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(54) Title: PROCESS FOR PREPARING VITAMIN D ₂ COMPOUNDS AND THE CORRESPONDING 1 ALPHA-HYDROXYLATED DERIVATIVES (57) Abstract This invention relates to hydroxylated derivatives of vitamin D ₂ and a process for preparing such compounds. In particular, a process for preparing the 24-epimer of 25-hydroxyvitamin D ₂ , the 24-epimer of vitamin D ₂ and the corresponding 1 α -hydroxylated derivatives thereof is disclosed. The vitamin D ₂ derivatives would find application in the treatment of or prophylaxis for various disease states characterized by calcium and phosphorous imbalances.		

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PROCESS FOR PREPARING VITAMIN D₂ COMPOUNDS AND
THE CORRESPONDING 1 ALPHA-HYDROXYLATED DERIVATIVES

Technical Field

This invention relates to biologically active vitamin D compounds.

More specifically, this invention relates to a
5 process for the preparation of hydroxylated
derivatives of vitamin D₂.

Background of the Invention

The D vitamins are very important agents for the control of calcium and phosphate metabolism in animals
10 and humans, and have long been used as dietary
supplements and in clinical practice to assure proper
bone growth and development. It is now known that the
in vivo activity of these vitamins, specifically of
vitamin D₂ and D₃, is dependent on metabolism to
15 hydroxylated forms. Thus, vitamin D₃ undergoes two
successive hydroxylation reactions in vivo, leading
first to 25-hydroxyvitamin D₃ and then to
1,25-dihydroxyvitamin D₃ and the latter is thought to
be the compound responsible for the well-known
20 beneficial effects of vitamin D₃. Likewise, vitamin
D₂, which is commonly used as a dietary supplement,
undergoes an analogous hydroxylation sequence to its
active forms, being first converted to
25 25-hydroxyvitamin D₂ (25-OH-D₂) and then to 1,25-
dihydroxyvitamin D₂ (1,25-(OH)₂D₂). These facts are
well established and well known in the art [see, for
example, Suda et al. Biochemistry 8, 3515 (1969) and
Jones et al. Biochemistry 14, 1250 (1975)].

Like the metabolites of the vitamin D₃ series,
30 the hydroxylated forms of vitamin D₂ named above are,
because of their potency and other beneficial
properties, highly desirable dietary supplements, or
pharmaceutical agents, for the cure or prevention of
bone or related diseases, and their value and possible

- 2 -

use is recognized in patents relating to these compounds [U. S. Letters Pat. Nos. 3,585,221 and 3,880,894].

Whereas many metabolites of vitamin D₃ have been prepared by chemical synthesis, there has been less work
5 on the preparation of vitamin D₂ metabolites. The known synthetic processes for the metabolites of the D₃-series (especially as far as they relate to the preparation of side chain hydroxylated compounds) are, of course, in general not suitable for the preparation of the
10 corresponding vitamin D₂ metabolites, since the latter are characterized by a side chain structure (i.e. presence of a double bond and an extra methyl group) which requires a different synthetic approach from that applicable to side chain hydroxylated D₃ compounds.

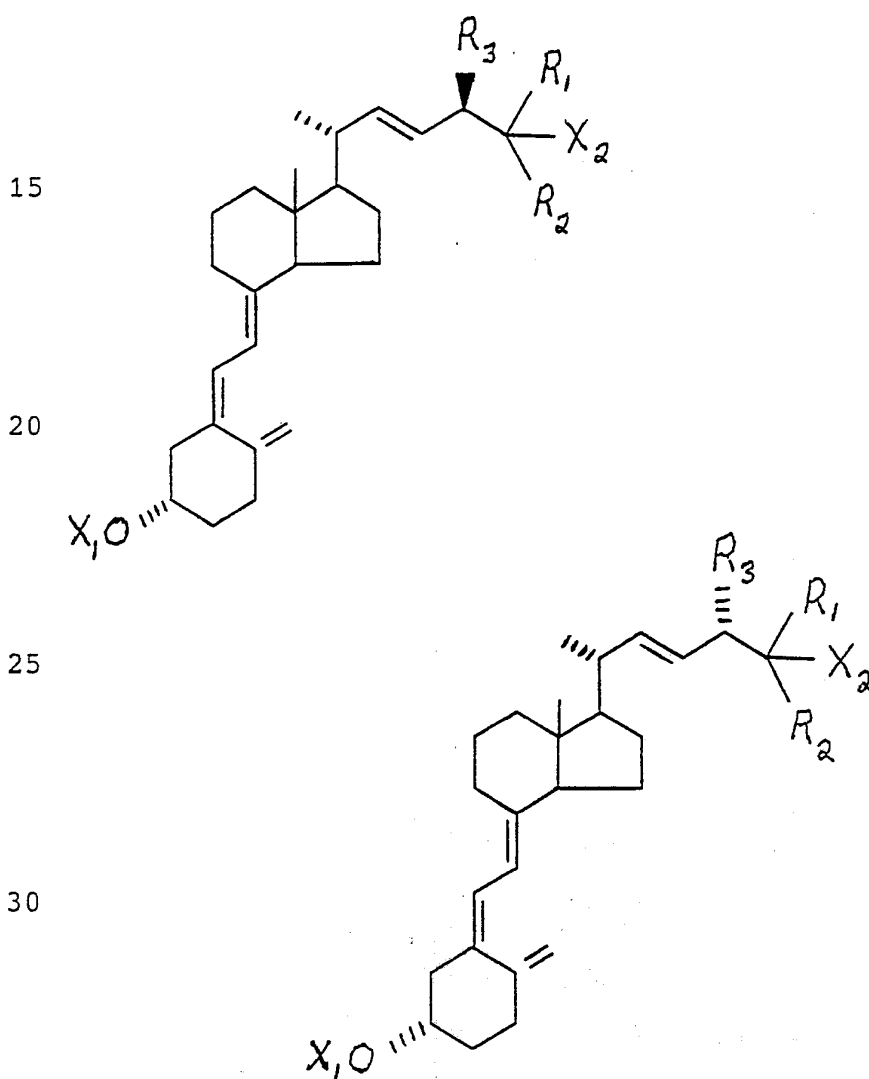
15 Various approaches for the preparation of vitamin D₂ metabolites are known, and are described in U. S. Patent Nos. 4,448,721, 4,847,012 and 4,769,181. Other preparations of 25-OH-D₂ and 1 α ,25-(OH)₂D₂ compounds involving condensation of side chains with a steroid
20 nucleus are shown in Yamada et al, "Facile And Stereoselective Synthesis of 25-hydroxyvitamin D₂", Tetrahedron Letters, Vol. 25, No. 33, pp. 3347-3350, 1984 and in Tsuji et al, "A New And Convenient Synthesis of 1 α ,25-Dihydroxyvitamin D₂ And Its 24R-Epimer", Bull,
25 Chem. Soc. Jpn., Vol. 62, No. 10, pp. 3132-3137, 1989. Perlman et al have reported the preparation of the epimer of 1 α -OH-D₂ by condensation of a suitable side chain fragment with a vitamin D nucleus in J. Chem. Soc. Chem. Com. pp. 1113-1115, 1989.

30 Disclosure of Invention

A novel and convenient synthesis of vitamin D₂ compounds has now been developed and is described herein. This synthesis provides vitamin D₂ compounds characterized by the structures shown below where X₂ is

- 3 -

hydrogen, such as vitamin D₂ itself and the 24-epimer of vitamin D₂, namely 24-epi-vitamin D₂ (24-epi D₂), characterized by the structures shown below where X₁ and X₂ are both hydrogen and R₁, R₂ and R₃ are methyl. This
5 synthesis also provides 25 hydroxylated vitamin D₂ compounds, such as 25-hydroxyvitamin D₂ (25-OH-D₂) and the 24-epimer of 25-hydroxyvitamin D₂, namely 25-hydroxy-24-epi-vitamin D₂ (25-OH-24-epi D₂), characterized by
10 the structures shown below where X₁ is hydrogen, X₂ is hydroxy and R₁, R₂ and R₃ are methyl.



- 4 -

This synthesis thus provides compounds where X_2 may be either hydrogen or hydroxy, as well as the corresponding alkyl or aryl analogs thereof, characterized by the structures above where R_1 and R_2 are alkyl or aryl, and
5 the corresponding side chain substituted derivatives where R_3 is alkyl, hydroxy, protected hydroxy (as defined below for X_1 and X_2), hydrogen or fluorine, and the hydroxy-protected derivatives of these compounds characterized by the structures above, where X_1 is
10 selected from the group consisting of acyl, alkylsilyl, or alkoxyalkyl and X_2 is selected from the group consisting of O-acyl, O-alkylsilyl, or O-alkoxyalkyl.

In addition, the present process provides the 5,6-trans-isomers of the above compounds. Furthermore, the
15 above compounds can be 1α -hydroxylated by known methods, so as to produce the corresponding 1α -hydroxyvitamin D derivatives. Especially preferred examples of the latter are 1α -hydroxyvitamin D_2 , $1\alpha,25$ -dihydroxyvitamin D_2 , 1α -24-epi-vitamin D_2 and $1\alpha,25$ -dihydroxy-24-epi-
20 vitamin D_2 .

The term "acyl", as used in this specification or in the claims, signifies an aliphatic acyl group of from 1 to about 6 carbons, in all possible isomeric forms (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl,
25 valeryl, etc.), or an aromatic acyl group (aroyl group) such as benzoyl, the isomeric methyl-benzoyls, the isomeric nitro- or halo-benzoyls, etc., or a dicarboxylic acyl group of from 2 to 6 atoms chain length, i.e. acyl groups of the type $ROOC(CH_2)_nCO-$, or
30 $ROCCH_2-O-CH_2CO-$, where n has values between 0 and 4 inclusive and R is hydrogen or an alkyl radical, such as oxalyl, malonyl, succinoyl, glutaryl, adipyl, diglycolyl. The term "alkyl" refers to a lower alkyl group of 1 to 6 carbons in all possible isomeric forms,

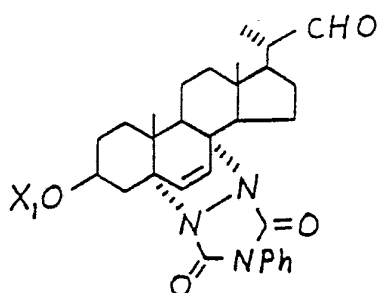
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e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, pentyl, etc., and the work "aryl" signifies a phenyl or substituted phenyl group, e.g. alkylphenyl, methoxyphenyl, etc. The term "alkylsilyl" refers to
5 trialkyl silicone groupings where the alkyl groups may be the same or different as exemplified by trimethylsilyl, triethylsilyl, dimethyl-tert.-butylsilyl and similar groupings. The term "alkoxyalkyl" refers to protecting groups such as methoxymethyl, ethoxymethyl,
10 methoxyethoxymethyl, and similar alkoxyethyl groups, as well as the related cyclic structures, such as tetrahydropyranyl or tetrahydrofuranlyl.

