulfur or nitrogen atom.

2. A 20-methyl-substituted vitamin D compound according to claim 1, wherein

\[ R^3 \]

\[ \text{OH} \]

\[ (n = 1 \cdot 3) \]

and \( R \) is \( C_1-C_4 \)-alkyl, \( C_1-C_4 \)-hydroxyalkyl, or \( C_1-C_4 \)-alkoxy.

3. A 20-methyl-substituted vitamin D compound selected from the group consisting of:

- \( 1\alpha,25 \)-dihydroxy-20,26,27-trimethyl-23-oxa-vitamin D₃;
- \( 1(S),3(R) \)-dihydroxy-20-(5-hydroxy-5-methyl-hexa-1E,3E-dien-1-yl)-20-methyl-9,10-secopregna-5Z,7E,10(19)-triene;
- \( 1\alpha,25 \)-dihydroxy-20-methyl-vitamin D₃;
- \( 1\alpha,25 \)-dihydroxy-20-methyl-24-homo-vitamin D₃;
- \( 1\alpha,24(S) \)-dihydroxy-20-methyl-vitamin D₃;
- \( 1\alpha,25 \)-dihydroxy-20-methyl-23-oxa-vitamin D₃;
1α,25-dihydroxy-20-methyl-23-dehydro-vitamin D₃;
1α,25-dihydroxy-20,26,27-trimethyl-23-dehydro-vitamin D₃;
1α,24(R),25-trihydroxy-20-methyl-vitamin D₃;
1α,24(S),25-trihydroxy-20-methyl-vitamin D₃;
1α,25-dihydroxy-20-methyl-24-oxo-vitamin D₃;
(5Z,7E)-(1S,3R)-20-methyl-20-vinyl-9,10-secopregna-
5,7,10(19)-triene-1,3-diol;
(5Z,7E)-(1S,3R)-20-ethyl-20-methyl-9,10-secopregna-
5,7,10(19)-triene-1,3-diol; and
(5Z,7E)-(1S,3R)-20-hydroxymethyl-20-methyl-9,10-secopregna-5,7,10(19)-triene-1,3-diol.

4. A 20-methyl-substituted vitamin D compound of
Formula I:

wherein

R¹ is a hydrogen atom, a hydroxy group, a C₁₋₅₋₀-
alkanoyloxy group, or a benzoyloxy group;
R² is a hydrogen atom, a C₁₋₁₂-alkanoyl group, or a benzoyl group; and
R³ is a saturated or unsaturated, straight-chain or branched C₁₋₁₈-hydrocarbon group, wherein said hydrocarbon group is interrupted and/or is substituted with a C₄₋₁₀-cycloalkyl or C₃₋₁₀-cycloalkenyl moiety;
said hydrocarbon group is substituted with at least one of hydroxy, oxo, amino, chloro, bromo, or iodo; and/or
at least one carbon atom of said hydrocarbon group is replaced by a sulfur or nitrogen atom.

5. A topical pharmaceutical composition, comprising the vitamin D compound according to any one of claims 1 to 4, and a pharmacologically compatible vehicle.

6. A pharmaceutical composition, comprising the vitamin D compound according to any one of claims 1 to 4, and a pharmacologically compatible vehicle.

7. The pharmaceutical composition according to claim 6, wherein the vehicle is compatible with oral administration.
8. The pharmaceutical composition according to claim 6, wherein the vehicle is compatible with intravenous administration.

9. A process for the manufacture of the vitamin D compound according to any one of claims 1 to 4, comprising the steps of:

   removing any hydroxy-protecting groups that are present in a compound of the general Formula II

   \[
   \text{(II)}
   \]

   wherein

   - \( R^{1'} \) is a hydrogen atom or a protected hydroxy group,
   - \( R^{2'} \) is an alkali-stable hydroxy-protecting group, and
   - \( R^{3'} \) has the same meaning as \( R^3 \) as defined in claim 1 or 2, any hydroxy groups that may be present in \( R^{3'} \) being protected, and
optionally, partially or completely esterifying the hydroxy group(s).

10. An intermediate compound of the general Formula V

\[ \begin{align*}
\text{CHO} \\
\text{R}^1, \text{R}^2
\end{align*} \]

wherein

\( R^{1'} \) and \( R^{2'} \) have the meanings defined in claim 9, with the proviso that Formula (V) is different from Formula (I) as defined in claim 1.

11. Use of the vitamin D compound according to any one of claims 1 to 4, in the manufacture of a medicament.

12. Use of the vitamin D compound according to any one of claims 1 to 4, for immunomodulation, for slowing down aging of the skin, or for the treatment of hyperproliferation, impaired cell differentiation, or calcium metabolism disorders.
13. Use of the vitamin D compound according to any one of claims 1 to 4, for the manufacture of a medicament for immunomodulation, for slowing down aging of the skin, or for the treatment of hyperproliferation, impaired cell differentiation, or calcium metabolism disorders.