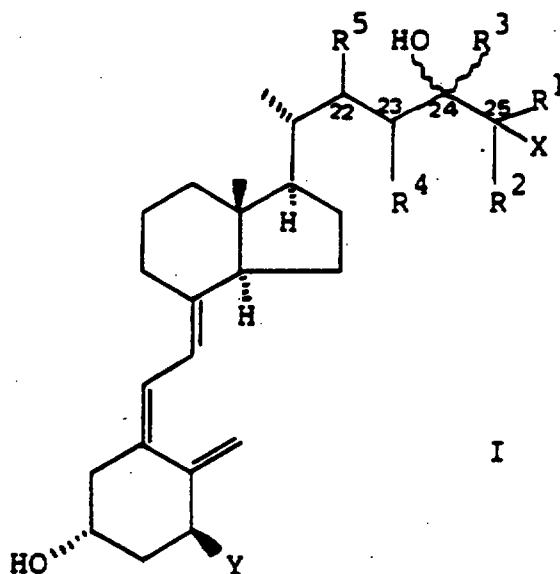


Description

This invention relates to a hitherto unknown class of compounds which shows strong activity in inducing differentiation and inhibiting undesirable proliferation of certain cells, including cancer cells and skin cells, to pharmaceutical Preparations containing these compounds, to dosage units of such Preparations, and to their use in the treatment of diseases characterized by abnormal cell differentiation and/or cell proliferation.

The compounds of the invention constitute a novel class of vitamin D analogues and are represented by the general formula I



in which formula (and also throughout the remainder of this disclosure) X stands for hydrogen, lower alkyl, halogen or hydroxy; Y stands for hydrogen or hydroxy; R¹ and R², which may be the same or different, stand for lower alkyl, optionally substituted with halogen or hydroxy (but with the proviso that R¹ and R² cannot both be methyl when X is other than lower alkyl), or, taken together with the carbon atom numbered 25, R¹ and R² can form a saturated or unsaturated C₃-C₉ carbocyclic ring (including an aromatic ring) which may optionally be substituted at any possible position(s) with lower alkyl, halogen or hydroxy; R³ stands for hydrogen or lower alkyl; and R⁴ and R⁵ represent either each hydrogen, or when taken together constitute a bond, with the result that a double bond connects carbon atoms numbered 22 and 23; and the two undulated bonds to carbon 24 indicate that both R and S forms at this centre are within the scope of the invention. In the context of this invention the expression "lower alkyl" indicates a straight or branched saturated or unsaturated carbon chain with a content of from 1 to 6 carbon atoms.

As it can be seen, the compounds of formula I, depending on the meanings of R¹, R², R³, R⁴ and R⁵, and/or X, contain one or more additional asymmetric carbon atoms and/or double bonds, and may thus form stereoisomeric forms. The invention covers all these compounds in pure form and also mixtures of them. It should be noted, however, that our investigations indicate a notable difference in activity between the stereoisomeric forms. In addition, derivatives of I in which one or more of the hydroxy groups are masked as groups which can be reconverted to hydroxy groups *in vivo* are also within the scope of the invention ("bioreversible derivatives or pro-drugs of I").

Especially preferred are compounds of formula I in which Y is hydroxy and R³ stands for hydrogen or methyl, and in particular compounds in which R⁴ and R⁵ taken together represent a bond, especially in such a way that the resulting 22, 23-double bond has the trans configuration.

The term "bioreversible derivatives or prodrugs of I" includes, but is not limited to, derivatives of the compounds of formula I in which one or more hydroxy groups have been transformed into -O-acyl or -O-glycosyl groups, such masked groups being hydrolyzable *in vivo*.

It has recently been shown that certain vitamin D derivatives, in particular 1,25(OH)₂D₃ (1 α ,25-dihydroxy-vitamin D₃) are able to stimulate the differentiation of cells and inhibit excessive cell proliferation, and it has been suggested that these compounds might be useful in the treatment of diseases characterized by abnormal cell proliferation and/or cell differentiation such as leukemia, myelofibrosis and psoriasis. However, the well known potent effects of these compounds on calcium metabolism prohibit the use of higher doses, which will give rise to hypercalcemia. Thus, these compounds are not completely satisfactory for use as drugs in the treatment of e. g. psoriasis or leukemia, which may require continuous administration of the drug in relatively high doses.

It has now surprisingly turned out that the compounds of the invention have a favourable therapeutic index and are particularly useful in the treatment of human and veterinary disorders which are characterized by abnormal cell proliferation and/or cell differentiation, such as certain dermatological disorders including

psoriasis and certain cancer forms, e. g. leukemia and myelofibrosis.

A number of cells, including skin cells and cancer cells, contain receptors for $1,25(\text{OH})_2\text{D}_3$. The compounds of the invention have thus been tested *in vitro* for their ability to interact with the receptor in such cells, and for their effect on the proliferation and differentiation of such cells (e. g. the human monocytic tumour cell line U 937). *In vivo*, the compounds were tested after p. o. and i. p. administration to rats for effects on calcium metabolism. The compounds were compared with $1,25(\text{OH})_2\text{D}_3$ in the *in vitro* experiments and with $1\alpha(\text{OH})\text{D}_3$ and $1,25(\text{OH})_2\text{D}_3$ in the *in vivo* experiments.

From the above tests, it was shown that e. g. compound 59* (* See Table 2) binds strongly to the receptor and is a potent inhibitor of cell proliferation and inducer of cell differentiation *in vitro*. *In vivo*, compared to $1,25(\text{OH})_2\text{D}_3$ and $1\alpha(\text{OH})\text{D}_3$, it showed only weak vitamin D activity and could be administered at much higher doses without having any toxic effects.

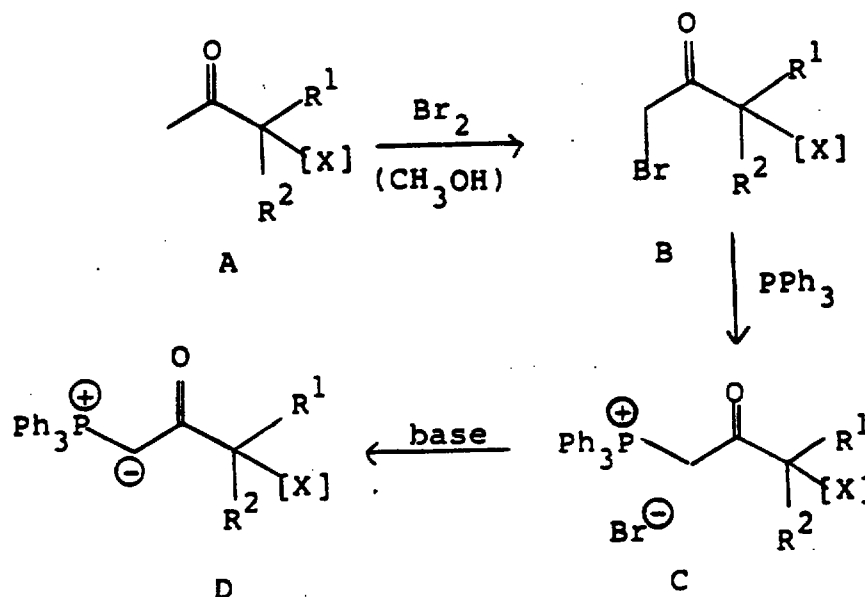
Thus, a favourable separation of the biological effects on cell differentiation/proliferation and on calcium metabolism has been clearly demonstrated.

Compound I can be prepared by total synthesis, or, more conveniently, by partial synthesis from readily available precursors, either steroidal, for example dinorcholenic acid, ergosterol, stigmasterol, or seco-steroidal e. g. vitamin D_2 . The route described below by way of example utilises vitamin D_2 as starting material, and is considered to be the most flexible of the routes explored to date, being very suitable for the synthesis of a large number of compounds represented by formula I. However, it should be noted that the synthesis of a particular compound on a production scale may well be more conveniently carried out from an alternative starting material and/or by an alternative route. Two such routes are outlined later on. The compound I can readily be obtained in crystalline form by crystallization from common organic solvents or mixtures thereof, as well known in the art.