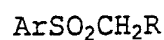
The overall process developed for the preparation of the above compounds may be divided into two general
15 phases, namely (a) addition of a completed, preformed side chain fragment to a suitable steroidal precursor to produce a 5,7-diene steroid as the central intermediate, and (b) conversion of this 5,7-diene to the vitamin D structure to produce the desired vitamin D compound,
20 and, if desired, (c) further conversion of the latter product to the corresponding 1 α -hydroxyvitamin D compound. This process avoids the relatively difficult step of isomer separation which is required after conversion in the process of U. S. patent No. 4,448,721.
25 The process of the present invention also increases the yield of the end product since it utilizes a completed, preformed pure isomer side chain fragment to make the desired end product, rather than a mixture of side chain isomers as in U. S. Patent No. 4,448,721.

30 In general terms, the process of this invention comprises the reaction of a steroidal 22-aldehyde of the structure:

- 6 -

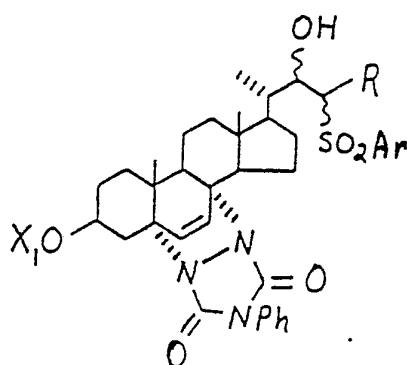


10 where X_1 is hydrogen or a hydroxy-protecting group, with
a sulfone derivative of the general formula,



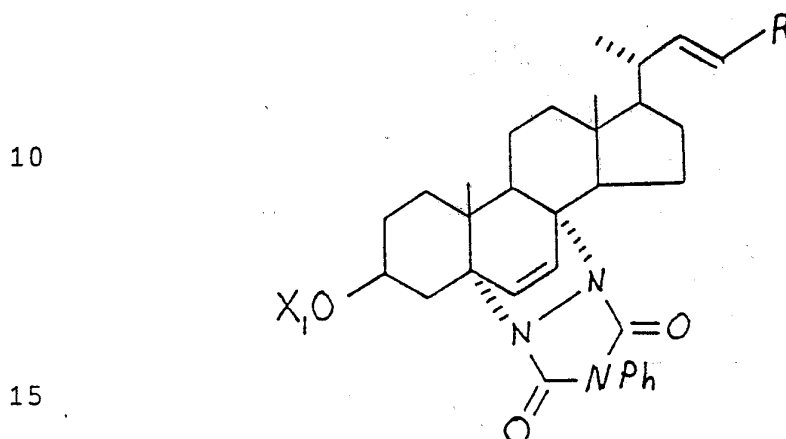
where Ar represents a phenyl or tolyl group, and R is
selected from the group consisting of straight or
branched, substituted or unsubstituted, hydrocarbon
15 radicals of from 1 to 25 carbon atoms, where the
substituents are selected from the group consisting of
hydroxy, protected hydroxy, and fluorine.

The coupling reaction, conducted in a basic medium,
between the above aldehyde and sulfone derivatives,
20 yields a condensation product of the formula:



- 7 -

which is then subjected to reduction (either as the 22-hydroxy, or as the corresponding 22-O-acylated derivative) using metal amalgams (Na, Al, Zn amalgams or related dissolving metal reduction systems, so as to provide the 22, 23-unsaturated steroid of the formula:



where R and X_1 represent the groupings defined above. This steroid intermediate can then be further converted by known reactions to the desired vitamin D compounds.

It is readily apparent that by suitable variation of R in the aryl sulfone derivative used in the above coupling process a range of different vitamin D compounds can be produced.

25-Hydroxylated Compounds (X_2 Is Hydroxy)

The reaction sequence illustrated by Process Scheme I presents a specific embodiment of the overall process, whereas Process Scheme II illustrates preparation of an appropriate side chain unit for addition to the steroid-22-aldehyde as shown in Scheme I.

Starting materials for the present process are steroidal 22-aldehydes, such as, for example, the PTAD-diene-protected-22-aldehyde (4) shown in Scheme I (where PTAD refers to the phenyltriazoledione-protecting

- 8 -

group shown), which in turn can be prepared from ergosterol by the known steps (Scheme I).

The first step of this process comprises the addition of a suitable side chain fragment. Thus, 5 condensation of aldehyde (4) with a sulfonyl-side chain fragment as shown in Scheme I (sulfone (21), further described below) present in the form of its anion, in an ether or hydrocarbon solvent, provides the hydroxy-sulfone intermediate (5). The anion of the sulfone (21) 10 side chain fragment is generated by treatment of the sulfone with a strong base, such as lithium diethylamide, n-butyl lithium or methyl or ethyl magnesium bromide (or similar Grignard reagent) in an ether or hydrocarbon solvent, and to this solution of sulfone anion the steroid aldehyde (compound 4) as an 15 ether or hydrocarbon solution is then added. The reaction is best effected under an inert atmosphere.

The next step comprises the removal of the hydroxy- and phenylsulfonyl groups in the side chain with formation of the 22(23)-trans-double bond. Thus, 20 treatment of compound (5), in methanol solution saturated with NaHPO_4 , with sodium amalgam under an inert atmosphere, gives compound (6) featuring the desired trans-22-double bond in the side chain. If desired, the 22-hydroxy group in compound (5) can also 25 be acylated or sulfonylated (e.g. mesylated) prior to the Na/Hg-reduction step, but this is not generally required.

It is to be noted that, as shown in Process Scheme I, addition of the side chain fragment, sulfone (21), to 30 the aldehyde (4), does not cause epimerization at the asymmetric center of carbon 20, i.e. the stereochemistry at that center is retained, as is required. If desired, retention of stereochemistry at carbon 20 may be checked

- 9 -

at this stage of the synthesis by the conversion of intermediates of type (6) back to the original aldehyde starting materials. For example, subjecting compound (6) to ozonolysis with reductive work-up, using fully conventional and standard conditions, yields the corresponding C-22-aldehyde, i.e. the aldehyde of structure (4). Spectroscopic and chromatographic comparison of the aldehyde obtained from ozonolysis with the original starting material confirms retention of C-20 stereochemistry.

The next operation of the process involves conversion of these ring B-protected steroids to the desired 5,7-diene intermediate (7). In the case of the PTAD-diene-protected compound (6), this conversion is accomplished in a single step, namely treatment of (6) with a strong hydride reducing agent (e.g. LiAlH_4) in an ether solvent at reflux temperature gives the diene (7). The diene (7) is then converted to its 25-hydroxylated form (8) by known procedures in accordance with Scheme I.

Conversion of 5,7-diene (8) to the final vitamin D products (10) or (15) comprises a sequence of several steps. The sequence shown in Process Scheme I involves first the irradiation of an ether or hydrocarbon solution of the 5,7-diene (8) with ultraviolet light to yield the previtamin analog (9) which by warming ($50^\circ\text{--}90^\circ\text{C}$) in a suitable solvent (e.g. ethanol, hexane) undergoes isomerization to the 25-hydroxyvitamin D_2 compound (10).

Thereafter, compound (10) may be converted to the 1,25-dihydroxyvitamin D_2 compound (15) by the known steps shown in Scheme I. Reference is made to U. S. Patent Nos. 4,260,549 and 4,554,106 for the prior art relevant to these transformations.

- 10 -

The side chain fragment, sulfone (21), as used in Scheme I is specifically the (R) enantiomer. Therefore, compounds (10) or (15) are obtained as the C-24-R-epimers, 25-hydroxy-24-epi-vitamin D₂ (10) or 1,25-dihydroxy-24-epi-vitamin D₂ (15), respectively. Thus, compound (10) or (15) are prepared in epimerically pure form, and C-24-epimer separation as required in the process disclosed in U. S. patent No. 4,448,721, is not necessary. Use of the (S)-epimer of sulfone (21) in the present process yields specifically 25-OH-D₂, as well as, of course, the respective 1,25-dihydroxyvitamin D₂ compound.

The 5,7-diene (7) may be used as the free hydroxy compound or as its hydroxy-protected form, where the hydroxy-protecting groups (at C-3 and/or C-25) may be acyl, alkylsilyl or alkoxyalkyl groups as previously defined. Thus, the 25-OH-D₂ product will be obtained as the free hydroxy compound or, if desired, as the C-3, or C-25-hydroxy-protected, or 3,25-dihydroxy-protected derivatives. Synthesis according to Scheme I would provide the 25-OH-D₂ products as the free hydroxy compounds but analogous conversion of 5,7-diene intermediate (7) as the 3-, or 25-protected, or 3,25-di-protected derivative will yield the corresponding hydroxy-protected derivatives of the 25-OH-D₂ products.

The individual 25-OH-D₂ epimers, i.e. 25-OH-D₂ or 25-OH-24-epi-D₂ (10) when obtained in the free hydroxy forms, are also conveniently hydroxy-protected at the C-3 or C-25, or at both positions, by conventional reactions known in the art. Thus, 25-OH-D₂ may be acylated to yield, for example, the 25-OH-D₂-3-acetate, or the corresponding 3,25-diacetate. The 3-monoacetate, in a like fashion, may be further acylated at C-25 by treatment with a different acylating reagent, or,

- 11 -

alternatively, the 3,25-diacetate may be selectively hydrolyzed by a mild base (KOH/MeOH) to give the 25-monoacetate, which if desired can be reacylated with a different acyl group at C-3. Other hydroxy-protecting groups can be introduced by analogous known reactions.

