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(54) Title: PROCESS FOR PREPARING 1α-HYDROXYLATED COMPOUNDS

(57) Abstract

The principal object of the invention is to provide a method for directly introducing an oxygen function at carbon 1 of the vitamin D molecule or precursors or derivatives thereof which comprises subjecting such molecule to allylic oxidation utilizing selenium dioxide as the oxidizing agent. It is recognized that 1α-hydroxylation is essential to impart biological activity to vitamin D compounds and their derivatives and the present invention provides an efficient and direct method for accomplishing the desired 1α-hydroxylation.

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Description

Process for Preparing 1α-Hydroxylated Compounds

Technical Field

This invention relates to a method for preparing compounds having vitamin D-like activity and to compounds which are key intermediates in such method.

More specifically, this invention relates to a method for preparing compounds having vitamin D-like activity which contain an oxygen function at carbon 1 in the molecule.

Still more specifically, this invention relates to a method for preparing 1α-hydroxylated compounds which are characterized by vitamin D-like activity via a cyclovitamin D intermediate.

It is well known that the D vitamins exhibit certain biological effects, such as stimulation of intestinal calcium absorption, stimulation of bone mineral resorption and the prevention of rickets. It is also well known that such biological activity is dependent upon these vitamins being altered in vivo, i.e. metabolized, to hydroxylated derivatives. For example, current evidence indicates that 1α, 25-dihydroxyvitamin-D_3 is the in vivo active form of vitamin D_3 and is the compound responsible for the aforementioned biological effects.

The synthetic 1α-hydroxyvitamin D analogs, such as 1α-hydroxyvitamin D_3, and 1α-hydroxyvitamin D_2 also exhibit pronounced biological potency and such compounds as well as the natural metabolites show great promise as agents for the treatment of a variety of calcium metabolism

and bone disorders, such as osteodystrophy, osteomalacia and osteoporosis.

Background Art

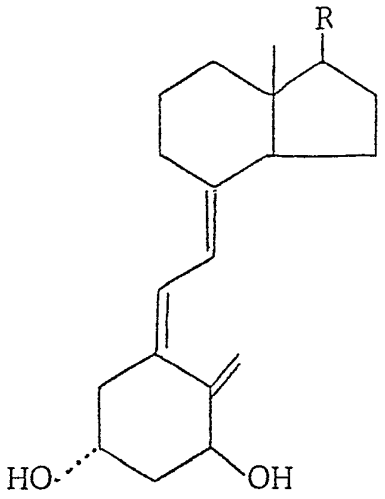
Since 1α-hydroxylation is an essential element in imparting biological activity to the vitamin D compounds and their derivatives there has been increasing interest in methods for chemically accomplishing such hydroxylation. Except for one suggested method for the total synthesis of 1α-hydroxyvitamin D_3 (Lythgoe et al, J. Chem. Soc., Perkin Trans I, p. 2654 (1974)), all syntheses of 1α-hydroxylated vitamin D compounds prior to the conception of the present invention involved the preparation of a 1α-hydroxylated steroid, from which, after conversion to the corresponding 1α-hydroxy-5,7-diene sterol derivative, the desired vitamin D compound is obtained by well known photochemical methods. Thus, available syntheses are multistep processes and in most cases are ineffecient and laborious.

Examples of other syntheses involving 1α-hydroxylation in vitamin D-related compounds can be found in: Process for Preparation of Steroid Derivative, Ishikawa et al, U.S. Patent No. 3,929,770, issued December 30, 1957; Process for Preparation of 1α,25-Dihydroxycholecalciferol, Matsunaga et al, U.S. Patent No. 4,022,768, issued May 10, 1977; 1α-Hydroxycholecalciferol, DeLuca et al, U.S. Patent No. 3,741,996, issued June 26, 1973; 1α-Hydroxyergocalciferol and Processes for Preparing Same, DeLuca et al, U.S. Patent No. 3,907,843, issued September 23, 1975; The Selenium Dioxide Oxidation of Cholcalciferol, Bohumil Pelc, Steroids, Volume 30, Number 2, August 1977.

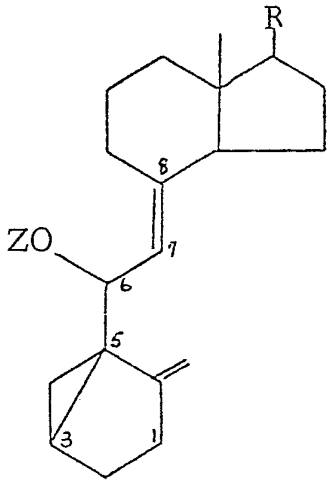
Disclosure of Invention

A new method for introducing a hydroxy group at the carbon 1 (C-1) position in the vitamin D or vitamin D derivative molecule has now been found which in concept and execution differs radically from existing syntheses. This method, which will be more fully described hereinafter, provides for the direct introduction of an oxygen function at C-1 by allylic oxidation.

In general, the method of this invention comprises preparing 1α-hydroxylated compounds having the following formula



by subjecting compounds (hereinafter referred to by the general term "cyclovitamin D") having the formula



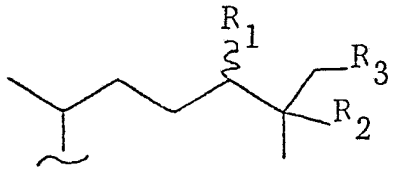
to allylic oxidation, recovering the resulting 1α-hydroxylated cyclovitamin D compound from the allylic oxidation reaction mixture, acylating the recovered compound and recovering the resulting 1α-O-acyl derivative, subjecting said derivative to acid catalyzed solvolysis, recovering the desired 1α-O-acyl vitamin D compound and hydrolyzing (or reducing with hydride reagents) the 1α-O-acylated product to obtain 1α-hydroxyvitamin D compounds.

In the above described process, R in the formulae represents a steroid side chain; most commonly a substituted or unsubstituted, or saturated or unsaturated, or substituted and unsaturated cholesterol side chain group and Z represents hydrogen or a lower alkyl or lower acyl group or aromatic acyl group. Preferably R will be a cholesterol or ergosterol side chain group characterized by the presence of a hydrogen or hydroxy group at what will be the 25-carbon (C-25) position in the desired product molecule.

Wherever herein and in the claims the word "lower" is used as a modifier for alkyl or acyl, it is intended to identify a hydrocarbon chain having from 1 to about 4 carbon atoms and can be either a straight chain or branched chain configuration. An aromatic acyl group is a group such as benzoyl or substituted benzoyl. Also, in the various formulae depicted, a wavy line to any substituent is indicative of that particular substituent being in either the α or β stereoisomeric form.

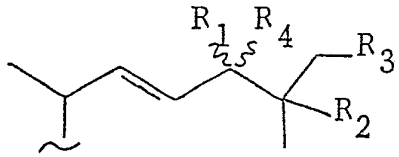
More specifically, in the practice of the process of

this invention, R in the formulae set forth above and those to follow, and in the claims, is preferably a cholesterol side chain group characterized by the formula



wherein each of R_1, R_2 and R_3 are selected from the group consisting of hydrogen, hydroxy, lower alkyl, substituted lower alkyl, 0-lower alkyl, substituted 0-lower alkyl, and fluorine. The most preferred side chain group having the above configuration is one where R_1 and R_3 are hydrogen and R_2 is hydroxyl. Other preferred side chain groups are those where R_1, R_2 and R_3 are hydrogen, or where R_1 is hydroxyl and R_2 and R_3 are hydrogen, or where R_1 and R_2 are hydroxyl and R_3 is hydrogen.

Another preferred side chain group represented by R is the ergosterol side chain group characterized by the formula

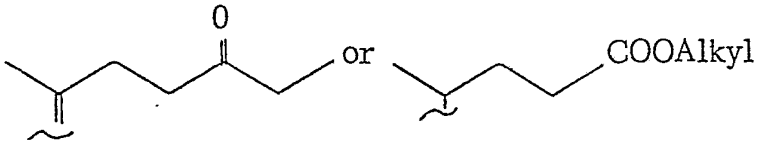


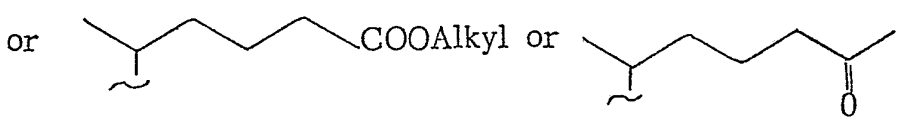
wherein each of R_1, R_2 and R_3 are selected from the group consisting of hydrogen, hydroxyl, lower alkyl, substituted lower alkyl, 0-lower alkyl, substituted 0-lower alkyl, and fluorine, and R_4 is selected from the group consisting of hydrogen and lower alkyl. The most preferred side chain groups having the designated ergosterol side chain con-

figuration are where R_1 and R_3 are hydrogen, R_2 is hydroxyl and R_4 is methyl or where R_1, R_2 and R_3 are hydrogen and R_4 is methyl and where the stereochemistry of R_4 is that of ergosterol.

It is understood that wherever hydroxy groups occur in the side chain group R of the cyclovitamin D starting material, such groups may be acylated, e.g. lower acyl such as acetyl or substituted lower acyl, benzoyl or substituted benzoyl, although such acylation is not required for success of the process.

It is to be noted further that the side chain group R need not be limited to the types enumerated above. The process described in this invention is a general one that is applicable to cyclovitamin D compounds prossessing many of the common steroid side chains, e.g. the side chain of pregnenolone, desmosterol, cholenic acid, or homocholenic acid. In addition to the side chain groups defined above, cyclovitamin D compounds wherein the side chain R group is represented for example by the following structures

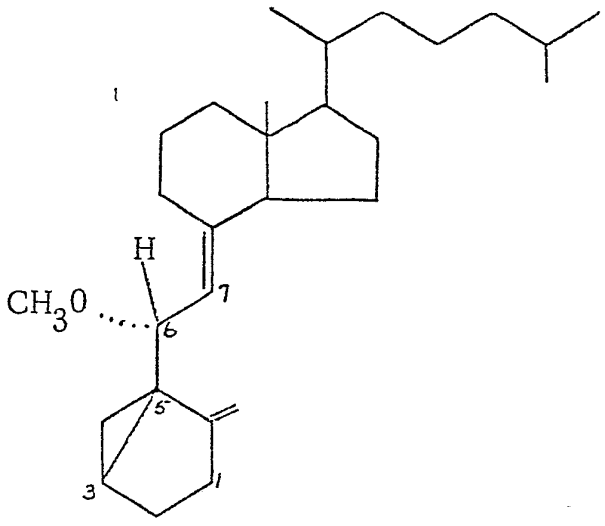




are conveniently prepared and are suitable starting materials for the process of this invention.

The cyclovitamin starting material for the oxidation process is conveniently prepared from a vitamin D compound by a two-step procedure which comprises converting a vitamin D compound carrying a 3β-hydroxy group to the corresponding 3β-tosylate derivative and then solvolyzing this tosylate in a suitable buffered solvent mixture, such as methanol/acetone containing sodium acetate, to yield the cyclovitamin product. Sheves and Mazur (J. Am. Chem. Soc. 97, 6249 (1975)) applied this sequence to vitamin D_3, and obtained as major product a cyclovitamin D_3 to which they assigned the structure shown below, i.e. 6R-methoxy-3,5-cyclovitamin D_3. A minor cyclovitamin formed in this process was identified as the corresponding compound with the methoxy in the 6S configuration.

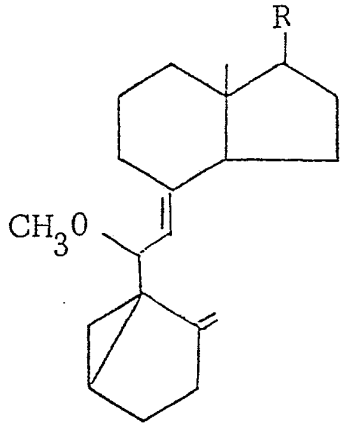
It has now been found that if the solvolysis reaction is carried out in methanol using $NaHCO_3$ buffer, a better yield of cyclovitamin product than that reported by Sheves and Mazur can be obtained.



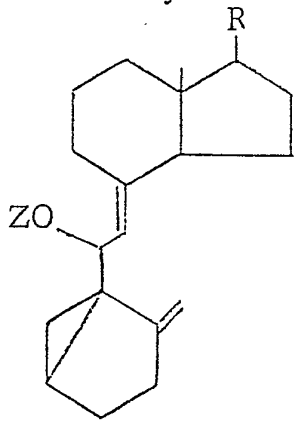
It has also been found that vitamin D compounds carrying other chemically reactive substituents (e.g., side chain hydroxy groups) can be converted efficiently to their cyclovitamin D derivatives. For example, with 25-hydroxyvitamin D_3 as the starting material in the above described process 25-hydroxy-6-methoxy-3,5-cyclovitamin D_3 is observed. The structure of this compound is shown below, where R represents the 25-hydroxycholesterol side chain. Similarly with 24,25-dihydroxyvitamin D_3 as starting material, the above described process leads to 24,25-dihydroxy-6-methyl-3,5-cyclovitamin D_3 represented by the structure shown below where R represents the 24,25-dihydroxycholesterol side chain. With vitamin D_2 as the starting material the same process sequence leads to cyclovitamin D_2, also represented by the structure below but where R signifies the ergosterol side chain. These cyclovitamin D compounds are new compounds.