The synthetic strategy involves the modification of the ring D side chain present in the (seco-)steroidal precursor to a 1S-formylethyl group followed by elaboration of the new side chain present in the particular target compound I. At some stage in the synthesis the rest of the full vitamin D skeleton must be elaborated. The way this is done in practice depends on the starting material and the new side chain in question, and in addition the order of some of the reaction steps can be altered with the result that not all the possible intermediates can be exemplified here. Furthermore, the nature of the various activating groups, protecting groups, and methods for masking the triene moiety can be different to those exemplified. However, any such changes still fall within the scope of this invention.

One synthetic route will now be described in detail. In the reaction scheme, the triene moiety of the vitamin D nucleus is masked as the adduct with SO_2 (other dienophiles which can be used include for example 4-phenyl-1,2,4-triazoline-3,5-dione and phthalazine-1,4-dione, as known in the art), and the ring A hydroxyl groups are protected as tert-butyldimethylsilyl (t-BuMe₂Si) ethers (other suitable protecting groups are well known in the art and include the etherifying and esterifying groups e. g. as described in "Protective Groups in Organic Synthesis", T.W. Greene, Wiley, New York, 1981). The coupling of the aldehyde function with a side chain fragment is done at the 5,6-trans vitamin stage (other possibilities include the *cis*-vitamin stage or masked triene stage, the requisite aldehyde being obtained by altering the order of reactions). The incorporation of the side chain fragment involves a Wittig reaction (other types of coupling, e. g. aldol reaction, or reaction with a sulphone anion, followed by elimination or reductive elimination, are well known in the art), the ylide being a triphenylphosphorane (other types of ylide being well known in the art). Finally, [X] represents either X of formula I, or a protected or masked derivative which can be converted to X at some stage in the synthesis (and not necessarily the last stage as indicated on the Scheme).

As shown on the Reaction Scheme which follows, the synthesis involves the Preparation of the important key intermediate 12 which is used to prepare compounds of formula I in which Y stands for OH. The corresponding compound I in which Y = H is prepared analogously from 13. An alternative key intermediate is the corresponding 5,6-*cis* aldehyde 14, which can be used analogously to 13 or 12 in the subsequent step on the Scheme to give the corresponding 5,6-*cis* isomer of II and hence III. Reaction h then converts these isomers directly to the corresponding V. The continuation of the synthesis after 12 or 13 (or 14) requires the reaction with a side chain fragment (D), the synthesis of which can be achieved for example by the following route:



The side chain fragments shown in Table I are selected for the purposes of illustration and are described in the Preparations.

Table I

Side Chain Fragment (D)	R ¹	R ²	X or [X]
D(i)		-(CH ₂) ₂ -	H
D(ii)		-(CH ₂) ₄ -	H
D(iii)		-(CH ₂) ₅ -	H
D(iv)	CH ₃	CH ₃	CH ₃
D(v)		=CH-(CH=CH) ₂ -	

The ketone A, if not commercially available, may be prepared by literature methods and is converted to the bromomethyl ketone B by literature methods. In some cases B are commercially available starting materials.

In the Preparations, the starting materials/intermediates A, B and C (if described) are also given corresponding suffixes (i) - (v) to indicate the nature of R¹, R² and [X] (e. g. for the sequence A(i) → B(i) → C(i) → D(i)).

In order to describe further the invention, but not in any way to limit it, the details for the synthesis of some particular examples of compounds of formula I are given.

For the purpose, the Reaction Scheme and Notes should be read with reference to Tables 1 and 2 and to the preparations and Examples.

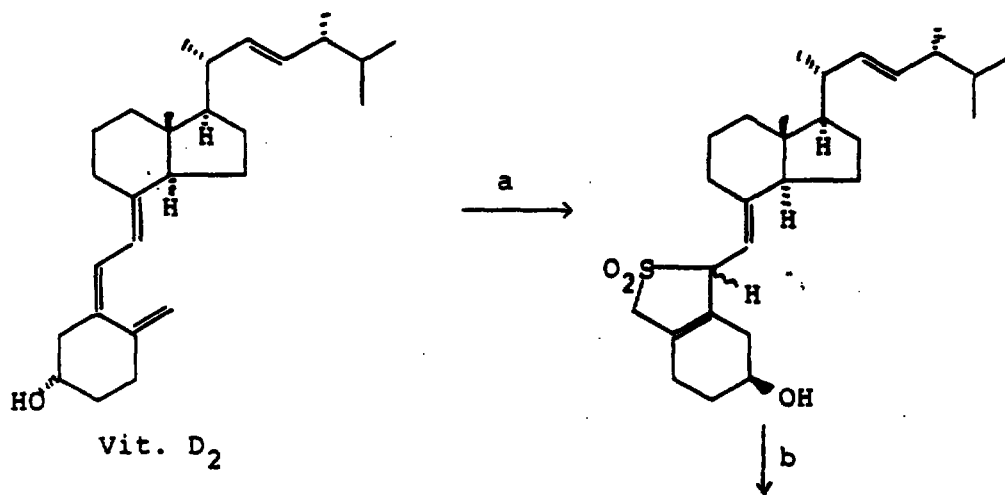
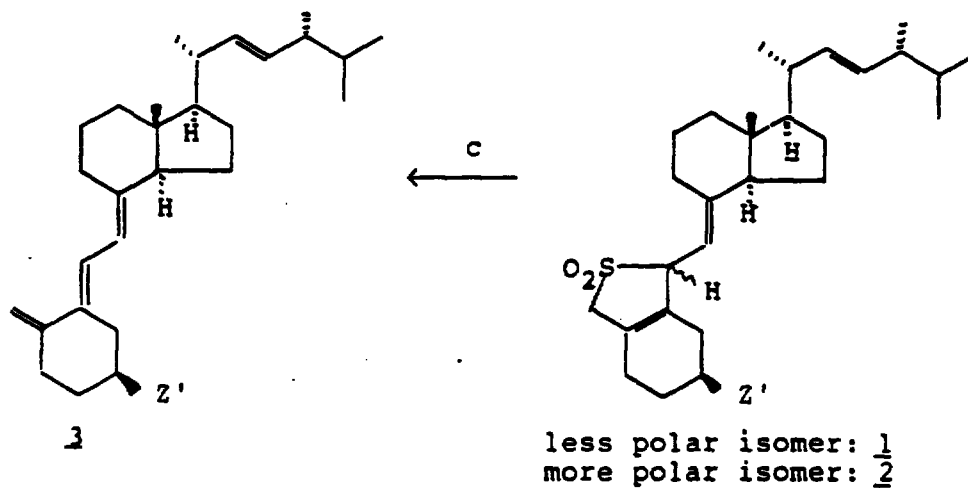
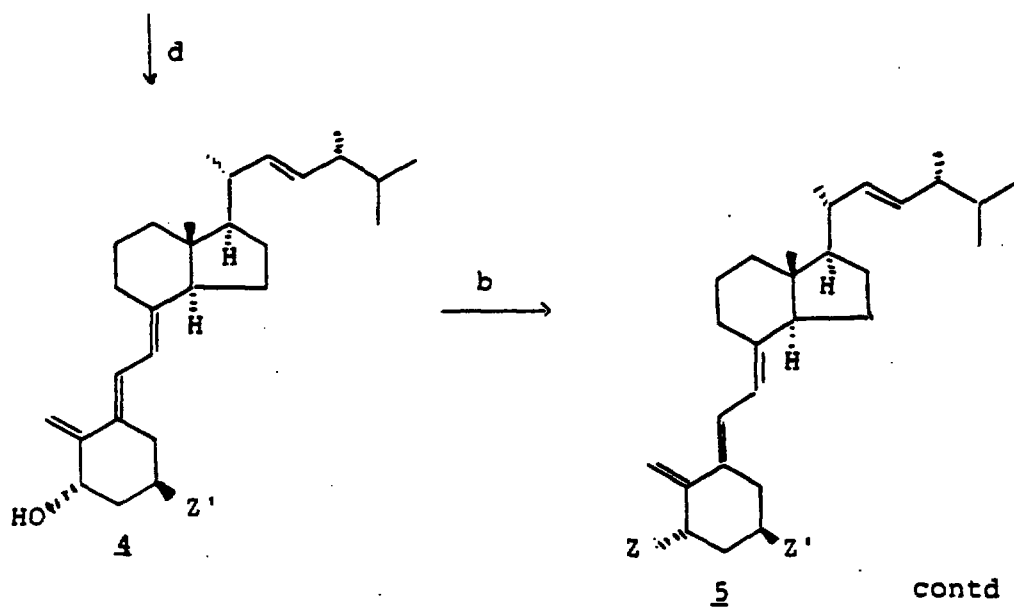
Notes to Reaction Scheme

On the Scheme, Z' represents an optionally protected hydroxy group, and Z also represents an optionally protected hydroxy group (which maybe the same or different to Z') unless it is stated that Z = H, in which case Z represents hydrogen.