In addition to the hydroxy-protected derivatives, the 5,6-trans-isomers of 25-OH-24-epi-D₂ as well as the 1,25-dihydroxy compounds are compounds of potential utility in medical applications because of their considerable vitamin D-like activity. These 5,6-trans-compounds are prepared from the 5,6-cis-isomers (i.e. 10 or 15) by iodine catalyzed isomerization according to the procedures of Verloop et al. Rec. Trav. Chim. Pays Bas 78, 1004 (1969), and the corresponding 3- and/or 25-hydroxy-protected derivatives are likewise obtained by analogous isomerization of the corresponding 5,6-cis-acylates, or by hydroxy-protection of the 5,6-trans-25-OH-D₂ compounds.

The required side chain fragment, sulfone (21), is itself prepared according to the process shown in Process Scheme II. This synthesis is straight-forward and involves as a first step the reaction of ester (16) in anhydrous tetrahydrofuran (THF) with methyl magnesium bromide to give the diol (17). Diol (17) is dissolved in anhydrous pyridine and reacted with p-toluenesulfonyl chloride to provide the tosylate (18). Tosylate (18) is dissolved in a solution of anhydrous dimethyl formamide and reacted with thiophenol and t-BuOK to yield the sulfide (19). The sulfide (19) in turn is dissolved in dichloromethane and reacted with 3-chloroperoxybenzoic acid to give the hydroxy sulfone compound (20). Pyridinium p-toluenesulfonate is then added to a solution of compound (20) in anhydrous dichloromethane and reacted with dihydropyran to yield the hydroxy

- 12 -

protected tetrahydropyranyl sulfone (21a). The corresponding (S)-epimer of sulfone (21) is prepared by the same process, using as starting material the ester corresponding to (16) but having the (S) configuration at carbon-2.

Non-25-Hydroxylated Compounds (X₂ Is Hydrogen)

The reaction sequence illustrated by Process Scheme III presents another specific embodiment of the overall process, whereas Process Scheme IV illustrates preparation of an appropriate side chain unit for addition to the steroid-22-aldehyde as shown in Scheme III.

Starting materials for the present process are steroidal 22-aldehydes, such as, for example, the PTAD-diene-protected-22-aldehyde (4) shown in Scheme I (where PTAD refers to the phenyltriazoline-3,5-dione-protecting group shown), which in turn can be prepared from ergosterol by the known steps (Scheme I).

The first step of this process comprises the addition of a suitable side chain fragment. Thus, condensation of aldehyde (4) with a sulfonyl-side chain fragment as shown in the Scheme III (sulfone (35), further described below) present in the form of its anion, in an ether or hydrocarbon solvent, provides the hydroxy-sulfone intermediate (22). The anion of the sulfone (35) side chain fragment is generated by treatment of the sulfone with a strong base, such as lithium diethylamide, n-butyl lithium or methyl or ethyl magnesium bromide (or similar Grignard reagent) in an ether or hydrocarbon solvent, and to this solution of sulfone anion the steroid aldehyde (compound 4) as an ether or hydrocarbon solution is then added. The reaction is best effected under an inert atmosphere.

- 13 -

The next step comprises the removal of the hydroxy- and phenylsulfonyl groups in the side chain with formation of the 22(23)-trans-double bond. Thus, treatment of compound (22), in methanol solution
5 saturated with NaHPO_4 , with sodium amalgam under an inert atmosphere, gives compound (23) featuring the desired trans-22-double bond in the side chain. If desired, the 22-hydroxy group in compound (22) can also be acylated or sulfonylated (e.g. mesylated) prior to
10 the Na/Hg-reduction step, but this is not generally required.

It is to be noted that, as shown in Process Scheme III, addition of the side chain fragment, sulfone (35), to the aldehyde (4), does not cause epimerization at the
15 asymmetric center of carbon 20, i.e. the stereochemistry at that center is retained, as is required. If desired, retention of stereochemistry at carbon 20 may be checked at this stage of the synthesis by the conversion of intermediates of type (23) back to the original aldehyde
20 starting materials. For example, subjecting compound (23) to ozonolysis with reductive work-up, using fully conventional and standard conditions, yields the corresponding C-22-aldehyde, i.e. the aldehyde of structure (4). Spectroscopic and chromatographic
25 comparison of the aldehyde obtained from ozonolysis with the original starting material confirms retention of C-20 stereochemistry.

The next operation of the process involves conversion of these ring B-protected steroids to the
30 desired 5,7-diene intermediate (24). In the case of the PTAD-diene-protected compound (23), this conversion is accomplished in a single step, namely treatment of (23) with a strong hydride reducing agent (e.g. LiAlH_4) in an

- 14 -

ether solvent at reflux temperature gives the diene (24).

Conversion of 5,7-diene (24) to the final vitamin D products (26) or (31) comprises a sequence of several steps. The sequence shown in Process Scheme III involves first the irradiation of an ether or hydrocarbon solution of the 5,7-diene (24) with ultraviolet light to yield the previtamin analog (25) which by warming (50°-90°C) in a suitable solvent (e.g. ethanol, hexane) undergoes isomerization to the vitamin D₂ compound (26).

Thereafter, compound (26) may be converted to the 1 α -hydroxyvitamin D₂ compound (31) by the known steps shown in Scheme III. Reference is made to U. S. Patent Nos. 4,260,549 and 4,554,106 for the prior art relevant to these transformations.

The side chain fragment, sulfone (35), as used in Scheme III is specifically the (R) enantiomer. Therefore, compounds (26) or (31) are obtained as the C-24-R-epimers, 24-epi-vitamin D₂ (26) or 1 α -hydroxy-24-epi-vitamin D₂ (31), respectively. Thus, compounds (26) or (31) are prepared in epimerically pure form, and C-24-epimer separation as required in the process disclosed in U. S. patent No. 4,448,721, is not necessary. Use of the (S)-epimer of sulfone (35) in the present process yields specifically vitamin D₂, as well as, of course, the respective 1 α -hydroxyvitamin D₂ compound.

The 5,7-diene (24) may be used as the free hydroxy compound or as its hydroxy-protected form, where the hydroxy-protecting groups (at C-3) may be acyl, alkylsilyl or alkoxyalkyl groups as previously defined. Thus, the vitamin D₂ product will be obtained as the free hydroxy compound or, if desired, as the C-3-hydroxy-protected derivatives. Synthesis according to Scheme

- 15 -

III would provide the vitamin D₂ products as the free hydroxy compounds but analogous conversion of 5,7-diene intermediate (24) as the 3-protected, derivative will yield the corresponding hydroxy-protected derivatives of the vitamin D₂ products.

The individual vitamin D₂ epimers, i.e. vitamin D₂ or 24-epi-D₂ (26) when obtained in the free hydroxy forms, are also conveniently hydroxy-protected at the C-3 position, by conventional reactions known in the art. Thus, vitamin D₂ may be acylated to yield, for example, the vitamin D₂-3-acetate. Other hydroxy-protecting groups can be introduced by analogous known reactions.

In addition to the hydroxy-protected derivatives, the 5,6-trans-isomers of 24-epi-D₂ as well as the 1 α -hydroxy compounds are compounds of potential utility in medical applications because of their considerable vitamin D-like activity. These 5,6-trans-compounds are prepared from the 5,6-cis-isomers (i.e. 26 or 31) by iodine catalyzed isomerization according to the procedures of Verloop et al. Rec. Trav. Chim. Pays Bas 78, 1004 (1969), and the corresponding 3-hydroxy-protected derivatives are likewise obtained by analogous isomerization of the corresponding 5,6-cis-acylates, or by hydroxy-protection of the 5,6-trans-D₂ compounds.

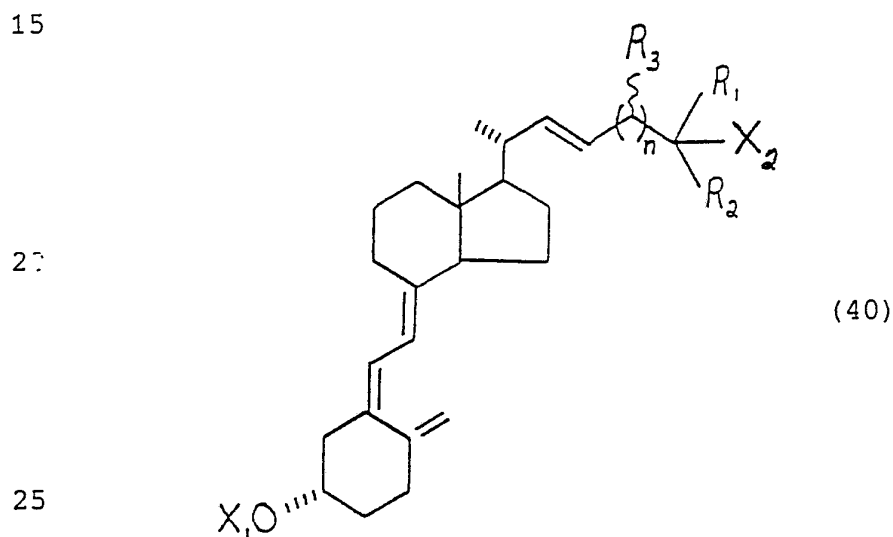
The required side chain fragment, sulfone (35), can be prepared according to Perlman et al, supra, or according to the process shown in Process Scheme IV. This synthesis is straightforward and involves as a first step dissolving alcohol (32) in anhydrous pyridine and reacting it with p-toluenesulfonyl chloride to provide the tosylate (33). Tosylate (33) is dissolved in a solution of anhydrous dimethyl formamide and reacted with thiophenol and t-BuOK to yield the sulfide

- 16 -

(34). The sulfide (34) in turn is dissolved in dichloromethane and reacted with 3-chloroperoxybenzoic acid to give the sulfone compound (35). The corresponding (*S*)-epimer of sulfone (35) can also be prepared according to Perlman et al *supra*, or according to Process Scheme IV, using as starting material the alcohol corresponding to (32) but having the (*S*) configuration at carbon-2.