In analogy with the results of Sheves and Mazur cited earlier, the 6R-methoxy sterochemistry can be assigned to the major cyclovitamin D product obtained in these reactions, and to the minor constituent (5-10%) of the cyclovitamin product mixture the 6S-methoxy configuration. The process of this invention does not require separation of these stereoisomers, it being understood, however, that, if desired, such separation can be accomplished by known methods, and that either C-(6)-epimer can be used although not necessarily with the same process efficiency. For these reasons stereochemical configuration at C-6 of the cyclovitamin D compounds is not designated in the struc-

tures of the specification and the claims.



By appropriate choice of suitable reagents or conditions the process of this invention will yield cyclovitamin D analogs illustrated by the following general structure



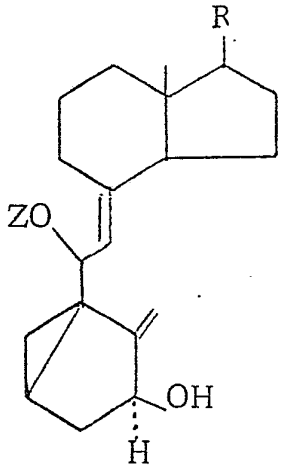
where Z represents hydrogen, alkyl or acyl, and R can represent any of the side chain structure types defined earlier. For example, if ethanol instead of methanol is used in the solvolyzing medium, a cyclovitamin of the structure shown above is obtained, where Z represents ethyl. It is evident that other 0-alkylated cyclovitamin D products can be obtained by the use of the appropriate alcohol in the reaction medium.

Similarly a solvolysis reaction medium composed of solvents containing H_2O, such as acetone/H_2O, or dioxane/H_2O, in the presence of an acetate salt or other buffering agent yields the corresponding cyclovitamin D compound of the formula shown above where Z is hydrogen. Sheves and Mazur (Tetrahedron Letters (No. 34) pp. 2987-29990 (1976)) have in fact prepared 6-hydroxycyclovitamin D_3, i.e. the compound represented by the structure above where Z is hydrogen and R represents the cholesterol side chain, by treating vitamin D_3 tosylate with aqueous acetone buffered with $KHCO_3$.

It has now been found that a 6-hydroxy cyclovitamin, if desired, can be converted to the corresponding acyl derivative (i.e. Z = acyl, such as acetyl or benzoyl) by acylation using standard conditions (e.g. acetic anhydride/pyridine). The acylated cyclovitamin D of the structure shown above, with Z representing acetyl, can also be obtained as a minor product, when the solvolysis reaction is carried out in a medium of dry methanol containing sodium acetate. The cyclovitamin D compound where Z represents methyl is a preferred starting material for subsequent reactions.

In the process of this invention the allylic oxidation is normally carried out in a suitable solvent, such as, for example, CH_2Cl_2, $CHCl_3$, dioxane or tetrahydrofuran, utilizing selenium dioxide as the oxidizing agent. Because of the nature of this oxidation reaction, it is preferable that it be carried out at room temperature or lower temperatures. The oxidation reaction is also

most advantageously conducted in the presence of a hydroperoxide such as tert-butyl hydroperoxide. The oxidation product, i.e. the 1α-hydroxycyclovitamin D compound, is readily recovered from the reaction mixture by solvent extraction (e.g. ether), and is conveniently further purified by chromatography. Other allylic oxidants can be used if desired, it being understood that with such other oxidants variation in product yield may be encountered and that adjustment of the conditions under which the oxidation reaction is carried out may have to be made, as will be evident to those skilled in the art. The products resulting from allylic oxidation of cyclovitamin D compounds of the structure shown above where Z represents lower alkyl (e.g. methyl) are readily illustrated by the following formula

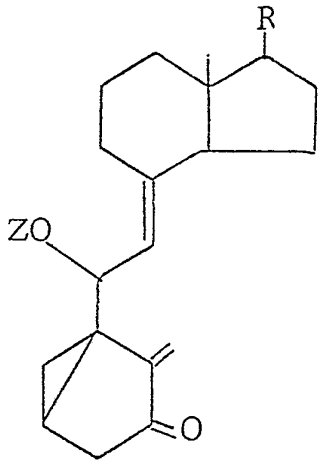


where R represents any of the side chain structures defined earlier, and Z represents lower alkyl (e.g. methyl).

Oxidation of the cyclovitamins by the process of this invention results in the formation of 1-hydroxycyclovitamins processing the 1α-stereochemistry which is

desired, i.e., the stereochemistry of biologically active 1-hydroxylated vitamin D metabolites. The positional and stereochemical selectivity and the remarkable efficiency of the oxidation process is both novel and unexpected and all 1α-hydroxycyclovitamins disclosed are new compounds.

Minor products resulting from selenium dioxide oxidation of cyclovitamin D compounds are 1-oxocyclovitamin D derivatives of the following structure

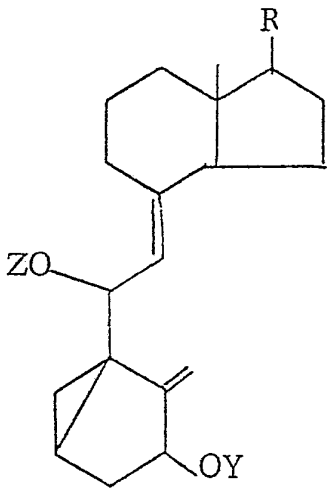


where Z represents lower alkyl and R represents any of the side chain groups defined earlier. These 1-oxocyclovitamin D derivatives are readily reduced by hydride reagents (e.g. $LiAlH_4$ or $NaBH_4$ or equivalent reagents) to form predominantly 1α-hydroxycyclovitamin D derivatives of the formula illustrated previously. The facile reduction of 1-oxocyclovitamin D compounds and especially the predominant formation of 1-hydroxycyclovitamin D compounds possessing the 1α-stereochemistry is an unexpected finding, since mechanistic arguments would have predicted approach of the hydride reducing agent from the less hindered side of the 1-oxocyclovitamin D molecule

which would lead to the predominant function of the 1β-hydroxycyclovitamin epimer.

The acylation of the recovered 1α-hydroxycyclovitamin D compound is conveniently accomplished by standard methods with well-known acylating reagents, acetic anhydride being one example, in a suitable solvent, e.g. pyridine, and is normally conducted at room temperature over a period of several hours, e.g. overnight. The product of acylation is the corresponding 1α-O-acylcyclovitamin D compound, which is conveniently recovered in a purity sufficient for further reactions by solvent (e.g. ether) extraction from the medium with subsequent evaporation of solvents.

Any primary or secondary hydroxyl groups present in the side chain (R) of the 1α-hydroxycyclovitamin D compound can be expected to be acylated also under these conditions. If complete acylation of tertiary hydroxy groups (e.g. the 25-hydroxy groups) is desired, more vigorous acylating conditions are normally required, e.g. elevated temperatures (75-100°C). It is advisable in such cases to conduct the reaction under a nitrogen atmosphere to avoid decomposition of labile compounds. Products of such acylations can be illustrated by the following formula



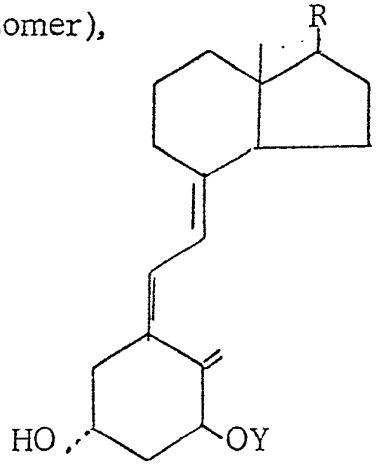
where Y represents a lower acyl group or aromatic acyl group and Z represents lower alkyl and where R can represent any of the steroid side chains defined earlier in this specification, it being understood that secondary or primary hydroxyl groups originally present, will now occur as the corresponding 0-acyl substituent, and any tertiary hydroxy group originally present, may be hydroxy or 0-acyl depending on the condition chosen.

Conversion of the 1α-0-acyl cyclovitamin to the 1α-0-acyl vitamin D derivative is accomplished by acid-catalyzed solvolysis of the cyclovitamin. Thus, warming 1α-0-acyl-cyclovitamin D with p-toluenesulfonic acid, in a suitable solvent mixture (e. g. dioxane/$H_2$0) yields 1α-0-acyl vitamin D compound. Sheves and Mazur used this reaction for the conversion of cyclovitamin D_3 to vitamin D_3 (J. Am. Chem. Soc. 97, 6249 (1975)).

A novel and unexpected surprising finding, not evident from the prior art, was that 1α-0-acyl cyclovitamin D compounds are cleanly converted and in good yield to the

corresponding 1α-0-acyl vitamin by acid solvolysis. This result was completely unpredictable since the allylic 1α-oxygen function of an 1α-hydroxycyclovitamin D compound would be expected to be labile to the solvolysis conditions. Direct solvolysis of the 1α-hydroxycyclovitamin D can be accomplished in the presence of organic carboxylic acids, e.g. acetic, formic, with subsequent recovery of the corresponding 3-0-acyl 1α-hydroxyvitamin D derivative and conversion of such derivative to the corresponding hydroxy compound.

It is also important that any tertiary or allylic alcohol functions that may occur in the side chain be protected as the corresponding acylates or other suitable, acid-stable protecting group. The product 1α-0-acyl vitamin D is readily recovered from the solvolysis mixture by solvent extraction and is further purified by chromatography. The solvolysis reaction yields both 1α-0-acyl vitamin D possessing the natural 5,6-cis double bond geometry, and the corresponding 1α-0-acyl vitamin D with a 5,6-trans geometry, in a ratio of ca. 5:1. These products are readily separated by solvent extraction and chromatography to yield in pure form 1α-0-acyl vitamin D product of the general formula illustrated below (as well as, if desired, the corresponding 5,6-trans-isomer),

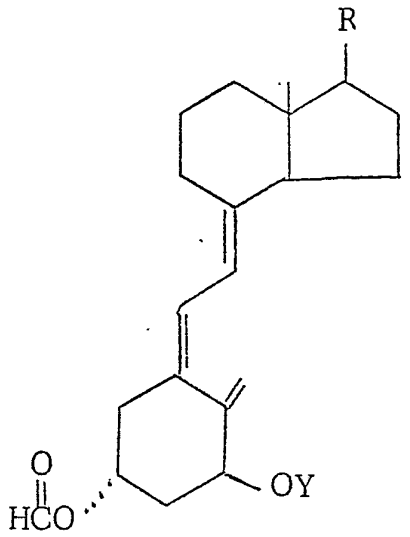


where Y represents a lower acyl group (e. g. acetyl) or aromatic acyl group (e. g. benzoyl) and where R represents any of the steroid side chains defined earlier, it being understood that all hydroxy functions are present as their corresponding 0-acyl derivatives.

1α-0-acyl vitamin D derivatives are readily converted to the desired 1α-hydroxyvitamin D compounds by hydrolytic or reductive removal of the acyl protecting group. The specific method chosen would depend on the nature of the compound, in particular also the nature of the side chain R group and its substituents. It is understood for example that hydride reduction would not be employed, if simultaneous reduction of another function susceptible to reduction, e. g. ketone or ester, is to be avoided, or else such functions would be suitably modified prior to reductive removal of acyl groups. Thus, treatment of the acylated compound with a suitable hydride reducing agent (e. g. lithium aluminum hydride) yields the corresponding 1α-hydroxyvitamin D compound. Similarly mild basic hydrolysis (e. g. KOH/MeOH) converts the acylated compound to the desired 1α-hydroxy derivative, it being understood that in cases where the side chain carries sterically hindered (e. g. tertiary) 0-acyl groups, more vigorous conditions (elevated temperatures, prolonged reaction times) may be required. The 1α-hydroxyvitamin D compound prepared by either method, is readily reacovered in pure form by solvent extraction (e. g. ether) and chromatography and/or crystallization from a suitable solvent.

An alternative and novel method for converting the 1α-0-acyl cyclovitamin D compounds to corresponding vitamin D derivatives consists of acid-catalyzed solvolysis of the cyclovitamin compound in a medium consisting of an organic acid (e.g. acetic acid, formic acid) or of an organic acid with a co-solvent, such as acetone, or dioxane, if required for solubilizing the cyclovitamin. It is a particular advantage of this method that if the side chain group R contains any tertiary hydroxy groups (e.g. the 25-hydroxy group) protection of such functionalities, e.g. as their acyl derivatives, is not necessary. Thus, by way of example, solvolysis of 1α-0-acetoxyvitamin D_3 in glacial acetic acid yields 1α-acetoxy vitamin D_3 3β-acetate, as well as some of the corresponding 5,6-trans-compound (product ratio ca. 3:1). These products can be separated by chromatography or the mixture can be hydrolyzed under basic conditions (such as KOH/MeOH) to yield 1α-hydroxyvitamin D_3 and the corresponding 1α-hydroxy-5,6-trans-5,6-vitamin D_3, which can then be separated by chromatography. This method can be applied to any 1α-0-acyl cyclovitamin D compound possessing any of the side chain groups R defined earlier in this specification.