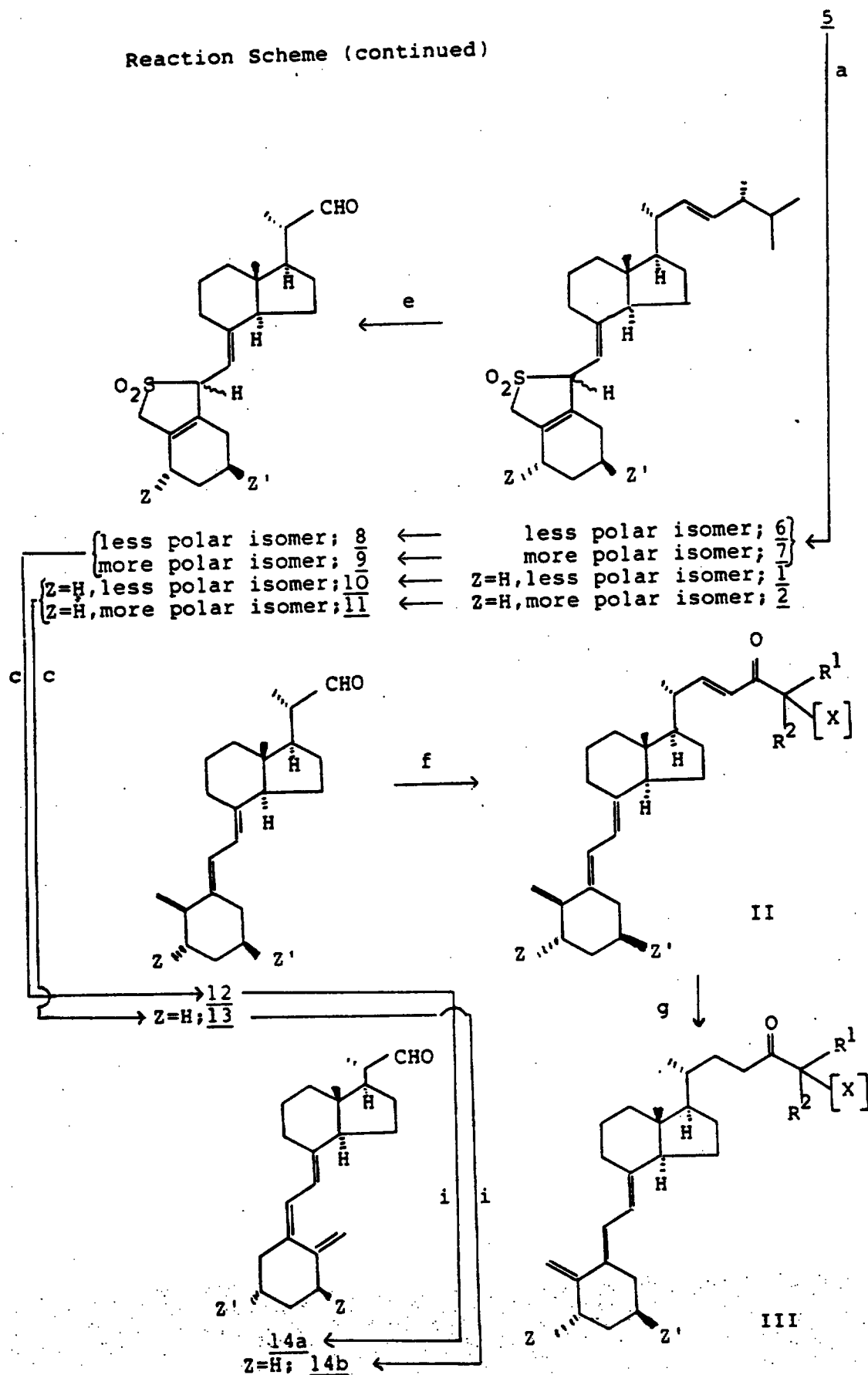
For the specific numbered compounds described in Table 2 and in the Preparations and Examples, Z' = t-BuMe₂SiO, and Z = Z' unless stated otherwise, which requires step "b" to be a tert-butyldimethylsilylation reaction e. g. with t-BuMe₂SiCl - imidazole) and step "j" to be a de-tertbutyldimethylsilylation reaction (e. g. with n-Bu₄NF).

a. SO₂; b. Optional hydroxyl protection reaction; c. NaHCO₃ (boiling EtOH); d. SeO₂ - N-methylmorpholine N-oxide (MeOH-CH₂Cl₂); e. (i) O₃ (ii) PPh₃; f. Side chain fragment D (see Table 1); g. 1, 4-Reduction under suitable conditions with a selective reducing agent, e. g. Na₂S₂O₄ under phase transfer conditions; h. Formal source of "R³ ⁻" - when R³ = H; e. g. NaBH₄ or other reducing agent; when R³ = alkyl, e. g. Grignard or other organometallic reagent. A radiolabel can be conveniently introduced at this stage by using a suitable source of radioactive R³ (e. g. for R³ = or ¹⁴CH₃); i. hy-triplet sensitizer; j. Optional hydroxyl deprotection reaction(s); k. Any necessary reaction (sequence) for converting [X] to X.

Reaction Scheme



Reaction Scheme (continued)



Reaction Scheme (continued further)