Analog Compounds

Furthermore, the present process also serves as a convenient method for the synthesis of vitamin D₂ analogs (where X₂ is hydrogen) including 25-CH-D₂ analogs (where X₂ is hydroxy), of the formula (40) shown below, or of the corresponding 1 α -hydroxy-analogs,

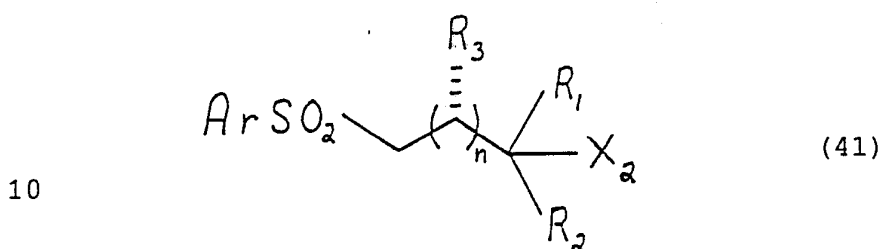


where n is an integer having a value of from 1 to 5, X₁ is selected from hydrogen and a hydroxy-protecting group, X₂ is selected from hydrogen, hydroxy and protected hydroxy, R₃ is alkyl, hydroxy, protected hydroxy, hydrogen or fluorine, and where R₁ and R₂, which may be the same or different, is an alkyl group or an aryl group and where the C-24-methyl group has either the (*R*)- or the (*S*)-stereochemical orientation. These

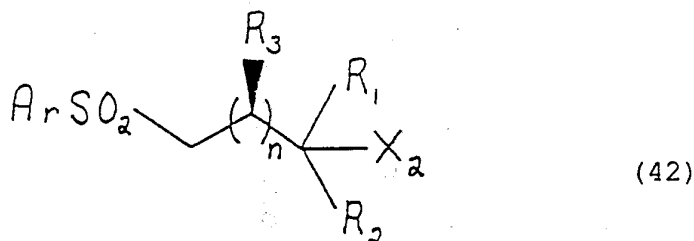
- 17 -

compounds are prepared by condensing compound (4) with the appropriate alkyl or aryl side chain fragment as shown by the following formulae,

5



15



where X_2 , R_1 , R_2 , R_3 and n are as defined above.

The use of compounds where (41) and (42) as side chain units in the synthetic process depicted as in Schemes I and III, then provides the 25-OH-D₂- or 25-OH-24-epi-D₂-homologs of general structure (40) where R_1 , R_2 and R_3 represent alkyl or aryl residues or other substitutes as defined above. The products of general structure (40) can then be 1 α -hydroxylated according to known methods (See U. S. Patent Nos. 4,260,549 and 4,554,106) so as to obtain the corresponding 1 α -hydroxylated vitamin D homologs.

Since the compounds where R_1 , R_2 or R_3 represent higher homologs of methyl, are generally more

- 18 -

lipophilic, the alkyl- or aryl-analogues represented by structure (40) above or their 5,6-trans-isomers, are expected to have utility in applications where a greater degree of lipophilicity is desired.

5 The present invention is further described by means of the following illustration. In this illustration, numerals designating specific products, e.g. compounds 1, 2, 3 etc. refer to the structures so numbered in Process Schemes I or II.

10

EXAMPLE IErgosterol Method

To a solution of 50g (0.13mol) of ergosterol 1 in 300ml of anhydrous pyridine was added 33.3ml (0.35mol) of acetic anhydride. The mixture was stirred at room
15 temperature overnight and 600ml of water was added. The precipitate was filtered off, washed several times with 200ml of water and recrystallized from ethanol to obtain 2, 42.0g (76%). [yellowish crystal]

To a solution of 33g (0.075mol) of 2 in 500ml of
20 chloroform was added 13.2g (0.075mol) of 4-phenyl-1,2, 4-triazoline-3,5-dione. The solution was stirred at room temperature for 30 min and 5ml of pyridine was added. The solution was cooled at -78°C and treated with an ozone-oxygen mixture for 30 min (TLC control) and
25 thoroughly purged with nitrogen. 50ml of dimethyl sulfide was added and the mixture was washed with 300ml of water, 200ml of 2N HCl (twice) and 300ml of water. The organic layer was separated and each washing was extracted with 400ml and 200ml of chloroform. The
30 combined extract was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified on a silica gel column (5.06X63cm, 550g of 150~ 425µm silica gel) using a mixture of ethyl acetate and hexane as eluant. 20.5g (50%) of 4 was eluted with 30% ethyl acetate in hexane.

- 19 -

To increase yield, the recovered 3 (eluted with 15% ethyl acetate in hexane) was treated with an ozone-oxygen mixture as above.

5 To a stirred solution of 12.1g (37.1mmol) of sulfone 21, 5.10ml (36.4mmol) of diisopropyl amine and 100ml of anhydrous tetrahydrofuran (containing 1,10-phenanthroline as indicator) under nitrogen atmosphere at -78°C was added 22.7ml (36.3mmol) of n-BuLi (1.6M in hexane). The solution was stirred under nitrogen at
10 -78°C for 30min, then 10.0g (18.3mmol) of 4 in 40ml of anhydrous tetrahydrofuran was added. The mixture was stirred at -78°C for 1hr, decomposed by the addition of 100ml of saturated NH₄Cl solution, warmed to 0°C and
15 extracted three times with 100ml of ethyl acetate. Each extract was washed with 100ml of saturated NaCl solution, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified on a silica gel column (3.2X60cm, 150g of 75-150µm silica gel). The unreacted sulfone 21 was eluted with benzene and 14.7g (92%) of 5
20 was eluted with ethyl acetate.

A mixture of 14.7g (16.9mmol) of hydroxysulfone 5, 110g of 5% sodium amalgam and 400ml of methanol saturated with Na₂HPO₄ was stirred under nitrogen
25 atmosphere at 5°C for 20 hrs. The reaction solution was decanted and concentrated in vacuo. The residue was dissolved in 200ml of ethyl acetate and washed with 400ml and 200ml of water. The ethyl acetate extract was separated and each of washing was extracted twice with
30 200ml of ethyl acetate. The combined extract was dried over Na₂SO₄ and concentrated in vacuo. 10.5g (91%) of 6 was obtained.

To a solution of 10.5g (15.4mmol) of 6 in 400ml of tetrahydrofuran was added 11.5g (303.0mmol) of LiAlH₄. The mixture was heated under reflux and nitrogen

- 20 -

atmosphere for 3 hrs, cooled with ice water and decomposed by the dropwise addition of 40ml of ethyl acetate and 60ml of water. Then, the mixture was filtered and the filtrate was concentrated in vacuo.

5 The residue was dissolved in 200ml of ethyl acetate and washed twice with 200ml of saturated NaCl solution. The ethyl acetate extract was separated and each washing was extracted with 200ml of ethyl acetate. The combined extract was dried over Na_2SO_4 and concentrated in vacuo.
10 Then, the residue was purified on a silica gel column (3.2X25cm, 80g of 75-150 μm silica gel) and 4.8g (63%) of 7 was eluted with 5% ether in benzene as eluant [yellow foam].

To a solution of 4.4g (8.9mmol) of 7 in 200ml of
15 methanol and 130ml of dichloromethane was added 2.0g (7.9mmol) of pyridinium p-toluenesulfonate. The mixture was stirred at room temperature overnight, dissolved in 300ml of saturated NaCl solution and extracted three times with 400ml of dichloromethane. Each extract was
20 washed with 400ml of saturated NaCl solution, combined, dried over Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from ethanol to obtain 2.5g (68%) of 8 [white crystal]. To increase yield, the mother liquor was concentrated in vacuo, purified with chromatography
25 and recrystallized from ethanol.

1.50g (3.6mmol) of 8 was dispersed in 500ml of a mixture of ether and benzene (4:1) and irradiated with stirring under nitrogen in a water-cooled quartz immersion well equipped with an ozone free filter using
30 Eikosha's high-pressure UV lamp for 25min. The reaction was monitored by HPLC using Lichrosorb Si 60 (5 μm) column and 3% 2-propanol in hexane at 265nm.

The solution was concentrated in vacuo, redissolved in 100ml of ethanol and heated under reflux and nitrogen

- 21 -

for 3 hrs. Then, the solution was concentrated in vacuo and the residue was purified on a silica gel column (3.2X50cm, 170g of 75-150 μ m of silica gel) using a mixture of ethyl acetate in hexane. 0.74g (50%) of 10 was eluted with 20% ethyl acetate in hexane. [white foam]

To a solution of 1.50g (3.6mmol) of 10 in 15ml of anhydrous pyridine was added 1.50g (7.9mmol) of tosyl chloride. The mixture was stirred under nitrogen at 5°C for 20 hrs. Then, the solution was poured into 200ml of cold saturated NaHCO_3 solution. The mixture was allowed to stand for 30 min and extracted three times with 150ml of a mixture of ether and dichloromethane (4:1). Each extract was washed with 150ml of saturated NaCl solution, 150ml of cold diluted HCl solution for twice, 150ml of saturated NaCl solution, 150ml of saturated NaHCO_3 solution and 150ml of saturated NaCl solution. The combined extract was dried over Na_2SO_4 and concentrated in vacuo. 1.90g (92%) of 11 was obtained and converted to 12 without further purification. [white foam]

4.40g of anhydrous KHCO_3 was dissolved in 200ml of anhydrous methanol under nitrogen at 50°C. To this solution was added dropwise a solution of 1.90g (3.4mmol) of 11 in 30ml of anhydrous dichloromethane. The mixture was stirred under nitrogen at 50°C for 21 hrs. Then, the solution was concentrated in vacuo, the residue was dissolved in 200ml of a mixture of ether and dichloromethane (4:1) and washed twice with 100ml of water. The organic extract was separated and each washing was extracted twice with 100ml of the same mixture of ether and dichloromethane. The combined extract was dried over Na_2SO_4 and concentrated in vacuo

- 22 -

to obtain 1.50g (105%) of 12 which was hydroxylated without further purification. [yellow oil]