Even more advantageously, solvolysis of 1α-0-acyl cyclovitamins can be carried out in formic acid or formic acid plus a suitable co-solvent such as dioxane. This process leads to the formation of 1α-0-acyl-vitamin D 3β-formate derivatives, illustrated by the following formula:

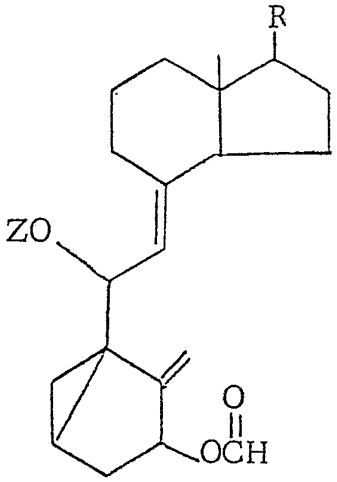


where Y is a lower acyl group (preferably not formyl) or aromatic acyl group and R represents any of the side chain groups defined earlier. Again the corresponding 5,6-trans compound is formed also as a minor product. Since the 3β-O-formyl group is very readily hydrolyzed under conditions where the 1α-O-acyl group is not affected (e.g. by treatment with potassium carbonate in a few minutes, as shown by the specific Examples), the above mixture of 3-O-formyl products are readily converted to 1α-O-acyl vitamin D and its corresponding 5,6-trans isomer. This mixture can be conveniently separated at this stage by chromatographic methods to yield pure 1α-O-acyl vitamin D and the corresponding 5,6-trans-1α O-acyl vitamin D which can now separately be subjected to basic hydrolysis, or to reductive cleavage of the acyl group to yield 1α-hydroxyvitamin D compound, and 5,6-trans-1α-hydroxyvitamin D compound.

Another novel procedure for the conversion of 1α-O-acyl cyclovitamin derivatives to 1α-O-acyl-3β-formyl vitamin D compounds of the formula illustrated above

involves use of "crown ether" catalysts. For example, a two-phase system consisting of formic acid and a hydrocarbon (e. g. hexane/benzene) solution of 1α-0-acyl cyclovitamin D containing a suitable crown ether (e. g. 15-crown-5, Aldrich Chemical Co., Milwaukee) and formate ion, converts the 1α-0-acyl cyclovitamin to the 1α-0-acyl-3β-0-formyl vitamin D derivative in good yield. The corresponding 5,6-trans isomer is formed as a minor product and is conveniently separated by chromatography.

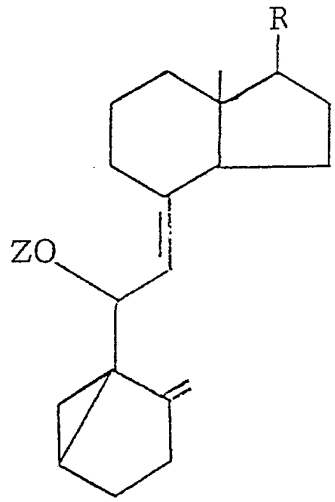
A further variation of the methods just described consists of converting a 1α-hydroxycyclovitamin D compound to the corresponding 1α-0-formyl derivative (e. g. by means of acetic-formic anhydride, in pyridine) represented by the following formula



where R represents any of the side chain groups defined herein before and Z represents lower alkyl, and subjecting this intermediate to solvolysis in glacial acetic acid, as previously described, to obtain, 1α-formyloxy vitamin D 3β-acetate and as a minor product the corresponding 5,6-trans isomer. Removal of the formyl group, as described above, yields 1α-hydroxyvitamin D 3-acetate and its

5,6-trans isomer which are conveniently separated at this stage by chromatography and then separately subjected to hydrolysis or reductive cleavage of the acetates to yield a pure 1α-hydroxyvitamin D compound and its 5,6-trans isomer.

The allylic oxidation process of this invention can also be applied to cyclovitamin D compounds bearing 6-hydroxy or 6-0-acyl groups. Thus, cyclovitamin D compounds of the following structure



where Z represents hydrogen and R represents any of the sidechain groups defined herein before can be oxidized at carbon 1 by the allylic oxidation process of this invention to yield 1α-hydroxy-6-hydroxycyclovitamin D compounds and 1-oxo-6-hydroxycyclovitamin cyclovitamin D compounds. Under the oxidation conditions previously described, some cycloreversion of the 1α-hydroxy-6-hydroxycyclovitamin D compound to a mixture of 5,6-cis and 5,6-trans-1α-hydroxyvitamin D compounds also occurs. All products are readily recovered from the oxidation mixture by chromatography. The 1α-hydroxy-6-hydroxycycyclovitamin D compounds obtained by allylic oxidation can be acylated (e.g. acety-

lated) by the standard process described previously and the resulting 1,6-diacyl cyclovitamin D intermediates are readily converted by acid solvolysis as discussed above to 5,6-cis and 5,6-trans-1α-0-acyl vitamin D compounds which are easily separated by chromatography. Hydrolysis (by known methods) of the 1-0-acyl derivatives leads to the desired 1α-hydroxyvitamin D products and their 5,6-trans isomers respectively. The 1-oxo-6-hydroxycyclovitamin D products are readily reduced by hydride reagents to 1α-hydroxycyclovitamin derivatives.

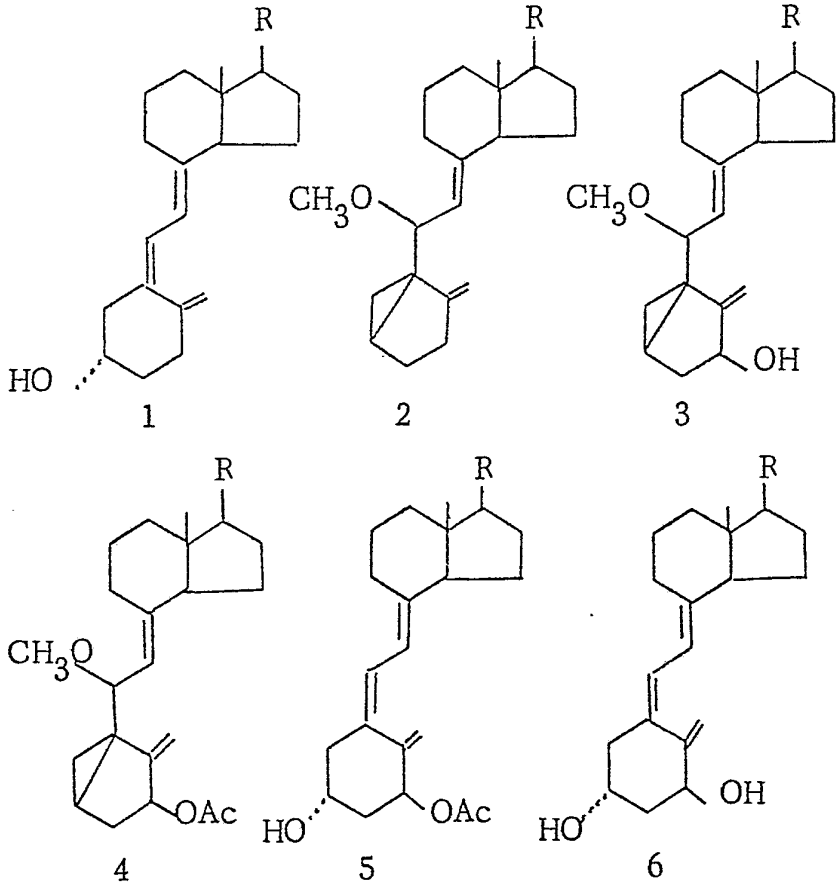
Similarly, cyclovitamin D compounds of the structure shown above where Z represents acyl (e.g. acetyl, benzoyl) and R represents any of the sidechain groups previously defined, can be converted by the sequence of allylic oxidation, acylation, acid solvolysis, and finally hydrolysis of the acyl groups as described for the case of the 6-hydroxy analogues to 1α-hydroxyvitamin D products and their corresponding 5,6-trans isomers.

A further noteworthy and unexpected finding made in the course of this invention is the discovery that 1α-hydroxyvitamin D compounds are readily and efficiently converted to 1α-hydroxycyclovitamin D compounds by solvolysis of the 3β-tosylates (or mesylates) of 1α-hydroxy- or 1α-0-acyl vitamin D derivatives. For example, 1α-acetoxyvitamin D_3 3-tosylate, upon solvolysis using conditions described herein before, e.g. heating in methanol solvent containing $NaHCO_3$, yields 1α-hydroxy-6-methoxy-3,5-cyclovitamin D_3. Oxidation of this product (e.g. with MnO_2 in CH_2Cl_2 solvent) yields the correspond-

-ing 1-oxo-6-methoxy-3,5-cyclovitamin D_3 analog as described in the specific examples.

Best Mode for Carrying Out the Invention

In the following examples, which are intended to be illustrative only, the numbers identifying particular products, e.g. 3a for 1α-hydroxycyclovitamin D_3, correspond to the numbers designating the various structures for such products as set forth below.



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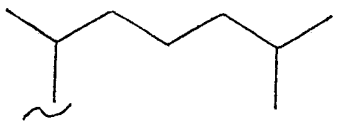

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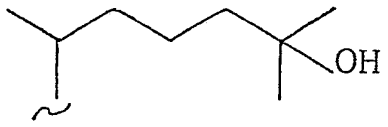

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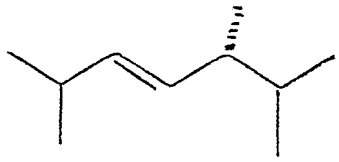
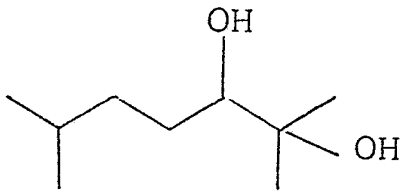
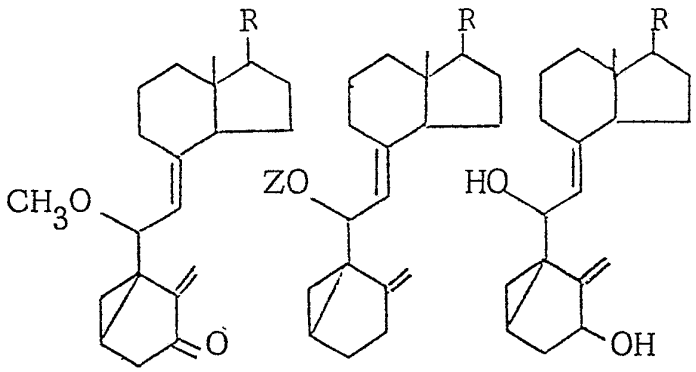


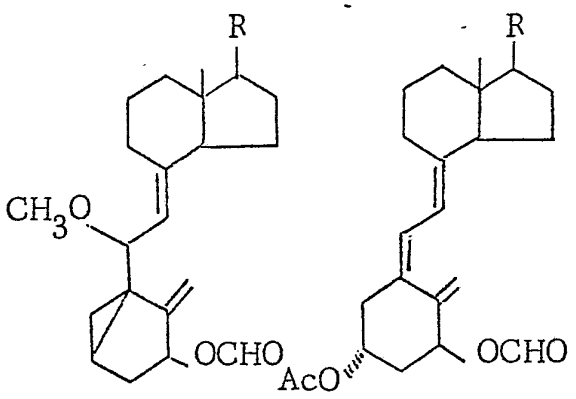
d: R =



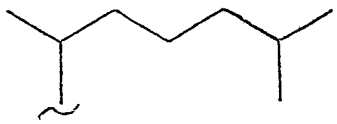


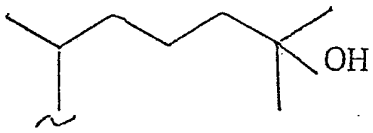
7 8 Z = H 10

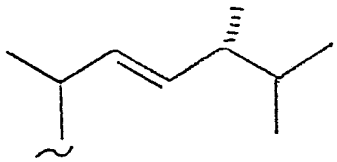
9 Z = Ac

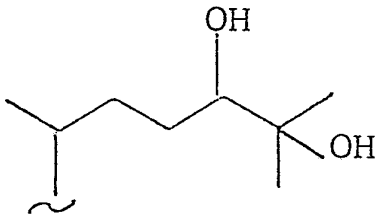


11 12

a: R = 

b: R = 

c: R = 

d: R = 

Example 1

1α-Hydroxycyclovitamin D_3 (3a) and 1-oxo-cyclovitamin D_3 (7a):

To a stirred suspension of 1.4 mg (1.2×10^{-5} moles) of SeO_2 in 1.0 ml of dry CH_2Cl_2 is added 7 µl (5.1×10^{-5} moles) of a 70% solution of tert. butyl hydroperoxide (t-BuOOH). After stirring for 25 min a solution of 9 mg (2.3×10^{-5} moles) of 3,5-cyclovitamin D_3 (compound 2a, prepared from vitamin D_3 (1a) by the method of Sheves & Mazur, J. Am. Chem. Soc. 97, 6249 (1975)) in 0.5 ml of CH_2Cl_2 is added dropwise. The mixture is stirred at room temperature for an additional 25 min. Then 2.0 ml of 10% NaOH is added, and this resulting mixture is diluted with 15 ml of diethylether. The organic phase is separated and washed successively with 10% NaOH (2 x 10 ml), H_2O (2 x 10 ml), sat. $FeSO_4$ (3 x 10 ml), and sat. NaCl (15 ml); and then dried over $MgSO_4$. Removal of solvent in vacuo yields a crude oily product that after chromatography on a silica gel thin layer plate (10 x 20 cm, 750 µm) developed in 30% ethylacetate: Skellysolve B yields 4.5 mg (43% yield) of a 1α-hydroxy-3,5-cyclovitamin D_3 (3a): mass spectrum: (m/e) 414(30), 382(70), 341(35), 269(20), 247(45), 174(25), 165(30), 135(65); NMR, δ, 0.53 (3H, s, 18-H_3), 0.61 (2H, m, 4-H_2), 0.87 (6H, d, 26-H_3 and 27-H_3), 0.92 (3H, d, 21-H_3), 3.26 (3H, s, 6-OCH_3), 4.18 (1H, d, J=9.0 Hz, 6-H), 4.22 (1H, m, 1-H), 4.95 1H, d, J=9 Hz, 7-H), 5.17 (1H, d, J=2.2 Hz, 19(Z)-H), 5.25 (1H, d, J=2.2 Hz, 19(E)-H).