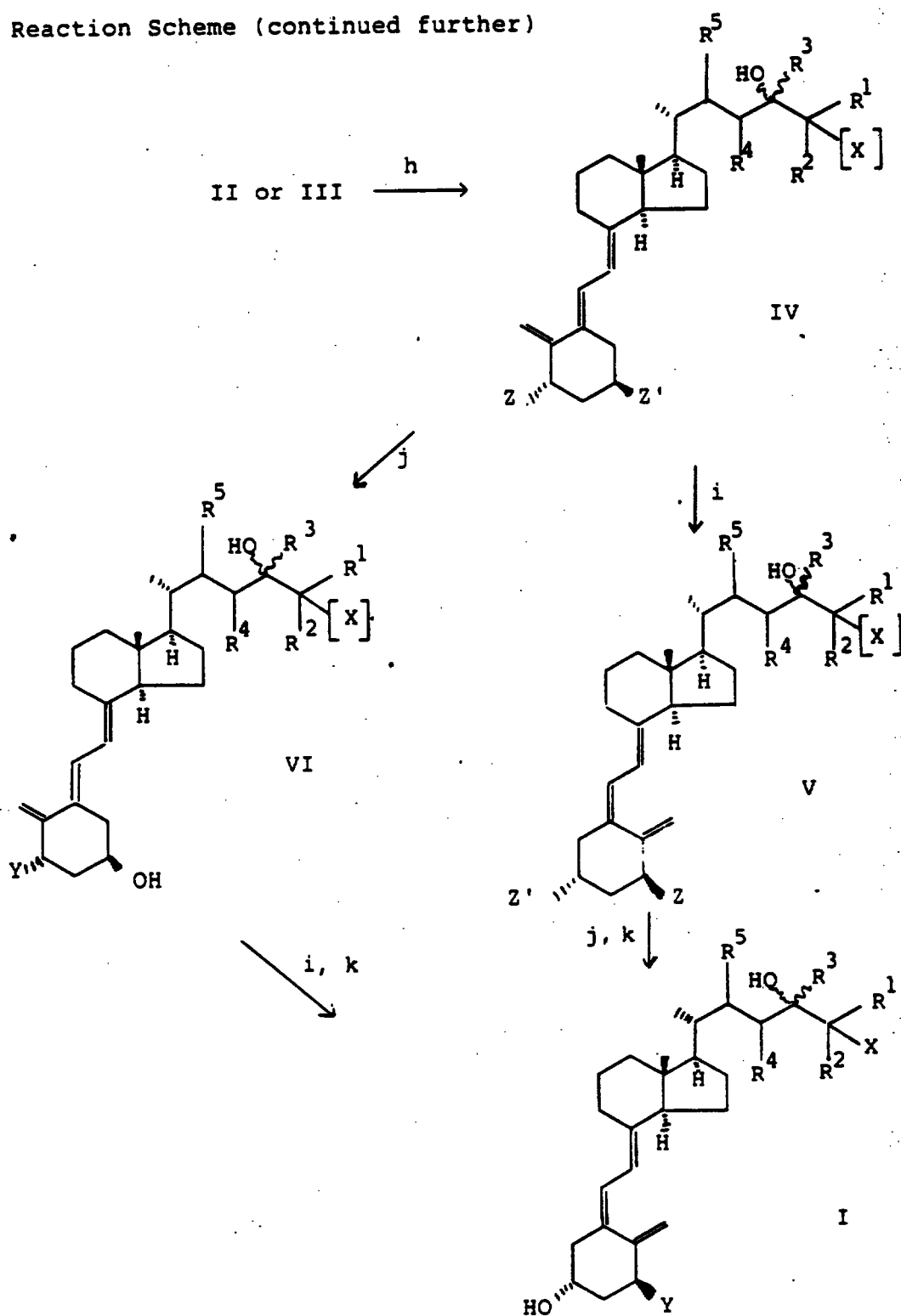


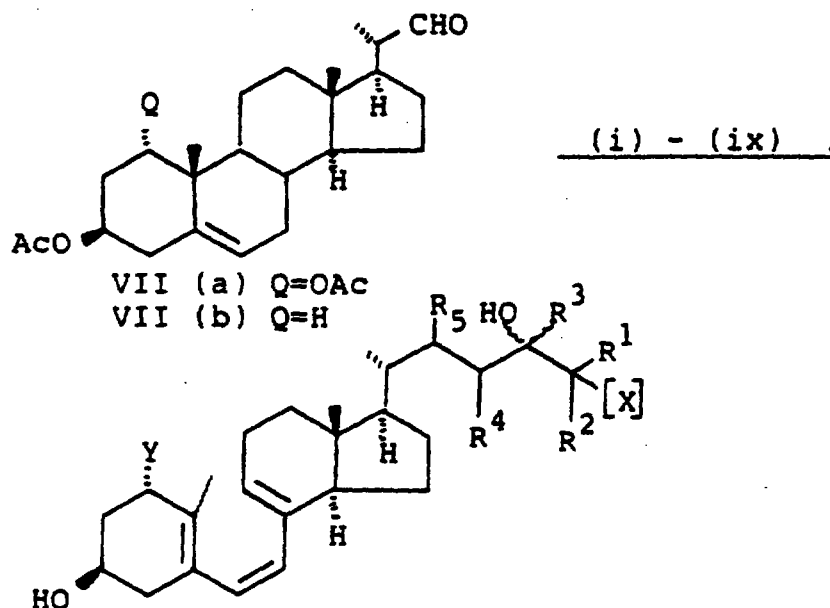
Table 2

Compounds Indicated on the Reaction Scheme and/or
Referred to by Number in the Preparations and Examples

Compound Number	Y or Z	Formula (Z' = t-BuMe ₂ SiO) X or [X]	R ¹	R ²	R ³	R ⁴	R ⁵
15	II	H	H	-(CH ₂) ₂ -	-	-	-
16	II	t-BuMe ₂ SiO	H	-(CH ₂) ₂ -	-	-	-
17	II	t-BuMe ₂ SiO	H	-(CH ₂) ₄ -	-	-	-
18	II	t-BuMe ₂ SiO	H	-(CH ₂) ₅ -	-	-	-
19	II	t-BuMe ₂ SiO	CH ₃	CH ₃ CH ₃	-	-	-
20	II	t-BuMe ₂ SiO	-(CH=CH) ₂ -CH=	-	-	-	-
21	III	t-BuMe ₂ SiO	H	-(CH ₂) ₂ -	-	-	-
22, 23	IV	H	H	-(CH ₂) ₂	H	bond	-
24, 25	IV	t-BuMe ₂ SiO	H	-(CH ₂) ₂ -	H	H	H
26, 27	IV	t-BuMe ₂ SiO	H	-(CH ₂) ₂ -	H	bond	-
28, 29	IV	t-BuMe ₂ SiO	H	-(CH ₂) ₄ -	H	bond	-
30, 31	IV	t-BuMe ₂ SiO	H	-(CH ₂) ₅ -	H	bond	-
32, 33	IV	t-BuMe ₂ SiO	CH ₃	CH ₃ CH ₃	H	bond	-
34, 35	IV	t-BuMe ₂ SiO	-(CH=CH) ₂ -CH=	-	H	bond	-
36, 37	IV	t-BuMe ₂ SiO	H	-(CH ₂) ₂ -	CH ₃	bond	-
38, 39	V	t-BuMe ₂ SiO	H	-(CH ₂) ₂ -	H	bond	-
40, 41	V	H	H	-(CH ₂) ₂ -	H	bond	-
42, 43	V	t-BuMe ₂ SiO	H	-(CH ₂) ₄ -	H	bond	-
44, 45	V	t-BuMe ₂ SiO	H	-(CH ₂) ₅ -	H	bond	-
46, 47	V	t-BuMe ₂ SiO	CH ₃	CH ₃ CH ₃	H	bond	-
48, 49	V	t-BuMe ₂ SiO	-(CH=CH) ₂ -CH=	-	H	bond	-
50, 51	V	t-BuMe ₂ SiO	H	-(CH ₂) ₂ -	H	H	H
52, 53	V	t-BuMe ₂ SiO	H	-(CH ₂) ₂ -	CH ₃	bond	-
54, 55	VI	OH	H	-(CH ₂) ₂ -	H	bond	-
72, 73	VIII	OH	H	-(CH ₂) ₂ -	H	bond	-
65, 57	I	H	H	-(CH ₂) ₂ -	H	bond	-
58, 59	I	OH	H	-(CH ₂) ₂ -	H	bond	-
60, 61	I	OH	H	-(CH ₂) ₄ -	H	bond	-
62, 63	I	OH	H	-(CH ₂) ₅ -	H	bond	-
64, 65	I	OH	CH ₃	CH ₃ CH ₃	H	bond	-
66, 67	I	OH	-(CH=CH) ₂ -CH=	-	H	bond	-
68, 69	I	OH	H	-(CH ₂) ₂	H	H	H
70, 71	I	OH	H	-(CH ₂) ₂	CH ₃	bond	-

Notes. (a) Where "bond" appears in the last column, the trans configuration of the 22, 23-double bond is to be understood; (b) Each formula I, IV, V, VI and VIII (and IX and XI, see later) represents two separate numbered compounds. These differ only in their absolute configuration at C-24. In the Preparations and Examples, no attempt has been made to identify these configurations, but it is clearly indicated which of the two isomers is concerned in relative terms by differentiating unambiguously between their physical and/or spectroscopic properties (when possible) and/or by correlation with a particular starting material.

The compounds I may also be synthesized from steroidal precursors. Such an approach is illustrated in the conversion of the compound VII(a) or VII(b) (both available from dinorcholenic acid acetate) into the "pre-vitamin" VIII(a) or VIII(b), respectively, as outlined below:-



- 30
- (i) Side chain Fragment (D) (see text) (dimethyl sulphoxide, 100° C);
(ii) N-bromosuccinimide (CCl₄, reflux);
(iii) (a) Bu₄NBr, then (b) Bu₄NF (tetrahydrofuran (THF), 20° C);
(iv) 4-Phenyl-1,2,4-triazoline-3,5-dione (CHCl₃, 20° C);
35 (v)* Na₂S₂O₄/(C₁₀H₂₁)₃NMeCl/NaHCO₃ PhH-H₂O reflux);
either (vi) + NaBH₄/CeCl₃ (THF - MeOH, 0° C) (for R³ = H);
or (vii) + R³MgBr or R³Li (THF, -10° C) (for R³ = C_nH_{2n+1}; n = 1 - 6);
(viii) LiAlH₄ (THF, reflux);
(ix)

40 Irradiation with medium-pressure Hg lamp through a Vycor filter (PhH-EtOH, 0° C)

* If step (v) is included, the compounds VIII having R⁵ = R⁴ = H are produced; if step (v) is omitted, the compound VIII having R⁵, R⁴ = bond (trans) are produced.

+ Chromatographic separation of C - 24 epimers may be conveniently effected after stage (vi) or (vii).