2.7ml (8.1mmol) of tert-butyl hydroperoxide (3.0M in 2,2,4-trimethylpentane) was added to a suspension of
5 220mg (2.0mmol) of selenium dioxide in 75ml of anhydrous dichloromethane. The mixture was stirred at room temperature under nitrogen for 30min. 0.3ml of anhydrous pyridine was added followed by a solution of 1.50g (3.5mmol) of 12 in 30ml of anhydrous
10 dichloromethane. The mixture was stirred under nitrogen at room temperature for 30min and heated under reflux for 10min. Then, 50ml of 10% NaOH solution was added and the mixture was extracted with 200, 100 and 100ml of ether. Each extract was washed with 50ml of 10% NaOH
15 solution and 50ml of saturated NaCl solution. The combined extract was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified on a silica gel column (3.2cmX15cm, 50g of 75-150 µm silica gel) using a mixture of ethyl acetate in hexane as eluant. 581mg
20 (37%) of 13 was eluted with 30% ethyl acetate in hexane. [yellow oil]

581mg (1.3mmol) of 13 was dissolved in 5ml of acetic acid and heated at 50°C under nitrogen for 1 hr. Then, the solution was poured over ice and neutralized
25 with 100ml of saturated NaHCO₃ solution. The mixture was extracted three times with 150ml of a mixture of ether and dichloromethane (4:1). Each extract was washed with 100ml of saturated NaHCO₃ solution and 100ml of saturated NaCl solution. The combined extract was dried
30 over Na₂SO₄ and concentrated in vacuo. Then, to a solution of the residue in 10ml of ethyl acetate was added 120mg of maleic anhydride and the mixture was allowed to stand under nitrogen at room temperature for 2 hrs. Then, the solution was concentrated in vacuo,

- 23 -

the residue was redissolved in 50ml of ether. 50ml of 0.1N KOH in methanol was added, the solution was stirred at room temperature for 1.5 hrs. and concentrated in vacuo. The residue was dissolved in 100ml of a mixture of ether and dichloromethane (4:1) and washed with 50ml of 10% NaOH solution for twice and 50ml of saturated NaCl solution. The organic extract was separated and each of washing was extracted twice with 100ml of the same mixture of ether and dichloromethane. The combined extract was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified on a silica gel column (2.3X8.0cm, 10g of 45~75 µm silica gel) using a mixture of ethyl acetate in hexane as eluant. 310 mg of 15 was eluted with 30% ethyl acetate in hexane, combined with another 337mg of 15 and recrystallized from methyl formate.

EXAMPLE 2

Intermediates for Side Chain

20g (0.169mol) of methyl (R)-(-)-3-hydroxy-2-methyl propionate 16 was dissolved in 60ml of anhydrous tetrahydrofuran and added under nitrogen atmosphere and ice cooling to a stirred solution of 245ml (0.735mol) of 3.0mol/l methyl magnesium bromide in ether. At the end of the addition 100ml of anhydrous tetrahydrofuran was added to facilitate stirring. The mixture was stirred at room temperature for 2 hrs, decomposed by the careful addition of 150ml of 5N HCl with ice cooling and extracted three times with 200ml of ether. Each extract was washed with 150ml of saturated NaCl solution, combined and dried over Na₂SO₄. Evaporation afforded 16.4g (82%) of 17 as yellow oil.

A mixture of 16.4g (0.139mol) of 17, 26.5g (0.139mol) of tosyl chloride and 30ml of pyridine was stirred at 4°C overnight. Then, the reaction mixture

- 24 -

was dissolved in 300ml of ether and washed with 200ml of water, 200ml of diluted HCl, 200ml of water and 200ml of saturated NaHCO₃ solution. The ether extract was separated and each washing was extracted twice with 200ml of ether. The combined extract was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified on a silica gel column (5.5X20cm, 200g of 150 425m silica gel) and 32.1g (85%) of tosylate (18) was eluted with 10-20% ethyl acetate in hexane. [red oil]

10 To a stirred solution of 14.4g (0.131mol) of thiophenol in 70ml of anhydrous dimethyl formamide 14.4g (0.131mol) of t-BuOK was added followed by 32.1g (0.118mol) of 18 in 90ml anhydrous dimethyl formamide. The mixture was stirred overnight, dissolved in 300ml of 15 ice water and extracted with 300, 200 and 200ml of ethyl acetate. Each extract was washed with 200ml saturated NaHCO₃ solution and water, combined, dried over Na₂SO₄ and concentrated in vacuo. 28.0g (113%, containing dimethyl formamide) of 19 was obtained and was oxidized 20 without further purification. [red oil]

28.0 (0.118mol) of 19 was dissolved in 400ml of dichloromethane and cooled with ice water. To this solution was added 51.7g (0.300mol) of m-chloroperbenzoic acid slowly, the mixture was stirred 25 at room temperature for 2 hrs. and filtered. The filtrate was washed with 300ml of saturated NaHCO₃ solution for twice, 300ml of saturated Na₂SO₃ solution for twice and 300ml of saturated NaHCO₃ solution. The organic phase was separated and each washing was 30 extracted twice with 300ml of dichloromethane. The combined extract was dried over Na₂SO₄, concentrated in vacuo and recrystallized from a mixture of ethyl acetate in hexane to obtain 20 25.2g (88%). [white crystals]

To a stirred solution of 20g (0.083mol) of 20 in

- 25 -

50ml of dichloromethane was added 20ml (0.221mol) of freshly distilled 2,3-dihydropyran followed by 0.8g of pyridinium p-toluenesulfonate. The mixture was stirred at room temperature for 2 hrs. and washed twice with
5 saturated NaCl solution. The organic phase was separated and each of washing was extracted twice with 50ml of dichloromethane. The combined extract was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified on a silica gel column (3.2X45cm, 150g of 75 -
10 150 µm silica gel) and 26.0g (96%) of 21a was eluted with benzene as eluant. [colorless oil]

EXAMPLE 3

To a solution of ergosterol 1 in anhydrous pyridine is added acetic anhydride. The mixture is stirred at
15 room temperature overnight and water is added. The precipitate is filtered off, washed several times with water and recrystallized from ethanol to obtain 2.

To a solution of the precipitate 2 in chloroform is added 4-phenyl-1, 2, 4-triazoline-3,5-dione. The
20 solution is stirred at room temperature and pyridine is added. The solution is cooled and treated with an ozone-oxygen mixture (TLC control) and thoroughly purged with nitrogen. Dimethyl sulfide is added and the mixture is washed with water, 2N HCl and then water again. The
25 organic layer is separated and each washing is extracted with chloroform. The combined extract is dried over Na₂SO₄ and concentrated in vacuo. The residue is purified by silica gel chromatography to obtain compound 4.

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To a stirred solution of sulfone 35, diisopropyl amine and anhydrous tetrahydrofuran (containing 1,10-phenanthroline as indicator) under nitrogen atmosphere is added n-BuLi (1.6M in hexane). The solution is

- 26 -

stirred under nitrogen, then, compound 4 in anhydrous tetrahydrofuran is added. The mixture is stirred, decomposed by the addition of saturated NH_4Cl solution, warmed and extracted three times with ethyl acetate.

5 Each extract is washed with saturated NaCl solution, dried over Na_2SO_4 and concentrated in vacuo. The residue is purified on a silica gel column to afford compound 22.

10 A mixture of hydroxysulfones 22, 5% sodium amalgam and methanol saturated with Na_2HPO_4 is stirred under nitrogen atmosphere. The reaction solution is decanted and concentrated in vacuo. The residue is dissolved in ethyl acetate and washed with water. The ethyl acetate extract is separated and each washing is extracted twice
15 with ethyl acetate. The combined extract is dried over Na_2SO_4 and concentrated in vacuo to obtain 23.

To a solution of compound 23 in tetrahydrofuran is added LiAlH_4 . The mixture is heated under reflux and nitrogen atmosphere, cooled with ice water and
20 decomposed by the dropwise addition of ethyl acetate and water. Then, the mixture is filtered and the filtrate is concentrated in vacuo. The residue is dissolved in ethyl acetate and washed twice with saturated NaCl solution. The ethyl acetate extract is separated and
25 each washing is extracted with ethyl acetate. The combined extract is dried over Na_2SO_4 and concentrated in vacuo. Then, the residue is purified on a silica gel column to provide compound 24.

30 Compound 24 is dispersed in a mixture of ether and benzene (4:1) and irradiated with stirring under nitrogen in a water-cooled quartz immersion well equipped with an ozone free filter using a high-pressure UV lamp. The reaction may be monitored by HPLC.

- 27 -

The solution is concentrated in vacuo, redissolved in ethanol and heated under reflux and nitrogen. Then, the solution is concentrated in vacuo and the residue is purified on a silica gel column to obtain compound 26.

5 To a solution of compound 26 in anhydrous pyridine is added tosyl chloride. The mixture is stirred under nitrogen. Then, the solution is poured into a cold saturated NaHCO_3 solution. The mixture is allowed to stand for 30min and extracted three times with a mixture
10 of ether and dichloromethane (4:1). Each extract is washed with saturated NaCl solution, cold diluted HCl solution twice, saturated NaCl solution, saturated NaHCO_3 solution and saturated NaCl solution. The combined extract is dried over Na_2SO_4 and concentrated in
15 vacuo. Compound 27 is obtained and converted to 28 without further purification.

Anhydrous KHCO_3 is dissolved in anhydrous methanol under nitrogen. To this solution is added dropwise a solution of compound 27 in anhydrous dichloromethane.
20 The mixture is stirred under nitrogen. Then, the solution is concentrated in vacuo, the residue is dissolved in a mixture of ether and dichloromethane (4:1) and washed twice with water. The organic extract is separated and each washing is extracted twice with
25 the same mixture of ether and dichloromethane. The combined extract is dried over Na_2SO_4 and concentrated in vacuo to obtain Compound 28 which is hydroxylated without further purification.