As a minor component 2.0 mg (19% yield) of 1-oxo-

cyclovitamin D_3 (7a) was isolated from the reaction mixture: mass spectrum: (m/e) 412 (40), 380 (50), 267 (15), 247 (23), 135 (50), 133 (100); NMR, δ, 0.49 (3H, s, 18-H_3), 0.58 (2H, m, 4-H_2), 0.87 (6H, d, 26-H_3), 0.93 (3H, d, 21-H_3), 3.30 (3H, s, 6-OCH_3), 4.07 (1H, d, J=9.0 Hz, 6-H), 5.02 (1H, d, J=9.0 Hz, 7-H), 5.62 (1H, s, 19(Z)-H), 6.04 (1H, s, 19(E)-H); UV 248 (4,000).

Example 2

1α-Acetoxy-cyclovitamin D_3 (4a):

Compound 3a (1.5 mg) is dissolved in 200 µl of dry pyridine and 50 µl of acetic anhydride. The reaction is kept at room temperature overnight, then diluted with 5 ml of sat. $NaHCO_3$ solution. This solution is extracted with three 5 ml portions of ether and the organic extracts are washed with H_2O (2 x 10 ml), dried over $MgSO_4$, and the solvent is removed in vacuo to give compound 4a: NMR, δ, 0.53 (3H, s, 18-H_3), 0.69 (2H, m, 4-H_2), 0.87 (6H, d, 26-H_3 and 27-H_3), 0.92 (3H, d, 21-H_3), 2.10 (3H, s, 1-OAc), 3.26 (3H, s, 6-OCH_3), 4.18 (1H, d, J=9.2 Hz, 6-H), 4.98 (1H, d, J=9.2 Hz, 7-H), 4.98 (1H, d, J=2.1 Hz, 19(Z)-H), 5.23 (1H, m, 1-H), 5.25 (1H, d, J-2.1 Hz, 19(E)-H).

Example 3

1α-Hydroxyvitamin D_3 (6a):

A solution of 1.3 mg of (4a) in 0.5 ml of a 3:1 mixture of 1,4-dioxane and H_2O is heated to 55°, 0.2 mg of p-toluenesulfonic acid in 4 µl of H_2O is added and heating is continued for 0.5 hr. The reaction is then quenched with 2 ml of sat. $NaHCO_3$ and extracted with two 10 ml portions

of ether. The organic extracts are dried over $MgSO_4$ and the solvent removed in vacuo. The crude product is then applied to a 10 x 20 cm silica gel plate developed in 30% EtOAc: Skellysolve B to yield 400 μg of product 5a: UV, λ_{max} 264 nm; mass spectrum, m/e 442 (M^+, 75), 382 (70), 269(15), 134(100); NMR, δ, 0.52 (3H, s, 18-H_3), 0.86 (6H, d, J=5.5 Hz, 26-H_3 and 27-H_3), 0.91 (3H, d, J=5.9 Hz, 21-H_3), 2.03 (3H, s, 1-$OCOCH_3$), 4.19 (1H, m, 3-H), 5.04 (1H, d, J=1.5 Hz, 19(Z)-H), 5.31 (1H, m(sharp), 19(E)-H), 5.49 (1H, m, 1-H), 5.93 (1H, d, J=11.4 Hz, 7-H), 6.37 (1H, d, J=11.4 Hz, 6-H).

Product 5a is taken up in 0.5 ml of ether and treated with excess $LiAlH_4$. The reaction is quenched with sat. NaCl solution and product is isolated by filtration and evaporation of the solvent in vacuo. The single product (6a) co-chromatographs with a standard sample of 1α-hydroxyvitamin D_3 in 97:3 $CHCl_3$: CH_3OH (1α-hydroxyvitamin D_3 R_f = 0.10, 1β-hydroxyvitamin D_3 R_f = 0.15, reaction product (6a), R_f = 0.10). This product possesses λ_{max} = 264 nm and a mass spectrum and nmr spectrum identical to that of authentic 1α-hydroxyvitamin D_3.

Example 4

25-Hydroxycyclovitamin D_3 (2b):

A solution of 100 mg of 25-hydroxyvitamin D_3 (1b) and 150 mg of p-toluene-solfonyl chloride in 0.5 ml of dry pyridine is allowed to react for 24 hr at 3°, and is then quenched with 5 ml of sat. $NaHCO_3$. The aqueous phase is extracted with ether (2 x 10 ml) and the ether extract is washed with sat. $NaHCO_3$ (3 x 10 ml), 3% HCl (2 x 10 ml),

and H_2O (2 x 10 ml) and then dried over $MgSO_4$. The solvent is removed in vacuo and the crude residue (25-hydroxyvitamin D_3 3-tosylate) is taken up in 1.5 ml of anhydrous methanol and 0.3 ml of anhydrous acetone; 170 mg (8 eq.) of NaOAc is added and the solution is warmed to 55° for 20 hr. The mixture is cooled, diluted with 10 ml of H_2O and extracted with 3 x 10 ml of ether. The organic extracts are washed with three 10 ml portions of H_2O, dried over $MgSO_4$, and the solvent is removed in vacuo. This crude residue is applied to a 20 cm x 20 cm silica gel TLC plate (750μm thick) which is developed once in a Skellysolve B:ethyl acetate (8:2) system to yield 48 mg (45% overall yield from 1b) of (2b): mass spectrum, m/e: 414 (M^+, 40), 399(10), 382(80), 253(50), 59(100); NMR, δ, 0.53 (3H, s, 18-H_3), 0.74 (2H, m, 4-H_2), 0.94 (3H, d, J=6.2 Hz, 21-H_3), 1.21 (6H, s, 26-H_3 and 27-H_3), 3.25 (3H, s, 6-OCH_3), 4.16 (1H, d, J=9.2 Hz, 6-H), 4.89 (1H, m(sharp), 19(Z)-H), 4.99 (1H, d, J=9.3 Hz, 7-H), 5.04 (1H, m(sharp), 19(E)-H).

Example 5

1α,25-Dihydroxycyclovitamin D_3 (3b) and 1-oxo-hydroxycyclovitamin D_3 (7b):

A mixture of 2.45 mg (0.5 eq.) of SeO_2, 14 μl (2 eq.) of t-BuOOH and 1.2 ml of dry CH_2Cl_2 is allowed to react at room temperature for 30 min. A solution of the cyclovitamin (2b) in 0.5 ml of CH_2Cl_2 is added dropwise to this oxidizing medium, and the reaction is continued for 15 min. The reaction is then quenched with 2.0 ml of 10% NaOH and diluted with 20 ml of diethyl ether. The organic

phase is separated and washed successively with 10% NaOH, H_2O, sat. $FeSO_4$ solution, sat. $NaHCO_3$, and again with H_2O, and then dried over $MgSO_4$. The solvent is removed in vacuo and the crude residue is applied to a silica gel thin layer plate (20 cm x 20 cm, 750 μm thick), which is developed in a Skellysolve B:ethyl acetate (6:4) system to yield 11 mg (53% yield) of (3b): mass spectrum: m/e 430(M^+, 15), 412(12), 380(35), 269(10), 59(100); NMR, δ, 0.53 (3H, s, 18-H_3), 0.61 (2H, m, 4-H_2), 0.93 (3H, d, J=6.2 Hz, 21-H_3), 1.21 (6H, s, 26-H_3 and 27- H_3), 3.25 (3H, s, 6-OCH_3), 4.17 (1H, d, J=9.2 Hz, 6-H), 4.20 (1H, m, 1-H), 4.95 (1H, d, J=9.2 Hz, 7-H), 5.19 (1H, d, J=1.9 Hz, 19(Z)-H), 5.22 (1H, d, J=1.9 Hz, 19(E)-H). As a minor component 1- oxo-25-hydroxycyclovitamin D_3 (7b) was isolated (15%) from the reaction mixture. Mass spectrum: m/e 428 (M^+).

Example 6

1α,25-Dihydroxycyclovitamin D_3-1,25-diacetate (4b-25-OAc):

A solution of 7 mg of (3b) in 200 μl of dry pyridine is treated with 10 μl of acetic anhydride. The system is flushed with N_2 and heated to 97° for 16.0 hr. After cooling, the mixture is diluted with 5 ml of sat. $NaHCO_3$. The aqueous mixture is extracted with two 10 ml portions of ether and the organic phase is washed successively with two 10 ml portions of sat. $NaHCO_3$, and then with 10 ml of H_2O. After drying over $MgSO_4$, the solvent and residual pyridine are removed by azeotropic distillation with benzene in vacuo. The crude product is then applied to a

silica gel thin layer plate (10 cm x 20 cm, 750 μm thick) developed in Skellysolve B:ethyl acetate (8:2) to yield 6 mg (72%) of the diacetate (4b, 25-OAc) and 1.2 mg of the corresponding 3-acetoxy-25-hydroxy derivative.

Example 7

1α,25-Dihydroxyvitamin D_3-1,25-diacetate (5b,25-OAc):

To 3.8 mg of (4b,25-OAc), dissolved in 400 μl of dioxane:H_2O (3:1) and warmed to 55°, is added 8 μl of a solution of p-toluene sulfonic acid in H_2O and heating is continued for 10 min. The reaction is quenched with sat. $NaHCO_3$ and extracted with two 10 ml portions of ether. The ether solution is washed with two 10 ml portions of H_2O and dried over $MgSO_4$. The solvent is removed in vacuo, and the residue is applied to a silica gel thin layer plate (5 x 20 cm, 250 μm thick) which is developed in Skellysolve B:ethyl acetate (8:2) to yield 1.8 mg (45%) of (5b,25-OAc): UV; λ_{max} 265 nm; mass spectrum: m/e 500(M^+, 25), 440(55), 422(15), 398(10, 380(45), 134(100); NMR, δ, 0.52 (3H, s, 18-H_3), 0.92 (3H, d, J=6.2 Hz, 21-H_3), 1.42 (6H, s, 26-H_3 and 27-H_3), 1.97 (3H, s, 25-$OCOCH_3$); 2.03 (3H, s, 1-$OCOCH_3$), 4.18 (1H, m, 3-H), 5.03 (1H, d, J=1.1 Hz, 19(Z)-H), 5.31 (1H, m(sharp), 19(E)-H), 5.49 (1H, m, 1-H), 5.93 (1H, d, J=11.4 Hz, 7-H), 6.37 (1H, d, J-11.4 Hz, 6-H).

Example 8

1α,25-Dihydroxyvitamin D_3 (6b):

To a stirred solution of 1.0 mg of the diacetate, (5b, 25-OAc) in 1.5 ml of ether is added 0.5 ml of an ether solution saturated with $LiAlH_4$. After 10 min at room temperature, the reaction is quenched with sat. NaCl

solution and the salts are dissolved by addition of 3% HCl. The aqueous phase is extracted with ether and the ether extracts are washed with H_2O and dried over $MgSO_4$. Thin layer chromatography (5 x 20 cm silica gel plates, 250 μm thick) using 5% MeOH: $CHCl_3$ yields 0.6 mg (70%) of 1α,25-dihydroxyvitamin D_3 (6b), exhibiting a UV-spectrum with λ_{max} 265 nm. The identity of 6b as 1α,25-dihydroxyvitamin D_3 is established by direct comparison of mass and nmr spectra with those of authentic material, as well as by co-chromatography of 6b with authentic 1α,25-dihydroxyvitamin D_3.