45 The pre-vitamin VIII may be partially converted to the corresponding compound I by keeping in an inert solvent (e. g. ether, ethanol or benzene, or a mixture) at a temperature from about 0° C to 100° C, preferably from about 20° C to about 80° C until equilibrium is reached or until an acceptable, less complete, conversion has been achieved (e. g. from two weeks at 20° C to a few minutes at 80° C). This equilibration may also be
50 performed on a hydroxy-protected derivative of VIII, such as an acylated or trialkylsilylated derivative to give the corresponding derivative of I which is converted to I by conventional deprotection reaction(s).

Implicit in the routes to the compound I illustrated heretofore is the key reaction establishing the 24-hydroxy group from a 24-oxo compound. The reactions exemplified all give rise to a mixture of diastereoisomers at this centre, which means that a separation step is required unless the particular compound I can be administered as a mixture. However, biological results have shown that of a pair of C - 24 diastereoisomeric compounds I, one isomer is normally more active than the other. It is therefore advantageous to increase the proportion of the intermediate having the C - 24 configuration corresponding to the more active compound I. This is possible by using a diastereoselective organometallic reagent (for R³ = alkyl) or reducing agent (for R³ = H). Methodology for the latter, reductive, reaction especially is now highly developed, and is particularly well
60 applicable to compounds in which the 22, 23-double bond is present in the 24-oxo intermediate.

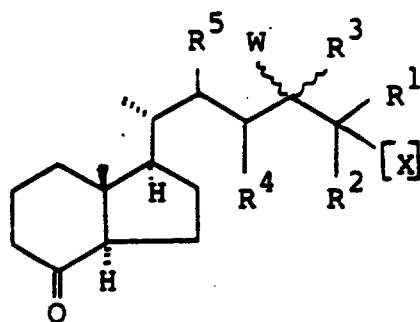
Thus, the proportion of for example either compound IV (see Reaction Scheme) in the mixture, obtained by reducing compound II or III, can be increased by the use of for example the one or the other antipode of a chiral reducing agent. Examples of this type or reaction are reviewed for example in "Asymmetric Synthesis", ed. J.D. Morrison, Academic Press, London, Volume 2, 1983.

65 An alternative practical approach to an efficient reduction process is to recycle the undesired C - 24 isomer

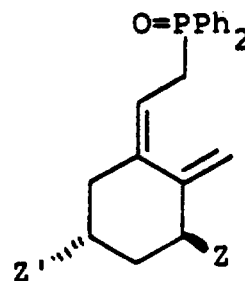
(either in essentially pure form or admixed with smaller amounts of the desired isomer) after separation of either essentially all or just some of the desired isomer. This recycling is achieved by a mild oxidation back to the 24-oxo compound. For example, either compound 26 or 27 (or a mixture) is readily reconverted to 16 by reaction with active manganese dioxide.

It should be noted however that a minor amount of the less active C - 24 isomer of I in admixture with the more active isomer does not interfere with the efficacy of the formulated drug.

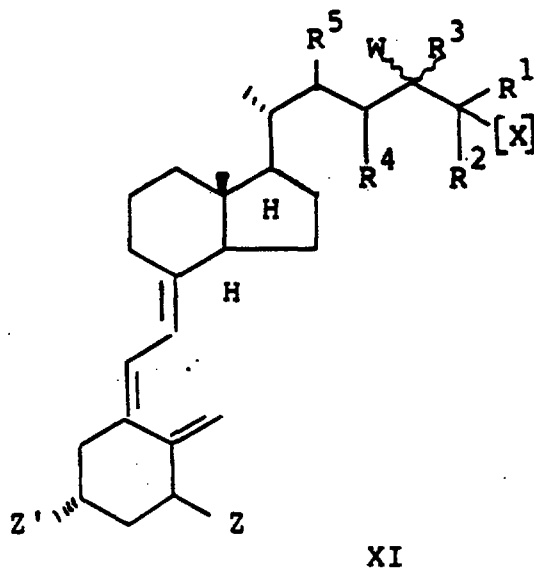
A second alternative synthesis of compound I is illustrated in the coupling of an optionally hydroxy-protected form of the "top-half" fragment IX of the molecule with the anion derived from the protected "bottom-half" fragment X to give XI, followed by conventional deprotection step(s) and any necessary modification of [X].



IX



X



In formulae IX, X and XI, Z' is protected OH, e. g. t-BuSiMe₂O; Z is either H or protected OH, e. g. t-BuSiMe₂O; W is either OH or protected OH, e. g. t-BuSiMe₂O; and [X] is either X of formula I or a group which can be converted to X.

The present compounds are intended for use in pharmaceutical compositions which are useful in the treatment of human and veterinary disorders which, as mentioned above, are characterized by abnormal cell-proliferation and/or differentiation.

The amount required of a compound of formula I (hereinafter referred to as the active ingredient) for therapeutic effect will, of course, vary both with the particular compound, the route of administration and the mammal under treatment. The compounds of the invention can be administered by the parenteral, enteral or topical routes. They are well absorbed when given enterally and this is the preferred form of administration in the treatment of systemic disorders. In the treatment of dermatological disorders like psoriasis, topical forms like ointments, creams or lotions are preferred. In the treatment of systemic disorders daily doses of from 1 - 1000 µg, preferably from 2 - 250 µg, of a compound of formula I are administered. In the topical treatment of dermatological disorders, ointments, creams or lotions containing from 1 - 1000 µg/g, and preferably from 10 - 500 µg/g, of a compound of formula I are administered. The oral compositions are formulated, preferably as tablets, capsules, or drops, containing from 0.5 - 500 µg, preferably from 1 - 250 µg, of a compound of formula I, per dosage unit.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. Conveniently, the active ingredient comprises from 1 ppm to 0.1 % by weight of the formulation.

By the term "dosage unit" is meant a unitary, i. e. a single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active material as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

The formulations, both for veterinary and for human medical use, of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefor and optionally other therapeutic ingredient(s). The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients

of the formulations and not deleterious to the recipient thereof.

The formulations include e. g. those in a form suitable for oral, rectal, parenteral (including subcutaneous, intramuscular and intravenous), and topical administration.

The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. The active ingredient may also be administered in the form of a bolus, electuary or paste.

A tablet may be made by compressing or moulding the active ingredient optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered active ingredient and a suitable carrier moistened with an inert liquid diluent.

Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and a carrier such as cocoa butter, or in the form of an enema.

Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous Preparation of the active ingredient which is preferably isotonic with the blood of the recipient.

Formulations suitable for topical administration include liquid or semi-liquid Preparations such as liniments, lotions, applications; oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops.

In addition to the aforementioned ingredients, the formulations of this invention may include one or more additional ingredients such as diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives, e. g. methyl hydroxybenzoate (including anti-oxidants), emulsifying agents and the like.

The compositions may further contain other therapeutically active compounds usually applied in the treatment of the above mentioned pathological conditions.

The invention will now be further described in the following non-limiting Preparations and Examples:

Preparations and Examples. General.

The compounds referred to in the Preparations and Examples are to be identified by number (Compounds 15 - 73 via Table 2) with the corresponding formulae in the Reaction Scheme or elsewhere in which $Z' = t\text{-BuMe}_2\text{SiO}$, and $Z = Z'$ unless otherwise stated.

For the cognate Preparations and Examples, only differences in the procedure and the new data are noted.

Analytical thin layer chromatography (TLC) was performed on Merck plates pre-coated with silica gel 60 F₂₅₄. The approximate R_f values quoted are only meant to be used for distinction in relative terms between pairs of isomers. Analytical high-performance liquid chromatography was performed on Lichrosorb Si 60 normal phase column (4 mm i. d. x 25 cm) at a flow rate of 3.5 ml/min. with 2 % methanol in dichloromethane as eluant. The quoted retention times, T_R, are used only for distinction in relative terms between pairs of isomers, and are not necessarily exactly reproducible. Nuclear magnetic resonance (NMR) (δ) spectra were run at 100 MHz for solutions in CDCl₃ using either TMS ($\delta = 0$) or CHCl₃ ($\delta = 7.25$) as internal standard. Coupling constants are given in Hertz and are approximated to the nearest unit. Mass spectra (m/z) were run at 70 eV and only the highest mass signal and base peak are quoted. Organic solutions were dried over dried magnesium sulphate.