30 Tert-butyl hydroperoxide (3.0M in 2,2-4-trimethylpentane) is added to a suspension of selenium dioxide in anhydrous dichloromethane. The mixture is stirred at room temperature under nitrogen. Anhydrous pyridine is added followed by a solution of compound 28 in anhydrous dichloromethane. The mixture

- 28 -

is stirred under nitrogen at room temperature and heated under reflux. Then, a 10% NaOH solution is added and the mixture is extracted with ether. Each extract is washed with a 10% NaOH solution and a saturated NaCl solution. The combined extract is dried over Na₂SO₄ and concentrated in vacuo. The residue is purified on a silica gel column to obtain compound 29.

Compound 29 is dissolved in acetic acid and heated under nitrogen. Then, the solution is poured over ice and neutralized with saturated NaHCO₃ solution. The mixture is extracted three times with a mixture of ether and dichloromethane (4:1). Each extract is washed with a saturated NaHCO₃ solution and a saturated NaCl solution. The combined extract is dried over Na₂SO₄ and concentrated in vacuo. Then, to a solution of the residue in ethyl acetate is added maleic anhydride and the mixture is allowed to stand under nitrogen at room temperature. Then, the solution is concentrated in vacuo, the residue is redissolved in ether. KOH in methanol is added, the solution is stirred at room temperature and concentrated in vacuo. The residue is dissolved in a mixture of ether and dichloromethane (4:1) and washed with 10% NaOH solution twice and a saturated NaCl solution. The organic extract is separated and each washing is extracted twice with the same mixture of ether and dichloromethane. The combined extract is dried over Na₂SO₄ and concentrated in vacuo. The residue is purified on a silica gel column using a mixture of ethyl acetate in hexane as eluant to obtain compound 31.

EXAMPLE 4

Intermediates for Side Chain

A mixture of compound 32, tosyl chloride and pyridine is stirred overnight. Then, the reaction

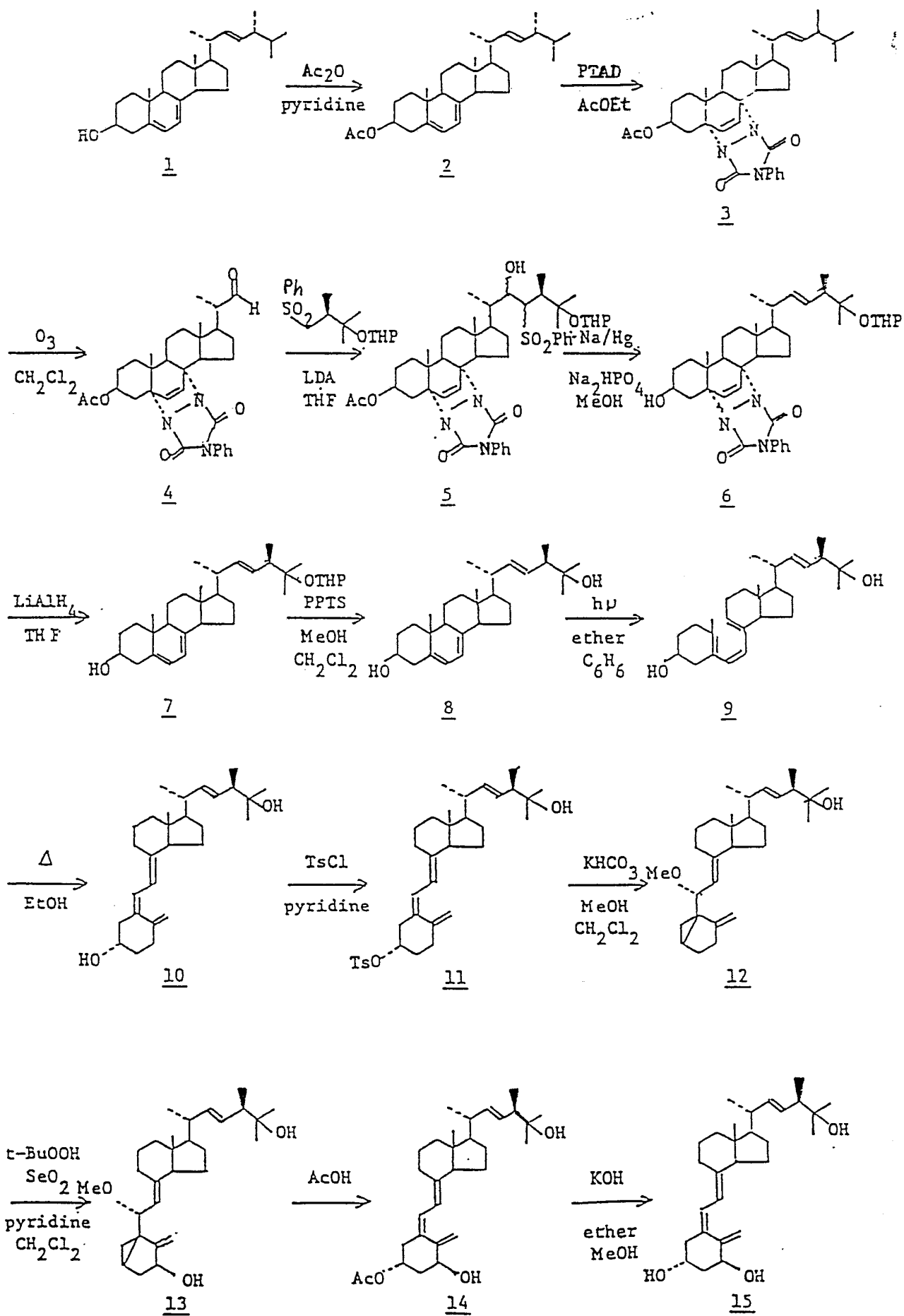
- 29 -

mixture is dissolved in ether and washed with water, diluted HCl, water and saturated NaHCO₃ solution. The ether extract is separated and each washing is extracted twice with ether. The combined extract is dried over
5 Na₂SO₄ and concentrated in vacuo. The residue is purified on a silica gel column to give tosylate (33).

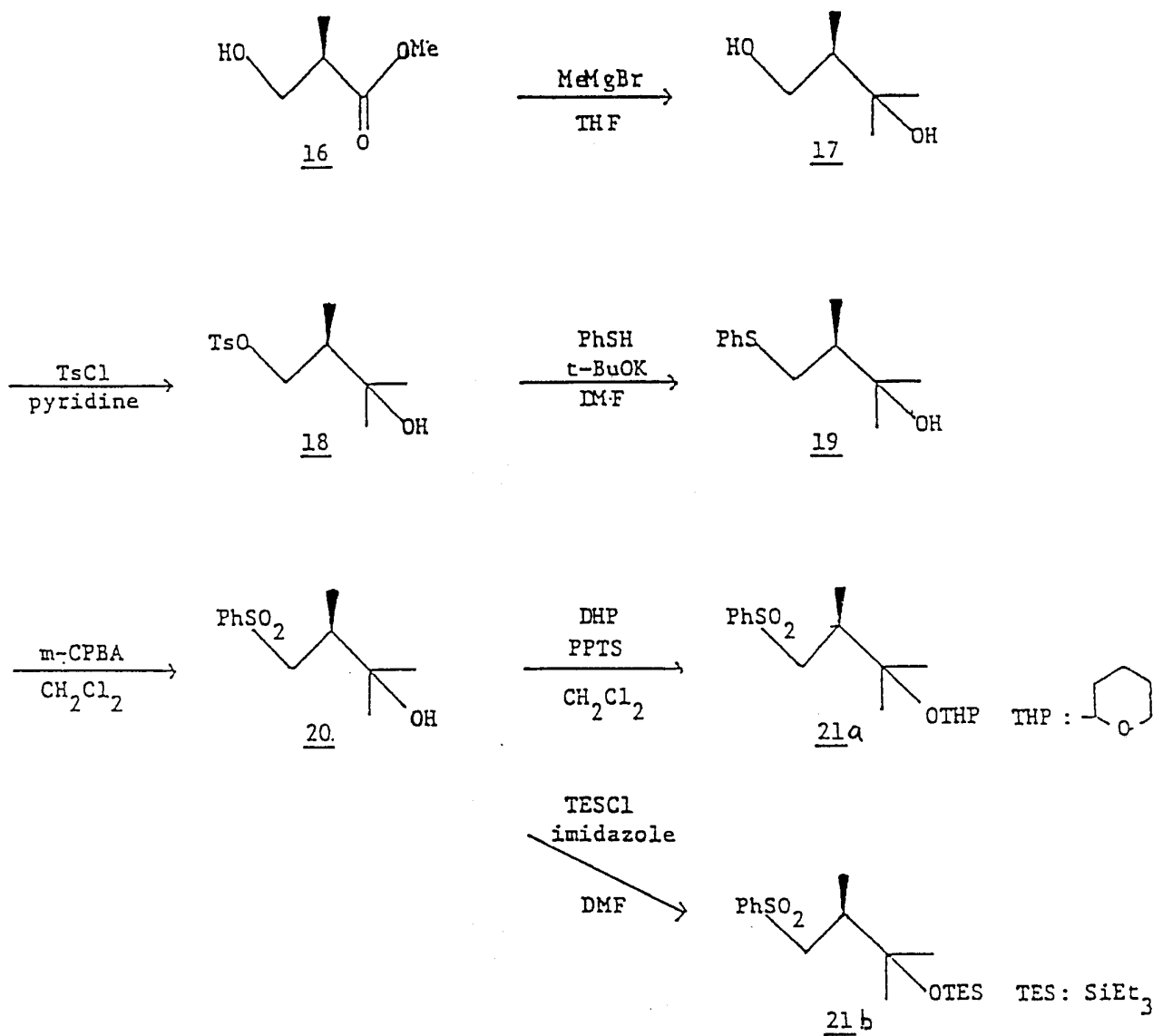
To a stirred solution of thiophenol in anhydrous dimethyl formamide t-BuOK is added followed by compound 33 in anhydrous dimethyl formamide. The mixture is
10 stirred overnight, dissolved in ice water and extracted with ethyl acetate. Each extract is washed with a saturated NaHCO₃ solution and water, combined, dried over Na₂SO₄ and concentrated in vacuo. Compound 34 is obtained and oxidized without further purification.