Example 9

Cyclovitamin D_2 (2c):

A solution of 100 mg of vitamin D_2 (1c) and 100 mg of p-toluenesulfonyl chloride in 0.3 ml of pyridine is allowed to react for 24 hr at 3°, and is then quenched with 10 ml of sat. $NaHCO_3$. The aqueous mixture is extracted with two 10 ml portions of ether and the ether extract is washed successively with sat. $NaHCO_3$ (3 x 10 ml), 3% HCl (2 x 10 ml), and H_2O (2 x 10 ml), and is then dried over $MgSO_4$. The solvent is removed in vacuo and the crude vitamin D_2-3-tosylate is taken up in 1.5 ml of anhydrous methanol and 0.3 ml of anhydrous acetone. After addition of 170 mg of sodium acetate, the solution is warmed to 55° for 20 hr. After cooling, the solution is diluted with 10 ml of H_2O and extracted with three 10 ml portions of ether. The organic extracts are washed with three 10 ml portions of H_2O, dried with $MgSO_4$, and the solvent is removed in vacuo. The residue is chromatographed on a silica gel

thin layer plate (20 x 20 cm, 750 μm) in Skellysolve B:ethyl acetate (8:2) to yield 60 mg (59%) of (2c): mass spectrum: m/e 410(M^+, 15), 378(40), 253(40), 119(60); NMR, δ, 0.55 (3H, s, 18-H_3), 0.74 (2H, m, 4-H_2), 0.82 and 0.84 (6H, dd, J-4.1 Hz, 26-H_3 and 27-H_3), 0.91 (3H, d, J=7.0 Hz, 21-H_3), 1.02 (3H, d, J=6.6 Hz, 28-H_3), 3.26 (3H, s, 6-OCH_3), 4.13 (1H, d, J=9.6 Hz, 6-H), 4.89 (1H, m, 19 (Z)-H), 5.00 (1H, d, J=9.4 Hz, 7-H), 5.04 (1H, m(sharp), 19(E)-H), 5.20 (2H, m, 22-H and 23-H).

Example 10

1α-Hydroxycyclovitamin D_2 (3c) and 1-oxo-cyclovitamin D_2 (7c):

A mixture of 2.7 mg of SeO_2 and 13.4 μl of 70% t-BuOOH, in 1.5 ml of dry CH_2Cl_2, is allowed to react for 30 min. Compound 2c (30 mg) in 0.5 ml of CH_2Cl_2 is then added dropwise, the reaction is continued for 15 min, and then quenched with 2.0 ml of 10% NaOH. The solution is diluted with 15 ml of ether, the ether phase is separated and washed successively with 10% NaOH, H_2O, sat. $FeSO_4$ solution, sat. $NaHCO_3$, and again with H_2O. After drying over $MgSO_4$, the solvent is removed in vacuo, and the residue is applied to a silica gel thin layer plate (20 x 20 cm, 750 μm) which is developed once in Skellysolve B:ethyl acetate (8:2) system to yield 9.5 mg (45%) of (3c): mass spectrum: m/e 426 (M^+, 55), 394(75), 353(30), 269(40), 135(95); NMR, δ, 0.53 (3H, s, 18-H_3), 0.63 (2H, m, 4-H_2), 0.82 and 0.84 (6H, dd, 26-H_3 and 27-H_3), 0.92 (3H, d, J=6.0 Hz, 21-H_3), 1.02 (3H, d, J=6.4 Hz, 28-H_3), 3.26 (3H, s, 6-OCH_3), 4.18 (1H, d, J=9.6 Hz, 6-H), 4.21 (1H, m, 1-H), 4.94 (1H, d, J=9.6 Hz, 7-H), 5.17 (1H, m(sharp),

19(Z)-H), 5.19 (2H, m, 22-H and 23-H), 5.24 (1H, m (sharp), 19(E)-H). A second minor component isolated from the reaction mixture proved to be 1-oxo-cyclovitamin D_2 (7c): mass spectrum, m/e 424 (M^+).

Example 11

1α-Hydroxycyclovitamin D_2-1-acetate (4c):

To 6.5 mg of (3c) in 300 µl of dry pyridine is added 150 µl of acetic anhydride. This solution is heated to 55° for 1.5 hr, then diluted with 5 ml of sat. $NaHCO_3$ and extracted with two 10 ml portions of ether. The organic extracts are washed with sat. $NaHCO_3$, and H_2O, dried over $MgSO_4$ and the residual pyridine and solvent is removed by azeotropic distillation with benzene in vacuo, to yield compound 4c: mass spectrum: m/e 468(M^+, 40), 408(20), 376(65), 251(60), 135(100).

Example 12

1α-Hydroxyvitamin D_2-1-acetate (5c):

A solution of 5.0 mg of (4c) in 400 µl of dioxane: H_2O (3:1) is heated to 55°; 12 µl of an aqueous solution of p-toluenesulfonic acid (50 µg/µl) is added and heating is continued for 10 min. The reaction is then quenched with sat. $NaHCO_3$ and extracted with two 10 ml portions of ether. The separated ether phase is washed with 10 ml of sat. $NaHCO_3$ and two 10 ml portions of H_2O dried over $MgSO_4$, and the solvent is removed in vacuo. Preparative thin layer chromatography on silica gel (Skellysolve B: ethyl acetate, 8:2) gives 1.6 mg of 5c (32% yield): UV; λ_{max} 265 nm; mass spectrum: m/e 454(M^+, 80), 394 (80), 376(20), 269(40), 135(100); NMR, δ, 0.53 (3H, s, 18-H_3), 0.81 and 0.84 (6H, d, J=4.4 Hz, 26-H_3 and 27-H_3),

0.91 (3H, d, J=7.0 Hz, 21-H_3), 1.01 (3H, d, J=6.7 Hz, 28-H_3), 2.03 (3H, s, 3-$OCOCH_3$), 4.18 (1H, m, 3-H), 5.03 (1H, d, J=1.5 Hz, 19(Z)-H), 5.19 (2H, m, 22-H and 23-H), 5.3 (1H, m(sharp), 19(E)-H), 5.48 (1H, m, 1-H), 5.92 (1H, d, J=11.0 Hz, 7-H), 6.37 (1H, d, J=11.0 Hz, 6-H).

Example 13

1α-Hydroxyvitamin D_2 (6c):

A solution of 1.1 mg of (5c) in 1.5 ml of ether is treated with 0.5 ml of an ether solution saturated with $LiAlH_4$. After 10 min at room temperature the reaction is quenched with sat. NaCl and the salts dissolved in 3% HCl. This aqueous solution is extracted with ether and the organic extracts are washed with water and dried over $MgSO_4$. TLC on 250 μ thick, 5 x 20 cm, plates in 5% methanol: chloroform yields 0.8 mg (75% yield) of 1α-hydroxyvitamin D_2: UV: λ_{max} 265 nm; mass spectrum: m/e 412(M^+), 394, 376, 287, 269, 251, 152, 134 (base peak); NMR: δ, 0.56 (3H, s, 18-H_3), 0.82 and 0.84 (6H, dd, J=4.4 Hz, 26-H_3 and 27-H_3), 0.92 (3H, d, J=6.6 Hz, 21-H_3), 1.02 (3H, d, J=6.6 Hz, 28-H_3), 4.23 (1H, m, 3-H), 4.42 (1H, m, 1-H), 5.00 (1H, m(sharp), 19(Z)-H), 5.20 (2H, m, 22-H and 23-H), 5.32 (1H, dd, J=1.4 Hz, 19(E)-H), 6.02 (1H, d, J=11.1 Hz, 7-H), 6.38 (1H, d, J=11.6 Hz, 6-H). These spectral data are in full accord with data obtained for 1α-hydroxyvitamin D_2, prepared by an entirely different method (Lam et al. Science, 186, 1038-1040 (1974)).

Example 14

Solvolysis of 1α-Acetoxycyclovitamin D in Acetic Acid:

A solution of 3.0 mg of 1α-hydroxycyclovitamin D_3-

1-acetate (4a) in 200 µl of glacial acetic acid is warmed to 55° for 15 min and subsequently quenched with ice-cold sat. $NaHCO_3$. The aqueous mixture is extracted with diethylether and the organic phase is washed with sat. $NaHCO_3$ and water, dried over $MgSO_4$, and filtered to yield a solution of 5,6-cis and 5,6-trans-1α-acetoxy-vitamin D_3 3-acetates (UV: λ_{max} 267-269 nm). The dried ether solution is treated with a small amount (1.0 mg) of lithium aluminum hydride, quenched with sat. NcCl, filtered and the solvent is removed in vacuo. The crude oil is applied to a 5 x 20 cm silica gel tlc plate (250 µm thick) which is developed in 5% methanol:chloroform to yield 1.6 mg of a mixture (UV, λ_{max} 267-269 nm) of 1α-hydroxyvitamin D_3 (6a) and the corresponding 5,6-trans isomer (5,6-trans-1α-hydroxyvitamin D_3) in a ratio of 3:1 as determined by NMR analysis: Characteristic resonances for the cis isomer (6a): δ, 6.38 and 6.01 (d, J-11.4 Hz, 6-H and 7-H), 5.33 (dd, J-1.5 Hz, 19(E)-H), 5.01 (sharp m, 19(Z)-H), 0.54 (s, 18-H_3); for the 5,6-trans isomer: 6.58 and 5.88 (d, J=11.4 Hz, 6-H and 7-H), 5.13 (d, J=1.4 Hz, 19(E)-H), 4.98 (sharp m, 19(Z)-H), 0.56 (s, 18-H_3).

The same procedure may be used to effect the cleavage of the cycloprane ring (cycloreversion) of other cyclovitamins or their C-1-oxygenated analogs. Thus heating 1α-acetoxy-25-hydroxyvitamin D_3 (compound 4b, no protecting group required for 25-OH function) in glacial acetic acid as described above, yields 1α-acetoxy-25-hydroxyvitamin D_3 3-acetate as the major product (plus

some of the corresponding 5,6-trans isomer, as minor product) and this mixture may be directly hydrolyzed (MeOH/KOH) or subjected to hydride reduction as described above, to yield 1α,25-dihydroxyvitamin D_3 as the major product and 5,6-trans-1α,25-dihydroxyvitamin D_3 as a minor product.

Example 15

Formic Acid Catalyzed Solvolysis of 1α-Acetoxycyclovitmain D_3:

A solution of the 1α-acetoxycyclovitamin D_3 (4a) in dry dioxane is warmed to 55° and treated with a 1:1 solution of 98% formic acid:dioxane (50 µl/mg cyclovitamin) for 15 min. The reaction is then quenched with ice-water and extracted with ether. The ether extracts are washed with water, sat. $NaHCO_3$, sat. NaCl, dried over $MgSO_4$, and the solvent removed in vacuo. The crude product (1α-acetoxy-3β-formylvitamin D_3 and its 5,6-trans isomer) is dissolved in a 1:1 solution of dioxane:methanol and an equivalent amount of aqueous K_2CO_3 (10 mg/100 µl) is added. After 5 min at room temperature, the solution is diluted with water and extracted repeatedly with ether. The ether extracts are washed with water, dried over $MgSO_4$, and the solvent is removed in vacuo. The crude cis and trans mixture of 1-acetoxy-3-hydroxyvitamins is then chromatographed on a 10 x 20 cm, 750 µm thick silica gel plate in 1:3 ethyl acetate:Skellysolve B to yield the pure cis-1α-acetoxyvitamin D_3. Basic hydrolysis, (NaOH in methanol) yields a product which is chromatographically and spectrally identical to an authentic sample of 1α-

hydroxyvitamin D_3.

Example 16

Cyclovitamin D_3 (2a) by $NaHCO_3$-Buffered Solvolysis of Vitamin D_3-Tosylate:

To a suspension of 170 mg of vitamin D_3-tosylate in 6.0 ml of anhydrous methanol is added 213 mg (8.0 eq.) of $NaHCO_3$. The system is flushed with nitrogen and heated to 58° for 20 hr. The reaction is then diluted with sat. NaCl solution, transferred to a separatory funnel and extracted with 2 x 10 ml portions of Et_2O. The organic extracts are washed with 1 x 10 ml portion of sat. NaCl and dried over $MgSO_4$. After removal of the solvent in vacuo, the oily residue is chromatographed on a 750 μm, 20 x 20 cm silica gel prep plate in ethyl acetate:Skellysolve B 2:8 to yield 94 mg (75%) of cyclovitamin D_3 (2a).

Example 17

6-Hydroxy-cyclovitamin D_3 (8a):

A solution of 100 mg of vitamin D_3, 100 mg of TsCl and 500 μl of dry pyridine is kept at 5° for 24 hr then diluted with ether and washed several times with sat. $NaHCO_3$. The organic layer is dried over $MgSO_4$ and the solvent is removed in vacuo. The crude D_3-tosylate is suspended in 4.0 ml of acetone:H_2O 9:1 along with 175 mg (8eq.) of $NaHCO_3$. The resulting mixture is heated at 55° overnight, diluted with sat. NaCl and extracted twice with ether. The ether extract is washed once with water, dried over $MgSO_4$, and the solvent removed in vacuo. Preparative TLC (20 x 20 cm, 750 μm, 8:2 Skellysolve B:

ethyl acetates yields 55 mg of the 6-hydroxy-3,5-cyclo-vitamin D_3 (8a); mass spectrum, m/e 384 (M^+), 366, 253, 247.