Preparation 1. Compound 5 (via Compounds 1 and/or 2, 3, and 4)

Vitamin D₂ (12.5 g) was dissolved in liquid SO₂ (50 ml) and the mixture stirred under reflux for 30 min. The SO₂ was distilled off, and the residue was dried *in vacuo* to give a foam. This was dissolved in N,N-dimethylformamide (100 ml), and imidazole (4.5 g) and tert-butyldimethylsilyl chloride (5 g) were added. The mixture was stirred under N₂ for 90 min. and then partitioned between ethyl acetate and water. The organic layer was washed with water, dried and concentrated to give a mixture of 1 and 2 as a crystalline solid which was triturated with ethanol, filtered off, and dried *in vacuo*.

[A portion of the mixture was separated by chromatography (silica; 30 % ether in petroleum ether as eluant) to give pure 1, less polar isomer, needles (from dichloromethane-ethanol), δ 0.06 (6H, s), 0.67 (3H, s), 0.88 (9H, s), 1.03 (3H, d, J 7 Hz), 3.64 (2H, broad s), 4.0 (1H, m), 4.4 - 4.8 (2H, 2 broad d, J 10 Hz) and 5.2 (2H, m); m/z 510 M⁺ - SO₂) and 119, and pure 2, more polar isomer, needles (from dichloromethane-ethanol); δ 0.06 (6H, s), 0.58

(3H, s), 0.88 (9H, s), 1.03 (3H, d, J 7 Hz), 3.65 (2H, broad s), 3.95 (1H, m), 4.5 - 4.9 (2H, 2 broad d, J 10 Hz), and 5.2 (2H, m); m/z 510 ($M^+ - SO_2$) and 119.]

The product (the pure isomers can also be used separately) was suspended in 96 % ethanol (250 ml) and sodium hydrogen carbonate (20 g) added. The stirred mixture was heated under reflux for 100 min under N_2 , cooled, partially concentrated *in vacuo*, and partitioned between ethyl acetate and water. The organic layer was washed with water, dried and concentrated to give 3, δ 0.07 (6H, s), 0.57 (3H, s), 0.88 (9H, s), 1.02 (3H, d, J 6 Hz), 3.85 (1H, m), 4.64 (1H, broad s), 4.91 (1H, broad s), 5.2 (2H, m), 5.85 (1H, d, J 11 Hz), and 6.47 (1H, d, J 11 Hz).

This was dissolved in dichloromethane (160 ml) containing dried N-methyl morpholine N-oxide (15 g). The stirred solution was heated under reflux under N_2 and a solution of selenium dioxide (3 g) in methanol (160 ml) was added rapidly. Heating under reflux was continued for 50 min. before the reaction mixture was cooled, diluted with more dichloromethane, washed with water, dried and concentrated to give 4, of sufficient purity for use in the next stage. [An analytical sample was obtained after chromatography (silica gel; 15 % ether in petroleum ether as eluant), λ_{max} (EtOH) 270 nm; δ 0.07 (6H, s), 0.57 (3H, s), 0.87 (9H, s), 1.02 (3H, d, J 7 Hz), 4.2 (1H, m), 4.5 (1H, m), 4.94 (1H, broad s), 5.06 (1H, broad s), 5.2 (2H, m), 5.86 (1H, d, J 11 Hz), and 6.51 (1H, d, J 11 Hz).]

This was dissolved in N, N-dimethylformamide (80 ml), and imidazole (3.8 g) and tert-butyldimethylsilyl chloride (4.5 g) was added. The mixture was stirred under N_2 for 90 min. and then partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water, dried and concentrated to give a crystalline solid which was purified by chromatography on silica (eluting with 2 % ether in petroleum ether) followed by recrystallisation from ether-ethanol to give 5 as colourless needles, λ_{max} (EtOH) 270 nm; δ 0.07 (12H, s), 0.57 (3H, s), 0.88 (9H, s), 0.91 (9H, s), 1.03 (3H, d, J 7), 4.22 (1H, broad s), 4.54 (1H, broad dd, J 5 and 9 Hz), 4.97 (2H, m), 5.20 (2H, m), 5.82 (1H, d, J 11 Hz), and 6.47 (1H, d, J 11 Hz); m/z 640 (M^+) and 248.

Preparation 2: Compounds 6 and 7

5 (4.0 g) was dissolved in diethyl ether (10 ml) and liquid SO_2 (50 ml) and the mixture was stirred under reflux for 30 min. The SO_2 and ether were distilled off, and the residue was dried *in vacuo* to give white needles, showing two spots on thin layer chromatography (silica; 10 % ether in petroleum ether as eluant) corresponding to 6 (Rf ca. 0.25) and 7 (Rf ca. 0.1). (Found: C, 67.97; H, 10.26; S, 4.37. $C_{40}H_{72}O_4S$ Si_2 requires C, 68.12; H, 10.29; S, 4.55 %); ν_{max} ($CHCl_3$) 1310 and 1160 cm^{-1} ; δ 0.05 (12H, broad s), 0.57 and 0.65 (3H, 2 s), 0.87 (9H, s), 0.88 (9H, s), 3.4 - 4.1 (2H, broad ABq, J 16 Hz), 4.17 (1H, m), 4.35 (1H, m), 4.7 (2H, m) and 5.2 (2H, m). Pure 6 and 7 were separated from a sample of the mixture by chromatography (silica; 20 % ether in petroleum ether as eluant): 6, δ 0.65 (3H, s) and 4.67 (2H, m); 7, δ 0.57 (3H, s) and 4.5 - 4.9 (2H, 2 br d, J 10).

Preparation 3: Compounds 8 and 9

The mixture of 6 and 7 from Preparation 2 (4.4 g) was dissolved in dichloromethane (120 ml) and methanol (40 ml). The stirred solution was cooled to $-60^\circ C$ and treated with ozonised oxygen until TLC showed essentially complete consumption of starting materials. The solution was then purged with N_2 and triphenyl phosphine (2.5 g) was added. After warming slowly to room temperature, the reaction mixture was diluted with more dichloromethane, washed with water, dried and concentrated. The residue was purified by chromatography (silica gel; 30 % ether in petroleum ether as eluant). 8 and 9 can be collected separately or, more conveniently, as a mixture, which crystallises and was used directly in Preparation 6. The data refer to the separated isomers. First eluted was 8, obtained as white needles; ν_{max} ($CHCl_3$) 1720 (aldehyde), 1310 and 1160 cm^{-1} ; δ 0.06 (12H, broad s), 0.70 (3H, s), 0.87 and 0.88 (18H, 2 s), 1.13 (3H, d, J 7 Hz), 3.45 - 4.1 (2H, broad AB q, J 16 Hz), 4.2 (1H, m), 4.35 (1H, m), 4.7 (2H, m), and 9.58 (1H, d, J 3 Hz). Second eluted was 9, ν_{max} ($CHCl_3$) 1720 (aldehyde), 1310 and 1160 cm^{-1} ; δ 0.07 (12H, broad s), 0.61 (3H, s), 0.88 and 0.89 (18H, 2H), 1.14 (3H, d, J 7 Hz), 3.45 - 4.1 (2H, broad AB q, J 16 Hz), 4.15 (1H, m), 4.4 (1H, m), 4.5 - 4.95 (2H, 2 broad d, J 10 Hz), and 9.57 (1H, d, J 3 Hz). It should be noted that the use of the pure isomers 6 and 7 separately as starting materials in this Preparation gives respectively 8 and 9 free from the other isomer.

Preparation 4: Compound 10

The use of compound 1 (from Preparation 1) (3.6 g) as starting material instead of 6 and/or 7 in Preparation 3, but using 50 % ether in petroleum ether as eluant for the chromatography step, gave 10, δ 0.04 (6H, br s), 0.70 (3H, s), 0.86 (9H, s), 1.13 (3H, d, J 7), 3.63 (2H, br s), 4.0 (1H, m), 4.4 - 4.85 (2H, 2 br, d, J 10) and 9.58 (1H, d, J 3).

Preparation 5: Compound 11

The use of compound 2 (from Preparation 1) (3.5 g) as starting material instead of 6 and/or 7 in Preparation 3, but using 50 % ether in petroleum ether as eluant for the chromatography step, gave 11, δ 0.04 (6H, br s), 0.60 (3H, s), 0.87 (9H, s), 1.14 (3H, d, J 7), 3.65 (2H, br s), 4.0 (1H, m), 4.5 - 4.95 (2H, 2 br d, J 10) and 9.56 (1H, d, J 3).