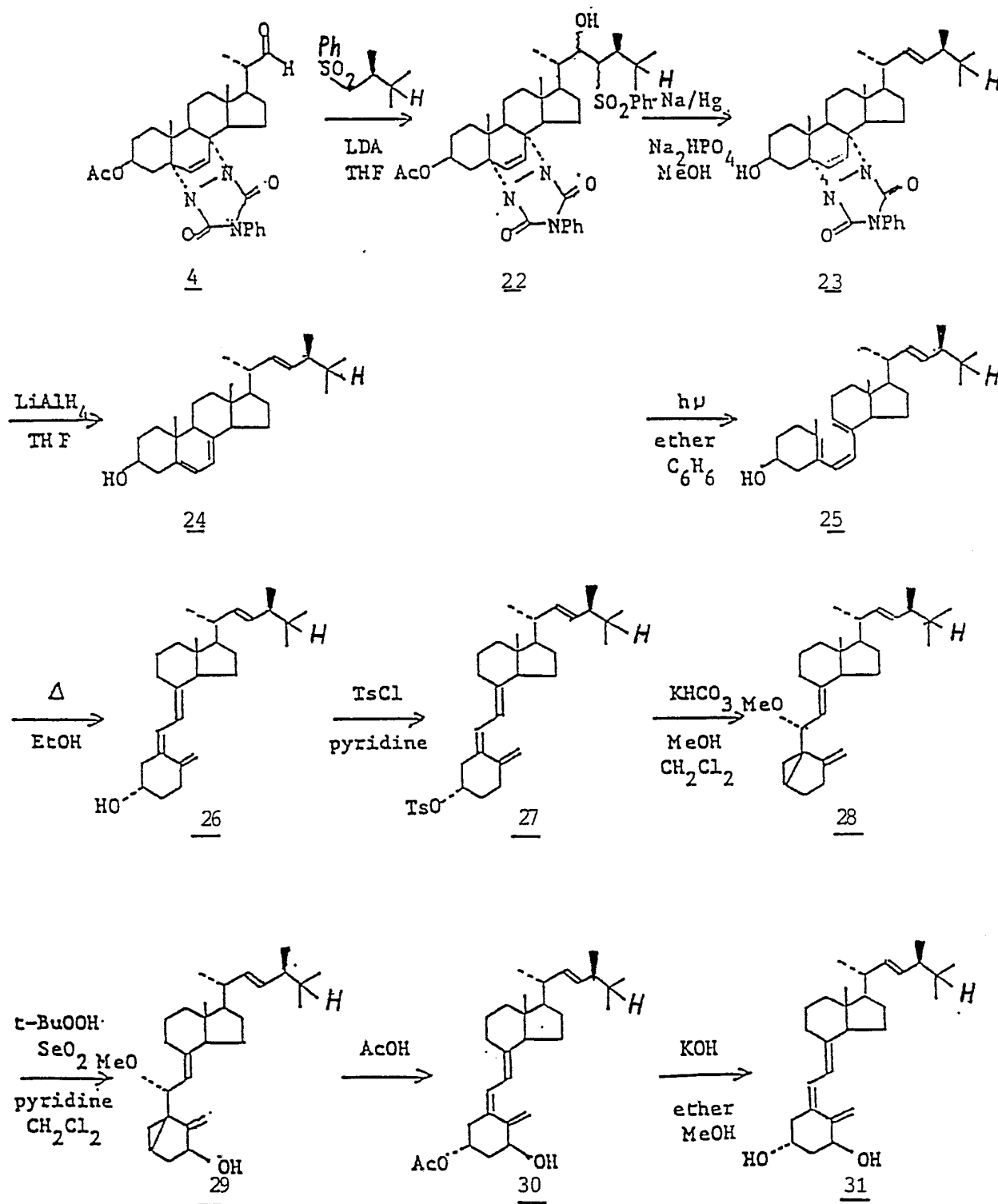
15 Compound 34 is dissolved in dichloromethane and cooled with ice water. To this solution is added m-chloroperbenzoic acid slowly, the mixture is stirred at room temperature for 2 hrs. and filtered. The filtrate is washed with a saturated NaHCO₃ solution twice, a
20 saturated Na₂SO₃ solution twice and a saturated NaHCO₃ solution. The organic phase is separated and each washing is extracted twice with dichloromethane. The combined extract is dried over Na₂SO₄, concentrated in vacuo and recrystallized from a mixture of ethyl acetate
25 in hexane to form compound 35.

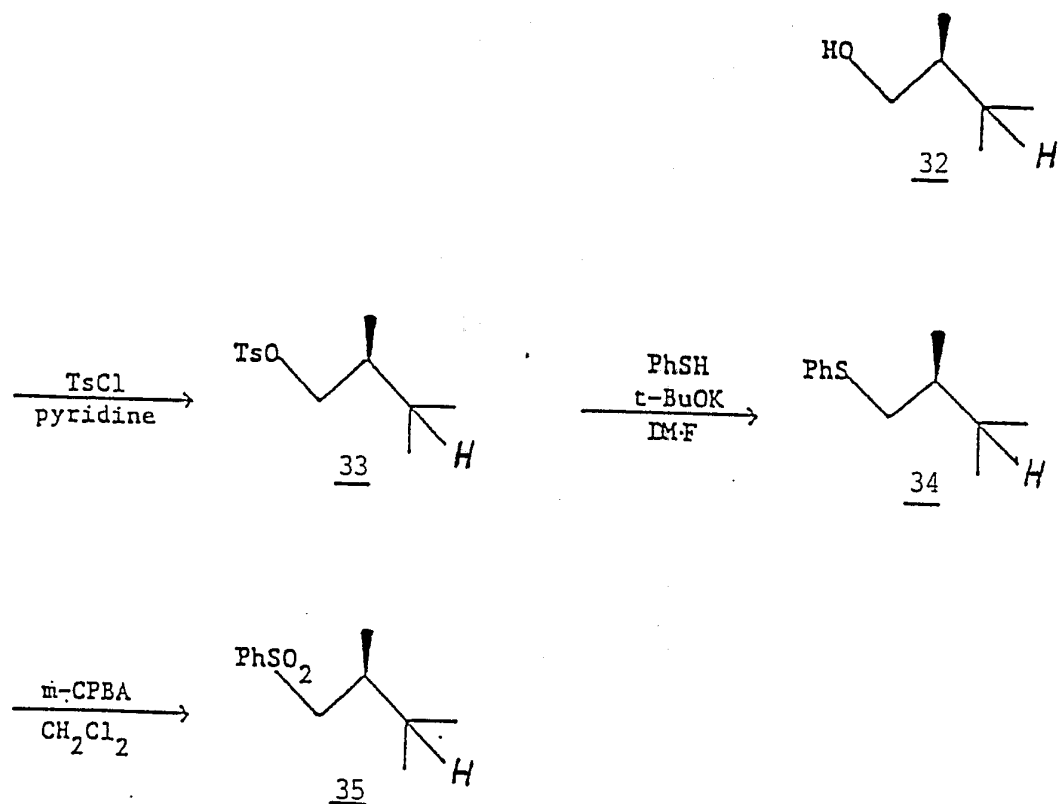
PROCESS SCHEME I



-31-

PROCESS SCHEME II

PROCESS SCHEME III

PROCESS SCHEME IV

- 34 -

Various modes of carrying out the invention are contemplated as being within the scope of the following claims particularly pointing out and distinctly claiming the subject matter regarded as the invention.

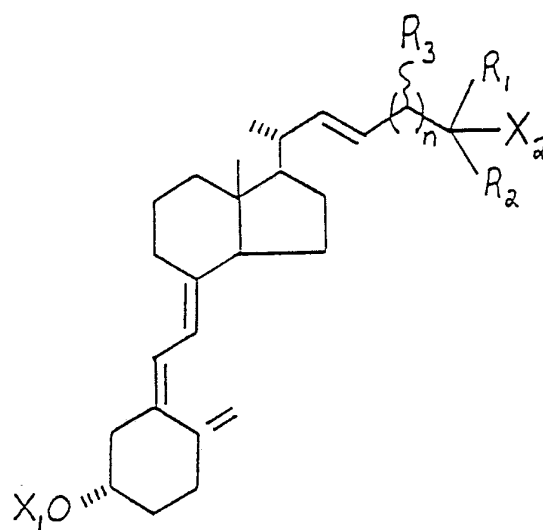
We claim:

1. A method for preparing vitamin D compounds having the formula

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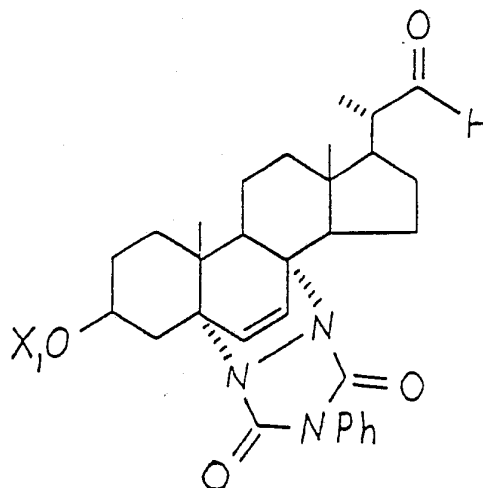
25

where R_3 may have the R or S configuration and wherein n is an integer having a value of from 1 to 5, X_1 is selected from hydrogen or a hydroxy protecting group, X_2 is selected from hydrogen, hydroxy, and protected hydroxy, R_3 is selected from alkyl, hydroxy, protected hydroxy, hydrogen or fluorine, and wherein R_1 and R_2 , which may be the same or different, are each selected from an alkyl or aryl group, which comprises condensing a steroidal aldehyde of the formula

- 35 -

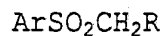
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wherein X_1 is as defined above, with a arylsulfone of the formula