Example 18

6-Acetoxycyclovitamin D_3 (9a):

To a solution of 300 µl of dry pyridine and 200 µl of Ac_2O is added 6 mg of 6-hydroxy-cyclovitamin D_3 (8a) in 200 µl of pyridine. The reaction is warmed at 55° for 2.0 hr under N_2 then diluted with a large excess of toluene. The solution is evaporated to dryness at 40° in vacuo to yield the crude 6-acetoxycyclovitamin D_3 (9a); mass spectrum, m/e 426 (M^+).

Example 19

Hydride Reduction of 1-oxo-cyclovitamin D_3 (7a) to 3a:

A solution of 2.0 mg of 1-oxo-cyclovitamin D_3 in 500 µl of ether is treated with 300 µl of ether saturated with $LiAlH_4$. After 30 min the reaction is carefully quenched by the dropwise addition of sat. NaCl. The insoluble salts are removed by filtration and the filtrate is dried over $MgSO_4$. The solvent is removed in vacuo to yield 1.7 mg of a 95:5 mixture of 1α-hydroxycyclovitamin D_3 (3a) and the corresponding 1β-hydroxycyclovitamin D_3 isomer, which are separated by chromatography. Similar treatment of 1-oxo-cyclovitamin D_3 with 300 µl of 100% ethanol saturated with $NaBH_4$ yields an 8:2 mixture of 1α-hydroxy and 1β-hydroxycyclovitamin D_3 compounds (3a and its 1β-epimer).

Example 20

SeO_2/t-BuOOH Oxidation of 6-Hydroxy Cyclovitamin D_3 (8a):

To a stirring suspension of 2.0 mg of SeO_2 in 1.5 ml dry CH_2Cl_2 is added 10 µl of 70% t-BuOOH. When homogeneous, a solution of 14 mg of 6-hydroxy-cyclovitamin D_3 (8a) in 500 µl of dry CH_2Cl_2 is added dropwise and the reaction is continued for 1.5 hr at room temperature. The reaction is quenched with 10% NaOH, diluted with ether, washed with 10% NaOH and water, dried over $MgSO_4$, and the solvent removed in vacuo. The crude oily residue is chromatographed (10 x 20 cm, 750 µm, 1:1 ethyl acetate:Skellysolve B) to yield 1.5 mg (10%) 1-oxo-6-hydroxy-cyclovitamin D_3: mass spectrum, (m/e), 398 (35), 380 (25), 247 (25), 135 (40), 133 (100); 2.0 mg (15%) of 1α,6-dihydroxy cyclovitamin D_3 (10a): mass spectrum; (m/e), 400 (50), 382 (80), 269 (20), 247 (40), 135 (80), 133 (40); and 2.0 mg (15%) of 1α-hydroxy-vitamin D_3 (6a), and the corresponding 1α-hydroxy-5,6-trans isomer.

Example 21

Conversion of 1α,6-dihydroxy-cyclovitamin D_3 (10a) to 1α-Hydroxyvitamin D_3 (6a):

A solution of 400 µl dry pyridine, 200 µl acetic anhydride, and 2.0 mg of 1α,6-dihydroxy-cyclovitamin D_3 (10a) is warmed to 55° for 2.0 hr. The reaction is then diluted with toluene and stripped to dryness. The resulting oil (1α,6-diacetoxy-cyclovitamin D_3) is taken up in 100 µl of THF and treated with 200 µl of 97% HCO_2H for

15 min at 55°. Dilution with sat. NaCl, extraction with ether, washing with sat. $NaHCO_3$, drying over $MgSO_4$, and removal of the ether in vacuo gives the crude 1-acetoxy-3-formate cis- and trans- vitamin derivatives. Selective formate hydrolysis with K_2CO_3 followed by chromatography yields pure 1α-acetoxyvitamin D_3 (5a) which is converted to 1α-hydroxyvitamin D_3 (6a) by simple KOH/MeOH hydrolysis.

Example 22

24(R),25-Dihydroxy-cyclovitamin D_3 (2d):

To 150 µl of dry pyridine is added 10.4 mg of 24R,25-$(OH)_2D_3$ and 7.13 mg (1.5 eq.) of TsCl. The reaction is maintained at 0° for 72 hr then diluted with sat. $NaHCO_3$ and extracted with ether. After washing the ether extract with sat. $NaHCO_3$, drying over $MgSO_4$, and removing the solvent in vacuo, the crude tosylate (~70% by TLC) is suspended in 2 ml of anhydrous MeOH along with 25 mg of $NaHCO_3$ and heated under N_2 at 58° for 20 hr. The reaction is then diluted with sat. NaCl and extracted with ether. The ether extracts are washed with water, dried over $MgSO_4$ and the solvent removed in vacuo. Preparative TLC (10 x 20 cm, 750 µm silica gel, 6:4 Skellysolve B: ethyl acetate) yields 2.5 mg of recovered 24R,25-$(OH)_2D_3$ and 4.4 mg of 24R,25-dihydroxy-cyclovitamin D (2d): mass spectrum, (m/e), 430 (15), 398 (65), 253 (40), 159 (45), 119 (55), 59 (100); NMR, δ, 0.55 (3H, s, 18-H_3), 0.74 (2H, m, 4-H_2), 0.94 (3H, d, J=6.2 Hz, 21-H_3), 1.17 (3H, s, 26-H_3), 1.22 (3H, s, 27-H_3), 3.26 (3H, s, 6-OCH_3), 3.34 (1H, m, 24-H), 4.17 (1H, d, J=9.0 Hz, 6-H),

4.88 (1H, m(sharp), 19(Z)-H), 5.00 (1-H, d, J=9.0 Hz, 7-H), 5.04 (1H, m(sharp), 19(E)-H).

Example 23

1α,24(R),25-Trihydroxy-cyclovitamin D_3 (3d):

To a previously prepared solution of 1.12 mg SeO_2 and 12 µl of 70% t-BuOOH in 1.0 ml of dry CH_2Cl_2 is added 4.2 mg of 24R,25-dihydroxy-cyclovitamin D_3 in 500 µl of CH_2Cl_2. After 30 min an additional portion of 1.12 mg SeO_2 and 12 µl 70% t-BuOOH, in 500 µl of CH_2Cl_2 is added and the reaction continued for an hour longer. The reaction is quenched with 10% NaOH, diluted with ether, and washed twice with 10% NaOH followed by a water wash. The organic solution is dried over $MgSO_4$, the solvent removed in vacuo, and the resulting oil is chromatographed on a 5 x 20 cm, 250 µm silica gel plate in ethyl acetate:Skellysolve B 1:1 to yield 1.6 mg of 1α,24(R),25-trihydroxy-cyclovitamin D_3 (3d): mass spectrum, (m/e), 446 (30), 414 (50), 396 (40), 269 (30), 135 (80), 59 (100); NMR, δ, 0.55 (3H, s, 18-H_3), 0.65 (2H, m, 4-H_2), 0.96 (3H, d, J=6.0 Hz, 21-H_3), 1.19 (3H, s, 26-H_3), 1.24 (3H, s, 27-H_3), 3.28 (3H, s, 6-OCH_3), 3.35 (1H, m, 24-H), 4.20 (1H, d, J=9.0 Hz, 6-H), 4.22 (1H, m, 1-H, 4.97 (1H, d, J=9.0 Hz, 7-H), 5.18 (1H, m(sharp), 19(Z)-H), 5.26 (1H, d, J=2.2 Hz, 19(E)-H). 1-oxo-24(R),25-dihydroxy-cyclovitamin D_3 (7d) is also isolated as a minor component (<20%).

Example 24

1α,24(R),25-Trihydroxyvitamin D_3 (6d):

To 200 µl of dry pyridine and 150 µl of Ac_2O is added

1.4 mg of 1α,24R,25-trihydroxy-cyclovitamin D_3 (3d). The system is flushed with N_2 and heated to 95° for 20 hr. The reaction is then diluted with dry toluene and azeo-tropically distilled to dryness. The oily product 1α,24(R),25-triacetoxy-cyclovitamin D_3 (4d-24,25-diacetate), is dissolved in 200 µl of THF and added to 500 µl of a 1:1 solution of 97% HCO_2H:THF and heated to 55° for 15 min. The cooled reaction is diluted with ether, washed with H_2O, sat. $NaHCO_3$, sat. NaCl, and dried over $MgSO_4$. After removal of the solvent in vacuo the crude 1α,24R,25-triacetoxy-3β-formate vitamin D intermediate is dissolved in 200 µl of THF and treated with 1.0 mg K_2CO_3 in 10 µl H_2O and 90 µl MeOH for 5 min at room temperature. Dilution with sat. NaCl, extraction with ether, and chromatography on a 5 x 20 cm, 250 µm, silica gel plate in ethyl acetate: Skellysolve B 4:6 yields 1α,24R,25-triacetoxy-vitamin D_3. Treatment of this triacetate with $LiAlH_4$ gives 1α, 24R,25-trihydroxyvitamin D_3 (6d) which is identical in all respects to an authentic sample.

Example 25

Conversion of 1-hydroxycyclovitamin D_3 (3a) to 1α-hydroxy-vitamin D_3 (6a) via the 1-formyl intermediate (11a):

A 200 µl portion of acetic anhydride is cooled to 0° and 100 µl of 97% formic acid is added slowly. The solution is briefly (15 min) heated to 50° then cooled to 0°. A 100 µl portion of the acetic-formic anhydride is then added to a solution of 5 mg of 1α-hydroxy-cyclovitamin D_3 (3a) in pyridine at 0°. After 2.0 hr the reaction is diluted with

sat. NaCl, extracted with ether, washed with H_2O, and dried over $MgSO_4$. The crude 1α-formyl-cyclovitamin D_3 (11a) obtained after removing the solvent in vacuo is dissolved in glacial acetic acid and heated to 55° for 15 min. Dilution with sat. NaCl, extraction with ether, and isolation of the organic products give the crude product consisting of 1-formyloxyvitamin D_3 3-acetate (12a) and the corresponding 5,6-trans isomer. Treatment of the crude mixture with K_2CO_3 in H_2O/MeOH followed by chromatography (5 x 20 cm, 250 µm, silica gel, 3:7 ethyl acetate:Skellysolve B) yields the pure 1α-hydroxyvitamin D_3 3-acetate and 5,6-trans 1α-hydroxyvitamin D_3 3-acetate, which are hydrolytically converted (KOH/MeOH) to the corresponding 1α-hydroxyvitamin D_3 (6a) and its 5,6-trans isomer respectively.

Example 26

Crown Ether Catalyzed Cycloreversion of 1α-acetoxy-cyclovitamin D_3:

A 0.5 M hexane:benzene (1:1) solution of 15-crown-5 (Aldrich Chemical Co., Milwaukee) is saturated with finely divided anhydrous sodium acetate. to 300 µl of this solution is added 11.0 mg of 1α-acetoxy-cyclovitamin D_3 (4a) in 600 µl of dry hexanes followed by 200 µl of 97% formic acid. The two-phase mixture is vortexed occasionally over 30 min, then diluted with hexanes and the acid layer removed. The organic phase is washed with sat. $NaHCO_3$, sat. NaCl, dried over $MgSO_4$ and the solvent removed in vacuo. The crude oil is taken up in 300 µl of THF and 300 µl of methanol and treated with 10 mg of K_2CO_3 in 100 µl of H_2O. After 5 min at ambient

temperature the reaction is diluted with sat. NaCl and extracted with two portions of ether. The organic layer is washed with H_2O, dried over $MgSO_4$, and the solvent removed in vacuo. The resulting mixture is subjected to preparative TLC (750 μm, 10 x 20 cm, 75:25 Skellysolve B:ethyl acetate) to yield 5.7 mg (54%) of 1α-acetoxyvitamin D_3 (5a) and 2.1 mg (20%) of 5,6-trans-1α-acetoxy-vitamin D_3.

Example 27

Conversion of 1α-hydroxyvitamin D_3 (6a) to 1α-hydroxycyclovitamin D_3 (3a):

To 0.2 ml of pyridine is added 3.0 mg of 1α-acetoxyvitamin D_3 (5a), obtained by either selective acetylation of 1α-hydroxyvitamin D_3 (3a) (2 molar excess acetic anyhydride in pyridine, 4 hours, room temperature, followed by separation of the desired 1α-acetoxyvitamin D_3 derivative on preparative silica gel tlc, using Skellysolve B:ethyl acetate, 3:1) or as the product from Example 2, and 6.0 mg of tosylchloride. After 18 hr. at 3° the reaction is quenched with saturated NaCl solution, extracted with ether, and the ether extracts washed repeatedly with a saturated $NaHCO_3$ solution. After drying over $MgSO_4$, and removal of the solvent in vacuo the crude 1α-acetoxyvitamin D_3 3-tosylate is taken up in 3.0 ml of anhydrous MeOH buffered with 12.0 mg of $NaHCO_3$. The reaction mixture is heated to 55° overnight, quenched with saturated solution of NaCl, extracted with ether and the solvent is removed in vacuo. The crude product is subjected to preparative tlc (5 x 20 cm, 250 μm silica

gel, Skellysolve B:ethyl acetate, 3:1) to yield 2.2 mg of 1α-hydroxycyclovitamin D_3 (3a) which is identical in all respects to the product obtained in Example 1.