Preparation 6: Compound 12

The mixture of 8 and 9 from Preparation 3 (the pure isomers may also be used separately, but there is no advantage in separating them since both give 12 on elimination of SO_2) (1.12 g) was suspended in 96 % ethanol (50 ml) and sodium hydrogen carbonate (2 g) added. The stirred mixture was heated under reflux under N_2 for 100 min., cooled, partially concentrated in vacuo, and partitioned between ethyl acetate and water. The organic layer was washed with water, dried, and concentrated to give 12 of sufficient purity for subsequent use. An analytical sample was obtained after chromatography (silica gel; 5 % ether in petroleum ether as eluant) and crystallization from ethanol; needles, m. p. 113 - 5°C; λ_{max} (EtOH) 270 nm; ν_{max} (CHCl_3) 1720 cm^{-1} (aldehyde); δ 0.08 (12H, s), 0.61 (3H, s), 0.88 and 0.92 (18H, 2 s) 1.16 (3H, d, J 7 Hz), 4.2 (1H, m), 4.5 (1H, m), 4.98 (2H, m), 5.85 (1H, d, J 11 Hz), 6.46 (1H, d, J 11 Hz), and 9.60 (1H, d, J 3 Hz), m/z 572 (M^+) and 248.

Preparation 7: Compound 13

The use of compound 10 or 11 (or a mixture) (0.9 g) as starting material instead of 8 and/or 9 in Preparation 6 gave 13, δ 0.06 (6H, s), 0.61 (3H, s), 0.88 (9H, s), 1.14 (3H, d, J 7), 3.85 (1H, m), 4.65 (1H, br s), 4.91 (1H, br s), 5.88 (1H, d, J 11), 6.48 (1H, d, J 11), and 9.59 (1H, d, J 3).

Preparation 8: Bromoacetylcyclopropane (B(i))

To a stirred, ice-cooled solution of acetylcyclopropane (A(i)) (22 g) in methanol (150 ml) was added bromine (40 g) at such a rate that the temperature was maintained below 20°C. Stirring was then continued at room temperature for 30 min. before water (75 ml) was added. After a further 15 min. the mixture was diluted with water (225 ml) and extracted with ether. The ether extracts were washed with saturated sodium carbonate solution, water, and dried. After removing the solvent in vacuo, the residue was distilled to give B(i), b. p. 71 - 73°C/13 mmHg, δ 0.9 - 1.3 (4H, m), 2.05 - 2.35 (1H, m) and 4.02 (2H, s).

Preparation 9: Cyclopropylcarbonylmethyltriphenylphosphonium bromide (C(i))

Starting material (B(i)), and triphenylphosphine were mixed in equimolar amounts and allowed to react spontaneously. The resulting solid cake was dissolved in dichloromethane and treated with ether to precipitate pure C(i) as colourless needles, m. p. 204 - 205°C, δ 1.02 (4H, m), 2.75 (1H, m), 5.89 (2H, d, J 12 Hz), and 7.45 - 8.0 (15H, m).

Preparation 10: Cyclopentylcarbonylmethyltriphenylphosphonium bromide (C(ii))

Method: as Preparation 9; starting material: bromoacetylcyclopentane (B(ii)).

Preparation 11: Cyclohexylcarbonylmethyltriphenylphosphonium bromide (C(iii)).

Method: as Preparation 9; Starting material: Bromoacetylcyclohexane (B(iii)); Data: m. p. 244 - 7°C.

Preparation 12: Pivaloylmethyltriphenylphosphonium bromide (C(iv)).

Method: as Preparation 9; Starting material: Bromomethyl tert-butyl ketone (B(iv)); Data: m. p. 234 - 7°C.

Preparation 13: Phenacylmethyltriphenylphosphonium bromide (C(v)).

Method: as Preparation 9; Starting material: phenacyl bromide (B(v)); Modification: B(v) and triphenylphosphine were predissolved and combined in toluene solution with stirring. After the spontaneous reaction, C(v) was filtered off and washed with ether; Data: m. p. > 260°C.

Preparation 14: Cyclopropylcarbonylmethylenetriphenylphosphorane (D(i)).

Starting material (C(i)) (3 g) was dissolved in dichloromethane (30 ml), and the solution was extracted with sodium hydroxide solution (2N, 20 ml). The organic layer was washed with water, dried and concentrated in *vacuo* to give a product which was purified by recrystallisation from dichloromethane-acetone to give D(i) as needles, m. p. 181 - 182°C, δ 0.60 (2H, m), 0.85 (2H, m), 1.75 (1H, m), 3.77 (1H, br d, J 26) and 7.1 - 7.8 (15H, m).

Preparation 15: Cyclopentylcarbonylmethylenetriphenylphosphorane (D(ii)).

Method: as Preparation 14; Starting material: C(ii); Data: m. p. 159 - 60°C, δ 1.3 - 2.0 (8H, m), 2.75 (1H, m), 3.7 (1H, d, J 27) and 7.2 - 7.8 (15H, m).

Preparation 16: Cyclohexylcarbonylmethylenetriphenylphosphorane (D(iii)).

Method: as Preparation 14; Starting material: C(iii); Data: m. p. 159 - 61°C, δ 1.0 - 2.45 (11H, m), 3.65 (1H, m), and 7.2 - 7.9 (15H, m).

Preparation 17: Pivaloylmethylenetriphenylphosphorane (D(iv)).

Method: as Preparation 14; Starting material: C(iv); Data: m. p. 182 - 3°C, δ 1.20 (9H, s), 3.78 (1H, d, J 27) and 7.2 - 7.8 (15H, m).

Preparation 18: Phenacylmethylenetriphenylphosphorane (D(v)).

Method: as Preparation 14; Starting material: C(v); Modification: recrystallisation from dichloromethane-ether; Data: m. p. 183 - 4°C, δ 4.41 (1H, d, J 25) and 7.2 - 8.0 (20H, m).

Preparation 19: Compound 16.

A solution stirred under N₂ of the aldehyde 12 (0.93 g) and the phosphorane D(i) (1 g) in dimethyl sulphoxide (20 ml) was heated at 95°C for 90 min. then 105°C for 120 min. After cooling, the reaction solution was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water, dried, and concentrated in *vacuo* to give a residue which was purified by chromatography (silica gel; 10 % ether in petroleum ether as eluant) to give 16, colourless plates (from ether-methanol), m. p. 122 - 123°C; λ_{max} (EtOH) 270 nm, δ 0.06 (12H, s), 0.59 (3H, s), 0.87 and 0.90 (18H, 2 s), 1.13 (3H, d, J 7), 4.2 (1H, m), 4.5 (1H, m), 4.96 (2H, m), 5.8 (1H, d, J 11 Hz), 6.14 (1H, d, J 16 Hz), 6.45 (1H, d, J 11 Hz), and 6.78 (1H, dd, J 9 and 16 Hz); m/z 638 (M⁺) and 248.

Preparation 20: Compound 15.

Method: as Preparation 19; Aldehyde: 13 (1.06 g); Phosphorane: D(i) (1.64 g); Data: δ 0.06 (6H, s), 0.60 (3H, s), 0.88 (9H, s), 1.13 (3H, d, J 7), 3.85 (1H, m), 4.65 (1H, br s), 4.92 (1H, br s), 5.85 (1H, d, J 11), 6.14 (1H, d, J 16), 6.47 (1H, d, J 11) and 6.78 (1H, dd, J 9 and 16).

Preparation 21: Compound 17.

Method: as Preparation 19; Aldehyde: 12 (1.62 g); Phosphorane: D(ii) (2.60 g); Reaction conditions: 16 h at 110°C; Chromatography eluant: 5 % ethyl acetate in petroleum ether; Data: δ 0.06 (12H, s), 0.58 (3H, s), 0.87 and 0.90 (each 9H, s), 1.1 (3H, d, J 7), 4.2 (1H, m), 4.5 (1H, m), 4.96 (2H, m), 5.81 (1H, d, J 11), 6.44 (1H, d, J 11) and 6.79 (1H, dd, J 9 and 15).

Preparation 22: Compound 18.