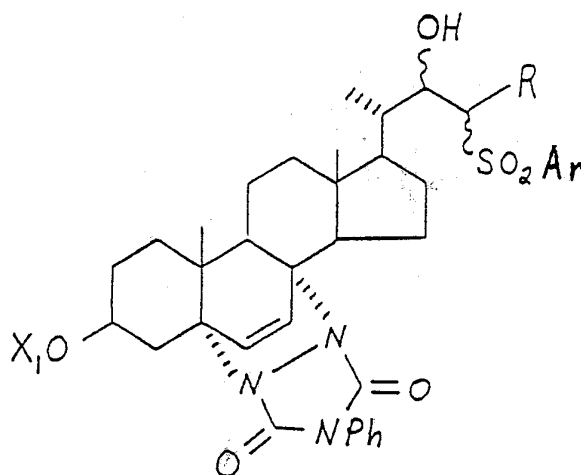


wherein R is selected from the group consisting of
 45 alkyl, hydroxylated alkyl, hydroxy-protected
 hydroxylated alkyl, fluoro-substituted alkyl, fluoro-
 substituted hydroxylated alkyl and fluoro-substituted
 hydroxy-protected alkyl, wherein a hydroxy-sulfonyl
 adduct of the formula

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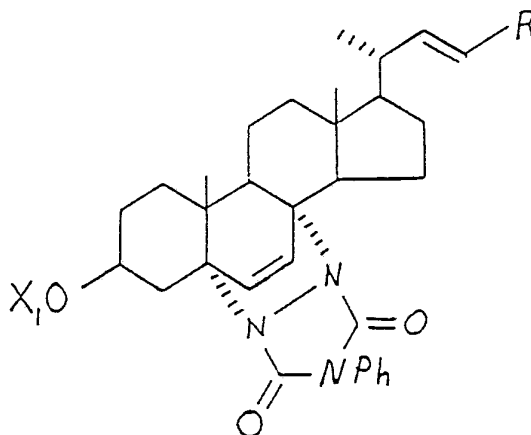


- 36 -

is obtained, wherein R and X₁ are as defined above, optionally acylating or sulfonylating the C-22-hydroxy group of said adduct, reducing said adduct to obtain an intermediate of the formula

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wherein R and X₁ are as defined above, and converting said intermediate to obtain the desired vitamin D compound.

2. The method of claim 1 wherein X₁ and X₂ are both hydrogen.

3. The method of claim 2 wherein R₁ and R₂ are both an alkyl group.

4. The method of claim 1 wherein X₁ is hydrogen and X₂ is hydroxy.

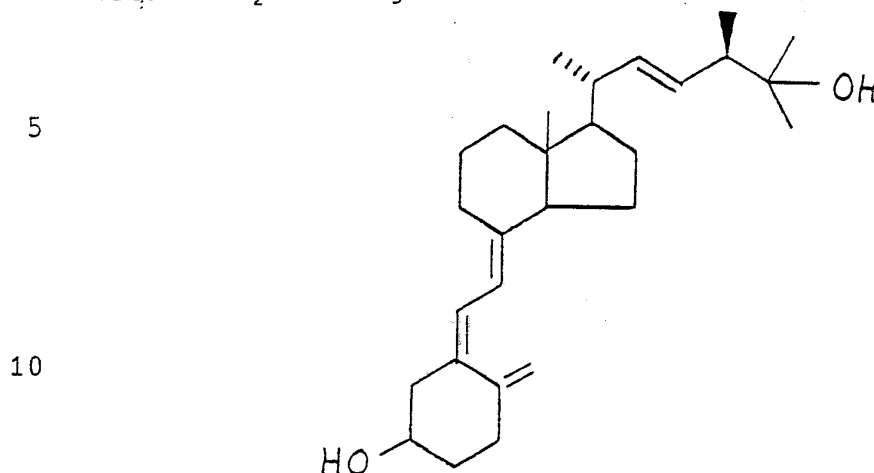
5. The method of claim 4 wherein R₁ and R₂ are both an alkyl group.

6. The method of claim 1 wherein the vitamin D compound is 25-hydroxy-24-epi-vitamin D₂.

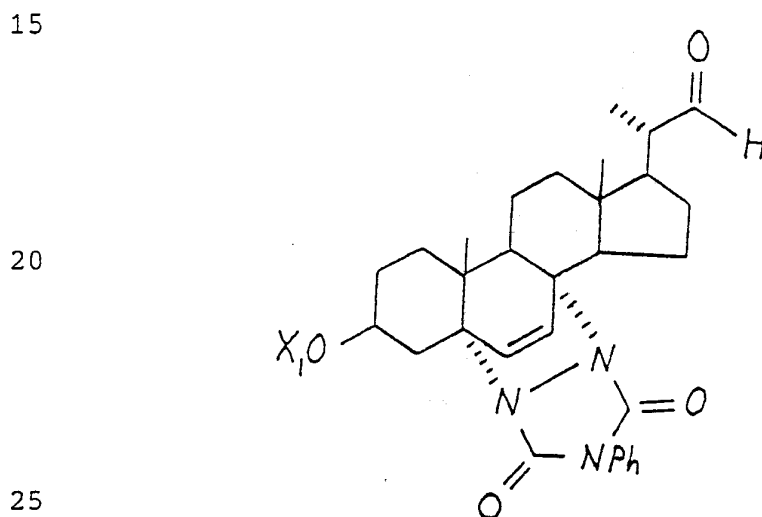
7. The method of claim 1 wherein the desired vitamin D compound is further subjected to a 1 α hydroxylation process so as to obtain the corresponding 1 α -hydroxylated vitamin D compound.

- 37 -

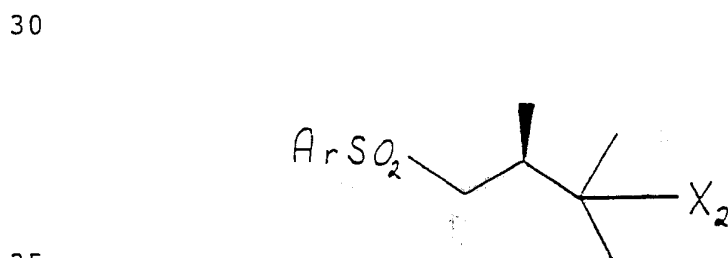
8. A method for preparing 25-hydroxy-24-epi-vitamin D₂ having the formula



which comprises condensing a steroidal aldehyde of the formula:



where X₁ is a hydroxy protecting group, with an arylsulfone of the formula

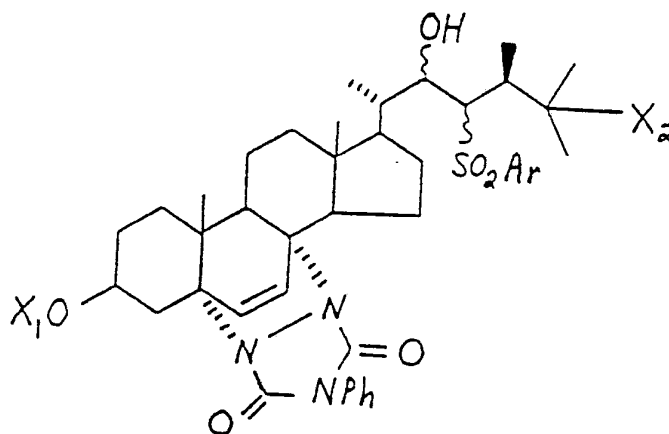


- 38 -

wherein X_2 is a protected hydroxy group whereby a hydroxy-sulfonyl adduct of the formula

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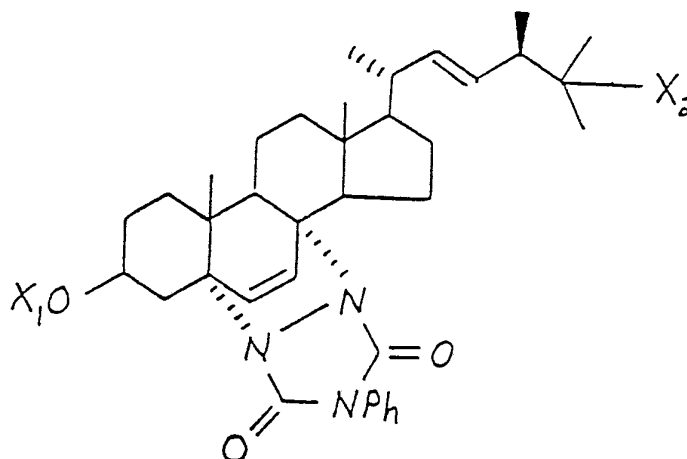


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is obtained wherein X_1 and X_2 are as defined above, optionally acylating or sulfonylating the C-22-hydroxy group of said adduct, reducing said adduct to obtain an intermediate of the formula

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where X_1 is hydrogen or a hydroxy protecting group, and X_2 is a protected hydroxy group, and converting said intermediate to obtain 25-hydroxy-24-epi-vitamin D_2 .

- 39 -

9. The method of claim 8 wherein 25-hydroxy-24-epi-vitamin D₂ is further subjected to a 1 α hydroxylation process so as to obtain the corresponding 1 α hydroxylated vitamin D compound.

10. The method of claim 9 wherein the compound is 1 α ,25-dihydroxy-24-epi-vitamin D₂.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 91/00977

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ⁵ : C 07 C 401/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC ⁵	C 07 C 401/00	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched *		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁸		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	WO, A, 8503939 (WISCONSIN ALUMINI RESEARCH FOUNDATION) 12 September 1985 see the whole document ---	1-10
X	Bioorganic Chemistry, volume 15, no. 2, June 1987, American Press, Inc., R.R. Sicinski et al.: " Δ^{22} -unsaturated analogs of vitamin D ₃ and their C(1)- hydroxylated derivatives", pages 152- 166 see the whole document ---	1-3,7
X	Tetrahedron Letters, volume 22, no. 27, 1981, Pergamon Press Ltd., (GB) S. Yamada et al.: "Stereoselective synthesis of (25S)-25-hydroxyvitamin D ₃ 26,23-lactone", pages 2591-2594 see the whole document --- ./.	1,4-5
* Special categories of cited documents: ¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published 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; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
21st May 1991	11. 07. 91	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	F.W. HECK 	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, " with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	The Journal of Organic Chemistry, volume 49, no. 12, 15 June 1984, American Chemical Society, J.W. Morzycki et al.: "Synthesis of 25-hydroxyvitamin D ₂ and its 24-epimer", pages 2148-2151 see the whole document ---	1,6
X	EP, A, 0337305 (NISSHIN FLOUR MILLING CO) 18 October 1989 see the whole document, especially pages 4-5 ---	1,8
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