Example 28

MnO_2 Oxidation of 1α-hydroxycyclovitamin D_3 (3a) to 1-oxo-cyclovitamin D_3 (7a):

To 1.0 ml of dry CH_2Cl_2 is added 3.0 mg of 1α-hydroxycyclovitamin D_3 (3a) and 35 mg of finely divided MnO_2. (See for example, Paaren et al, J. Chem. Soc., Chem. Comm. 890 (1977)). After 2.0 hr. the reaction mixture is filtered through celite to yield, after preparative tlc (5 x 20 cm, 250 μm, silica gel, Skellysolve B: ethyl acetate), 2.6 mg of 1-oxo-cyclovitamin D_3 (7a) identical in all respects to the product described in Example 1.

Example 29

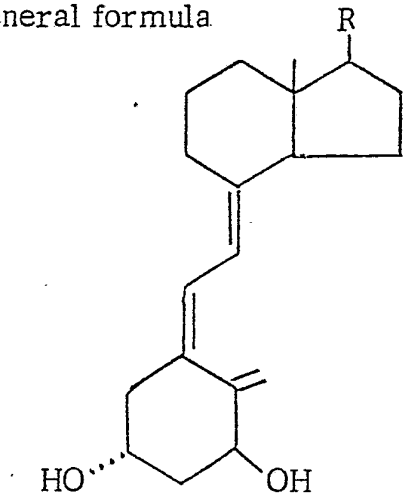
Direct solvolysis of 1α-Hydroxycyclovitamin D compounds

3.8 ml of glacial acetic acid is added to 380 mg of 1α-hydroxycyclovitamin D_3 and the solution warmed for 10 min at 60°. After cooling the mixture is added to a stirring solution of ice/$NaHCO_3$. The neutralized aqueous solution is extracted with diethyl ether, the combined organic extracts washed once with water and dried over $MgSO_4$. The crude product after solvent removal is chromatagraphed on a 1.5 x 60 cm column, of 50 g of neutral silica gel eluted with 100 ml of 4%, 100 ml of 8%, 100 ml of 12%, and 400 ml of 16% EtOAc/Skellysolve B. The desired 1α-hydroxyvitamin D_3 3-acetate isomer elutes before 1α-hydroxy-5,6-trans-vitamin D_3 3-acetate; 175 mg of 1α-hydroxyvitamin D_3 3-acetate is obtained; UV: λ_{max} 264 nm; MS (m/e) 442 (M^+, 8), 382 (70), 364 (15), 269 (20), 134 (100).

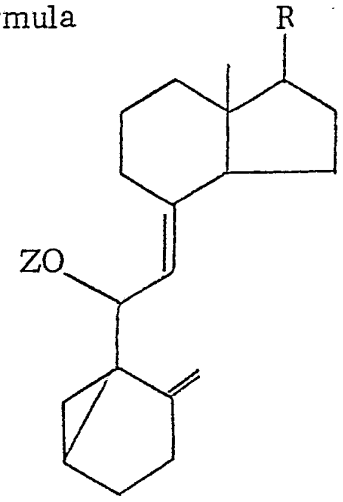
Hydrolysis of 1α-hydroxyvitamin D_3 3-acetate (10% NaOH/MeOH, 2 hr. RT) yields 1α-hydroxyvitamin D_3.

Claims

1. A method for preparing 1α-hydroxylated compounds having the general formula



where R is selected from the group consisting of substituted or unsubstituted, or unsaturated, or unsaturated and substituted cholesterol side chain groups, or where R may have the structure of the side chain of cholenic acid, or of homocholenic acid, or of 27-nor-25-ketocholesterol, or of 24-ketocholesterol, which comprises subjecting compounds having the general formula



where R is defined as above and Z is selected from the group consisting of hydrogen, lower alkyl, lower acyl and aromatic acyl to allylic oxidation recovering the corresponding 1α-hydroxy compound acylating the recovered 1α-hydroxy compound and recovering the 1α-O-acyl derivative solvolyzing said derivative and converting the solvolyzed product to the corresponding hydroxy compound.

2. The method of Claim 1 wherein Z is methyl.

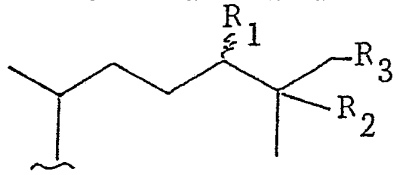
3. The method of Claim 1 wherein the allylic oxidation is carried out with selenium dioxide.

4. The method of Claim 3 wherein the allylic oxidation is carried out in the presence of a hydroperoxide.

5. The method of Claim 3 wherein the peroxide is hydrogen peroxide.

6. The method of Claim 3 wherein the peroxide is an alkyl hydroperoxide.

7. The method of Claim 1 where R has the formula



wherein each of R_1, R_2, and R_3 are selected from the group consisting of hydrogen, hydroxyl, lower alkyl, substituted lower alkyl, O-lower alkyl, substituted O-lower alkyl, and fluorine.

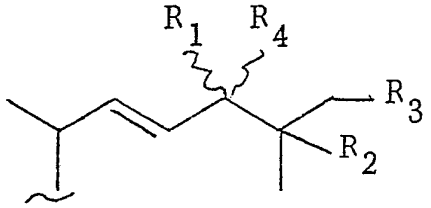
8. The method of Claim 7 wherein R_1 and R_3 are hydrogen and R_2 is hydroxyl.

9. The method of Claim 7 wherein R_1, R_2, and R_3 are hydrogen.

10. The method of Claim 7 wherein R_1 is hydroxyl and R_2 and R_3 are hydrogen.

11. The method of Claim 7 wherein R_1 and R_2 are hydroxyl and R_3 is hydrogen.

12. The method of Claim 1 where R has the formula



wherein each of R_1, R_2, and R_3 are selected from the group consisting of hydrogen, hydroxyl, lower alkyl, substituted lower alkyl, 0-lower alkyl, substituted 0-lower alkyl, and fluorine, and R_4 is selected from the group consisting of hydrogen and lower alkyl.

13. The method of Claim 12 wherein R_1, R_2, and R_3 are hydrogen and R_4 is methyl, having the stereochemistry of the ergosterol side chain.

14. The method of Claim 12 wherein R_1 and R_3 are hydrogen, R_2 is hydroxyl and R_4 is methyl, with the stereochemistry of the ergosterol side chain.

15. The method of Claim 1 wherein the solvolytic conversion of the 1α-0-acyl derivative is accomplished in the presence of an organic acid.

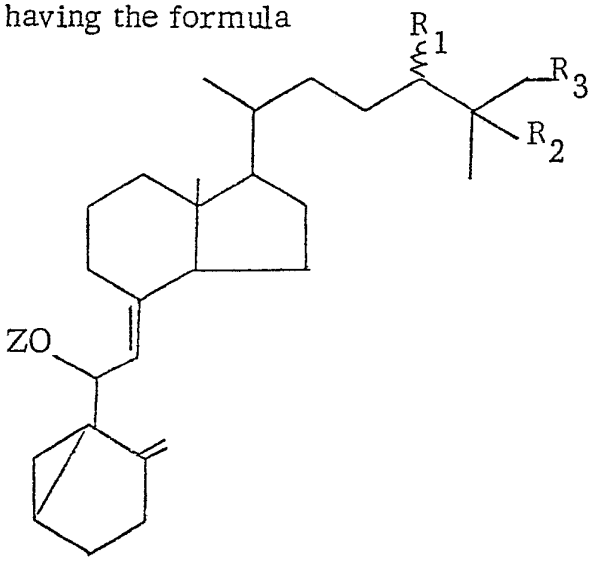
16. The method of Claim 15 wherein the acid is selected from the group consisting of p-toluensulfonic or acetic or formic acids.

17. The method of Claim 1 wherein the 1α-hydroxy com-

pound recovered from the allylic oxidation is directly solvolyzed in the presence of an organic carboxylic acid, the corresponding 3-0-acyl 1α-hydroxy vitamin D derivative is recovered and is converted to the corresponding hydroxy compound.

18. The method of Claim 1 wherein the solvolytic conversion of the 1α-0-acyl derivative is accomplished in the presence of a crown ether compound.

19. Compounds having the formula



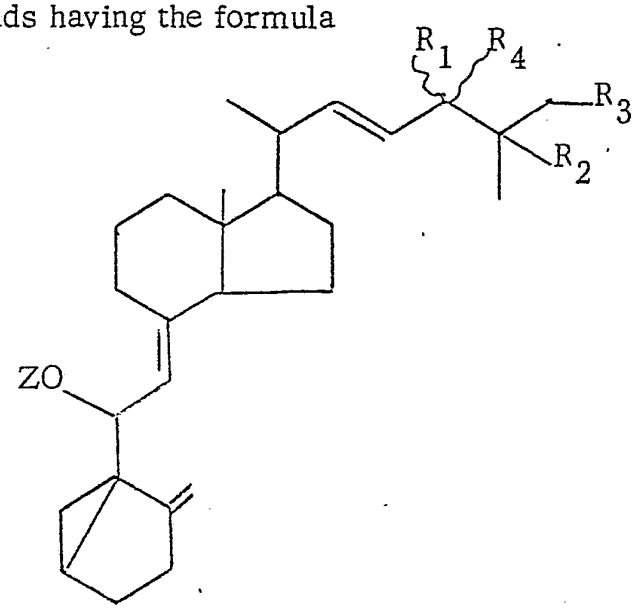
where Z is selected from the group consisting of hydrogen, lower alkyl, lower acyl, and aromatic acyl, and, each of R_1, R_2, and R_3 are selected from the group consisting of hydrogen, hydroxyl, lower alkyl, substituted lower alkyl, 0-lower alkyl, benzoate, substituted benzoate and fluorine and,

except that when Z is hydrogen or methyl and both R_1 and R_3 are hydrogen, R_2 cannot be hydrogen.

20. A compound according to Claim 19 where R_1 and R_3 are hydrogen and R_2 is hydroxyl.

21. Compounds according to Claims 19 and 20 where Z is methyl.

22. Compounds having the formula



where Z is selected from the group consisting of hydrogen, lower alkyl, lower acyl, and aromatic acyl, and each of R_1, R_2, and R_3 are selected from the group consisting of hydrogen, hydroxyl, lower alkyl, substituted lower alkyl, 0-lower alkyl, substituted 0-lower alkyl, 0-lower acyl, substituted 0-lower acyl, benzoate, substituted benzoate and fluorine and,

R_4 is selected from the group consisting of hydrogen and lower alkyl.

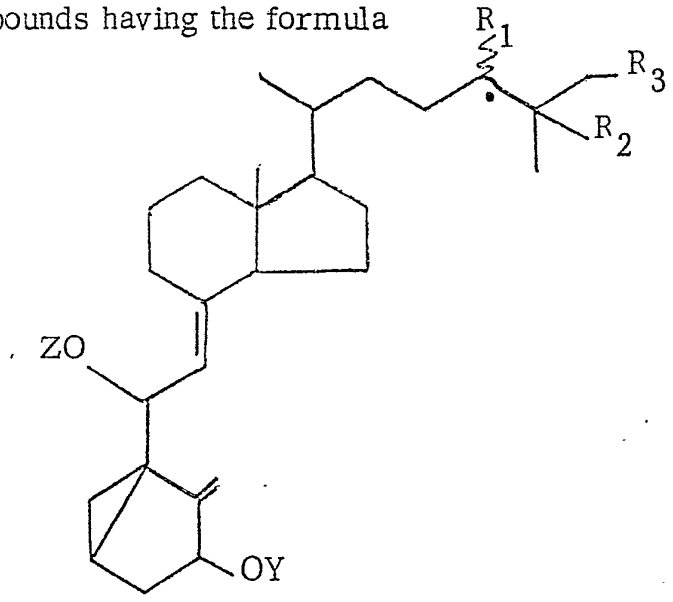
23. A compound according to Claim 21 where R_1, R_2, and R_3 are hydrogen and R_4 is methyl, having the stereochemistry of the ergosterol side chain.

24. A compound according to Claim 21 where R_1 and R_3 are hydrogen, R_2 is hydroxyl and R_4 is methyl, having the stereochemistry of the ergosterol side chain.

25. Compounds according to Claim 22 where Z is methyl.

26. Compounds according to Claims 23 and 24 where Z is methyl.

27. Compounds having the formula



where Z is selected from the group consisting of hydrogen, lower alkyl, lower acyl, and aromatic acyl, and,

each of R_1, R_2 and R_3 are selected from the group consisting of hydrogen, hydroxyl, lower alkyl, substituted lower alkyl, 0-lower alkyl, substituted 0-lower alkyl, 0-lower acyl, substituted 0-lower acyl,

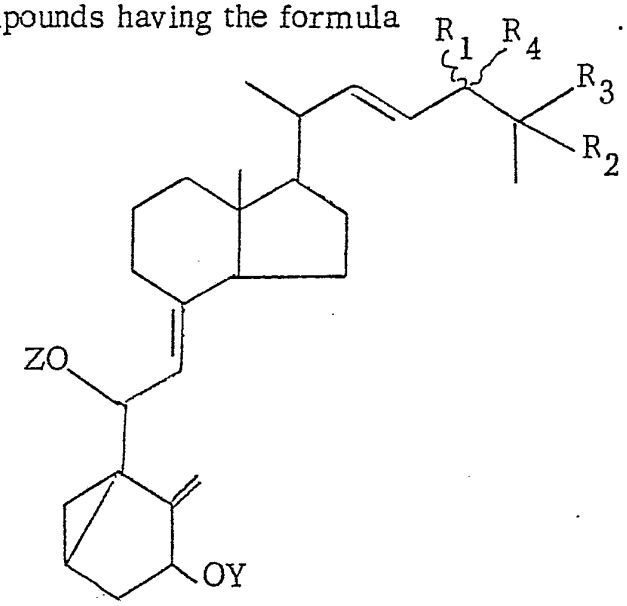
benzoate, substituted benzoate, and fluorine, and

Y is selected from the group consisting of hydrogen and lower acyl and aromatic acyl.

28. Compounds having the formula as shown in Claim 27, where Z is methyl and Y is hydrogen.

29. Compounds having the formula as shown in Claim 27 where Z is methyl and Y is lower acyl.

30. Compounds having the formula

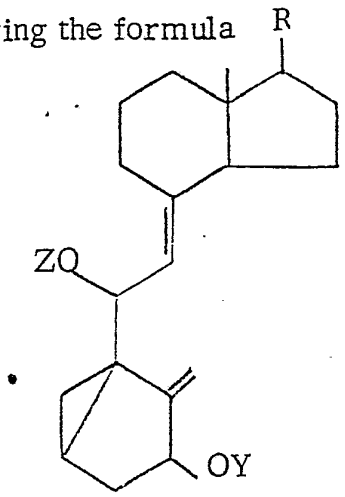


where Z is lower alkyl, lower acyl, aromatic acyl or hydrogen and where each of R_1, R_2, and R_3 are selected from the group consisting of hydrogen, hydroxyl, lower alkyl, substituted lower alkyl, 0-lower alkyl, substituted 0-lower alkyl, 0-lower acyl, substituted 0-lower acyl, benzoate, substituted benzoate and fluorine, and where R_4 is selected from the group consisting of hydrogen and lower alkyl, and where Y is hydrogen, lower acyl or aromatic acyl.

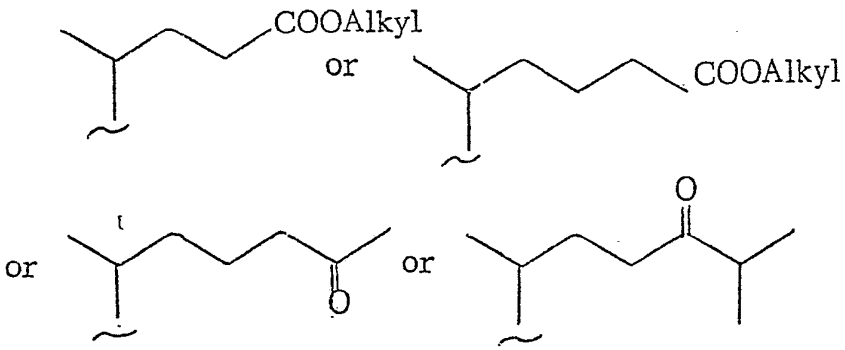
31. Compounds having the formula of Claim 30 where Z is methyl and Y is hydrogen.

32. Compounds having the formula of Claim 30, where Z is methyl and Y is lower acyl.

33. Compounds having the formula

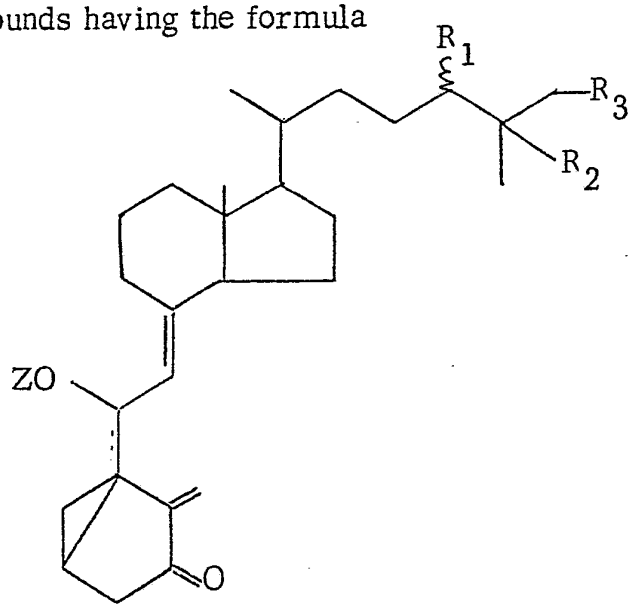


where R is selected from the group consisting of



and were Z represents lower alkyl and where Y is selected from the group consisting of hydrogen, lower acyl, or aromatic acyl.

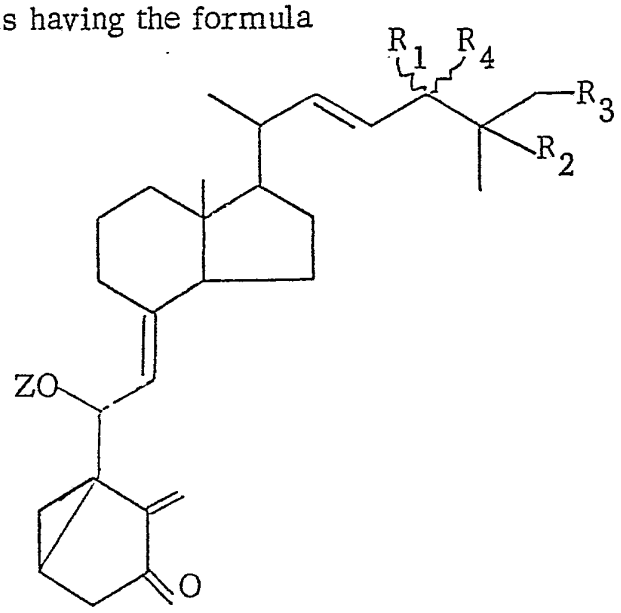
34. Compounds having the formula



where Z is hydrogen or lower alkyl and

each of R_1, R_2, and R_3 are selected from the group consisting of hydrogen, hydroxyl, lower alkyl, substituted lower alkyl, 0-lower alkyl, substituted 0-lower alkyl, 0-lower acyl, substituted 0-lower acyl, benzoate, substituted benzoate, and fluorine.

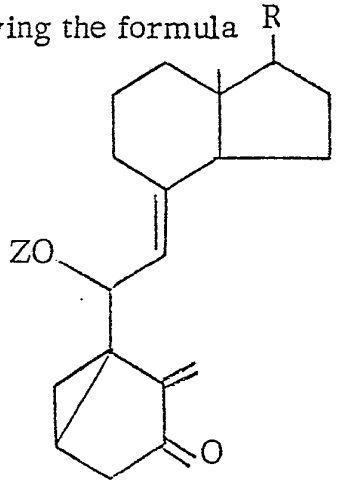
35. Compounds having the formula



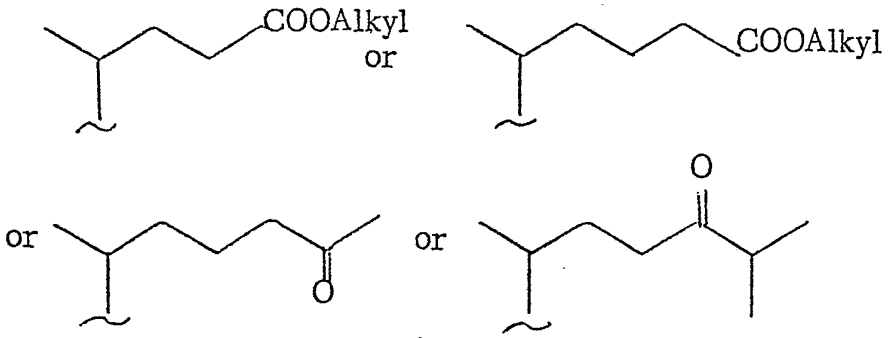
where Z is hydrogen or lower alkyl and where

each of R_1, R_2, and R_3 are selected from the group consisting of hydrogen, hydroxyl, lower alkyl, substituted lower alkyl, 0-lower alkyl, substituted 0-lower alkyl, 0-lower acyl, substituted 0-lower acyl, benzoate, substituted benzoate and fluorine, and where R_4 is selected from the group consisting of hydrogen and lower alkyl.

36. Compounds having the formula



where Z is hydrogen or lower alkyl and where R is selected from the group consisting of



37. 1α-hydroxy-6-alkanoxy-3,5-cyclovitamin D_3.
38. 1α-0-acyl derivative of the compounds of Claim 37.
39. 1α,25-dihydroxy-6-alkanoxy-3,5-cyclovitamin D_3.
40. 1α-0-acyl derivatives of the compounds of Claim 39.
41. 1α,25-0-diacyl derivatives of the compounds of Claim 39.
42. 1α-hydroxy-6-methoxy-3,5-cyclovitamin D_3.
43. The compound of Claim 42 in crystalline form.
44. 1α-acetoxy-6-methoxy-3,5-cyclovitamin D_3.
45. The compound of Claim 44 in crystalline form.
46. 1α,25-dihydroxy-6-methoxy-3,5-cyclovitamin D_3.
47. The compound of Claim 46 in crystalline form.
48. 1α-acetoxy-25-hydroxy-6-methoxy-3,5-cyclovitamin D_3.
49. The compound of Claim 48 in crystalline form.
50. 1α,25-diacetoxy-6-methoxy-3,5-cyclovitamin D_3.
51. The compound of Claim 50 in crystalline form.
52. 1α,25-dihydroxy-6-alkanoxy-3,5-cyclovitamin D_2.
53. 1α-0-acyl derivatives of the compounds of Claim 52.
54. 1α,25-0-diacyl derivatives of the compounds of Claim 52.
55. 1α-hydroxy-6-alkanoxy-3,5-cyclovitamin D_2.
56. 1α-0-acyl derivatives of the compounds of Claim 55.
57. 1α-hydroxy-6-methoxy-3,5-cyclovitamin D_2.
58. The compound of Claim 57 in crystalline form.
59. 1α-acetoxy-6-methoxy-3,5-cyclovitamin D_2.
60. The compound of Claim 59 in crystalline form.
61. 1α,25-dihydroxy-6-methoxy-3,5-cyclovitamin D_2.
62. The compound of Claim 61 in crystalline form.

63. 1α-acetoxy-25-hydroxy-6-methoxy-3,5-cyclovitamin D_2.
64. The compound of Claim 63 in crystalline form.
65. 1α,25-diacetoxy-6-methoxy-3,5-cyclovitamin D_2.
66. The compound of Claim 65 in crystalline form.
67. 1α,24,25-trihydroxy-6-alkanoxy-3,5-cyclovitamin D_3.
68. The 1α-0-acyl derivative of the compounds of Claim 67.
69. The 1α,24,25-tri-0-acyl derivative of the compounds of Claim 67.
70. The compound of Claim 67 wherein the alkanoxy is methoxy.
71. The 1α,24,25-tri-0-acyl derivative of the compound of Claim 70.
72. 1-oxo-6-alkoanoxy-3,5-cyclovitamin D_3.
73. 1-oxo-25-hydroxy-6-alkanoxy-3,5-cyclovitamin D_3.
74. 1-oxo-24,25-dihydroxy-6-alkanoxy-3,5-cyclovitamin D_3.
75. 1-oxo-6-alkanoxy-3,5-cyclovitamin D_2.
76. 1-oxo-25-hydroxy-6-alkanoxy-3,5-cyclovitamin D_2.

INTERNATIONAL SEARCH REPORT

WO79/00513

International Application No PCT/US79/00024

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl. C07J 9/00
US Cl. 260/397.2

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	260/397.2 424/236

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	N Steroids, Published August 1977 Vol. 30 No. 2 Pages 193-201 by Blanc	1-18
A	U S, A, 3,976,636 Pub. August 24, 1976	
A	U S, A, 3,929,770 Pub. Dec. 30, 1975	

* Special categories of cited documents: [15]

"A" document defining the general state of the art

"E" earlier document but published on or after the international filing date

"L" document cited for special reason other than those referred to in the other categories

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but on or after the priority date claimed

"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention

"X" document of particular relevance

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
June 22, 1979	29 JUN 1979
International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/US	Gilbert L. Robert

Form PCT/ISA/210 (second sheet) (October 1977)