Method: as Preparation 19; Aldehyde: 12 (1.0 g); Phosphorane: D(iii) (1.3 g); Reaction conditions: 4 h at 100°C followed by 2 h at 110°C; Chromatography eluant: 5 % ethyl acetate in petroleum ether; Data: δ 0.06 (12H, s), 0.58 (3H, s), 0.87 and 0.90 (each 9H, s), 1.1 (3H, d, J 7), 4.2 (1H, m), 4.5 (1H, m), 4.96 (2H, m), 5.81 (1H, d, J 11), 6.44 (1H, d, J 11) and 6.79 (1H, dd, J 9 and 15).

Preparation 23: Compound 19.

Method: as Preparation 19; Aldehyde: 12 (1.1 g); Phosphorane: D(iv) (2.1 g); Reaction conditions: 16 h at 110°C; Chromatography eluant: 5 % ether in petroleum ether; Data: δ 0.06 (12H, s), 0.58 (3H, s), 0.87 and 0.90 (each 9H, s), 1.10 (3H, d, J 7), 1.15 (9H, s), 4.2 (1H, m), 4.52 (1H, m), 4.96 (2H, m), 5.81 (1H, d, J 11), 6.40 (1H, d, J 15), 6.44 (1H, d, J 11), and 6.80 (1H, dd, J 9 and 15).

Preparation 24: Compound 20.

Method: as Preparation 19; Aldehyde: 12 (0.96 g); Phosphorane: D(v) (1.86 g); Reaction conditions: 16 h at 110°C; Chromatography eluant: 5 % ether in petroleum ether; Data: δ 0.07 (12H, s), 0.56 (3H, s), 0.87 and 0.90 (each 9H, s), 1.17 (3H, d, J 7), 4.2 (1H, m), 4.55 (1H, m), 4.97 (2H, m), 5.82 (1H, d, J 11), 6.45 (1H, d, J 11), 6.87 (2H, m), 7.5 (3H, m) and 7.9 (2H, m).

Preparation 25: Compound 21.

A mixture of 16 (200 mg), sodium hydrogen carbonate (0.5 g), sodium dithionite ($\text{Na}_2\text{S}_2\text{O}_4$) (0.5 g), and methyltridecylammonium chloride (0.05 g) in toluene (10 ml) and water (10 ml) under nitrogen was stirred vigorously at 80°C for 1 h and then 85°C for 30 min. After cooling, the reaction mixture was partitioned between ether and water, and the organic layer was washed with water, dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluant: 10 % ether in petroleum ether) to give 21, colorless plates (from ether-methanol); m. p. 93 - 94°C, ν_{max} 1700 cm^{-1} ; δ 0.06 (12H, s), 0.55 (3H, s), 0.87 and 0.90 (each 9H, s), 4.2 (1H, m), 4.5 (1H, m), 4.96 (2H, m), 5.82 (1H, d, J 11) and 6.45 (1H, d, J 11); m/z 640 (M^+) and 248.

Preparation 26: Compounds 24 and 25.

An ice-cooled, stirred solution of 21 (225 mg) in tetrahydrofuran (3 ml) was diluted with methanol (8 ml) and treated with sodium borohydride (140 mg) portionwise over 5 min. After a further 10 minutes, the reaction mixture was partitioned between ethyl acetate and water, and the organic layer was washed with water, dried, and concentrated in vacuo. The residue was crystallised from ether-methanol to give 24 and 25 as needles. 24 and 25 have essentially superimposable NMR-spectra: δ 0.06 (12H, s), 0.15 - 0.65 (4H, m), 0.55 (3H, s), 0.86 and 0.90 (each 9H, s), 4.2 (1H, m), 4.55 (1H, m), 4.96 (2H, m), 5.81 (1H, d, J 11.5) and 6.46 (1H, d, J 11.5).

Preparation 27: Compounds 26 and 27.

To an ice-cooled, stirred solution of starting material 16 (100 mg) in tetrahydrofuran (10 ml) under nitrogen was added sodium bis(2-methoxyethoxy) aluminium hydride (70 % solution in toluene) dropwise until TLC showed essentially complete consumption of starting material. The reaction mixture was then partitioned between ethyl acetate and sodium hydroxide solution (1 N), and the organic layer was washed with water, dried, and concentrated. The residue was purified by chromatography (silica gel; 10 % ethyl acetate in petroleum ether as eluant) to give the title compounds. First eluted isomer was 26, δ 0.06 (12H, s), 0.15 - 0.65 (4H, m), 0.57 (3H, s), 0.87 and 0.90 (18H, 2 s), 1.05 (3H, d, J 7 Hz), 3.45 (1H, m), 4.2 (1H, m), 4.55 (1H, m), 4.96 (2H, m), 5.51 (2H, m), 5.82 (1H, d, J 11 Hz) and 6.47 (1H, d, J 11 Hz). This was followed by the more polar isomer 27, δ 0.06 (12H, s), 0.15 - 0.65 (4H, m), 0.57 (3H, s), 0.87 and 0.90 (18H, 2 s), 1.05 (3H, d, J 7 Hz), 3.45 (1H, m), 4.2 (1H, m), 4.55 (1H, m), 4.96 (2H, m), 5.47 (2H, m), 5.82 (1H, d, J 11 Hz) and 6.47 (1H, d, J 11 Hz). [It is notable that a characteristic difference in the position and pattern of the two proton multiplet δ ca. 5.5 in the NMR spectra is observed for each of the pairs of 24-epimers 26/27, 38/39, 54/55 and 58/59.] 26 and 27 were each obtained as needles from petroleum ether-methanol, m. p. 117 - 118°C and 122 - 123°C, respectively.

Preparation 28: Compounds 26 and 27 (alternative method).

An ice-cooled, stirred solution of starting material 16 (0.82 g) in tetrahydrofuran (1 ml) was diluted with 0.4 N $\text{CeCl}_3 \cdot 6\text{H}_2\text{O}$ in methanol (4 ml) and further with methanol (2 ml), and treated with sodium borohydride (0.15 g), portionwise over 5 min. After a further 10 min., the reaction mixture was partitioned between ethyl acetate and water and the organic layer was washed with water, dried, and concentrated in vacuo. The residue was purified as described in Preparation 27, to give separately crystalline 26 and 27.

Preparation 29: Compounds 22 and 23.

Method: as Preparation 27; Starting material: 15; Data: 22 (less polar isomer), δ 0.07 (6H, s), 0.57 (3H, s), 0.15 - 0.65 (4H, m), 0.88 (9H, s), 1.05 (3H, d, J 7), 3.45 (1H, m), 3.85 (1H, m), 4.64 (1H, broad s), 4.91 (1H, broad s), 5.50 (2H, m), 5.85 (1H, d, J 11) and 6.47 (1H, d, J 11); 23 (more polar isomer); δ 0.07 (6H, s), 0.57 (3H, s), 0.15 - 0.65 (4H, m), 0.88 (9H, s), 1.05 (3H, d, J 7), 3.45 (1H, m), 3.85 (1H, m), 4.64 (1H, broad s), 4.91 (1H, broad s), 5.46 (2H, m), 5.85 (1H, d J 11) and 6.47 (1H, d, J 11).

Preparation 30: Compounds 28 and 29.

Method as Preparation 28; Starting material: 17 (0.65 g); Data: 28 (less polar isomer); needles (from ether-methanol); δ 0.06 (12H, s), 0.56 (3H, s), 0.87 and 0.90 (each 9H, s), 1.04 (3H, d, J 7), 3.81 (1H, m), 4.2 (1H, m), 4.55 (1H, m), 4.96 (2H, m), 5.46 (2H, m), 5.82 (1H, d, J 11) and 6.45 (1H, d, J 11); 29 (more polar isomer); needles (from ether-methanol); δ 0.06 (12H, s), 0.56 (3H, s), 0.87 and 0.90 (each 9H, s), 1.05 (3H, d, J 7), 3.78 (1H, m), 4.2 (1H, m), 4.55 (1H, m), 4.96 (2H, m), 5.42 (2H, m), 5.82 (1H, d, J 11) and 6.45 (1H, d, J 11).

Preparation 31: Compounds 30 and 31.

Method: as Preparation 28; Starting material: 18 (0.6 g); Data: 30 (less polar isomer); Needles (from methanol), m. p. 107 - 108°C; δ 0.06 (12H, s), 0.56 (3H, s), 0.87 and 0.90 (each 9H, s), 1.05 (3H, d, J 7), 3.75 (1H, m), 4.2 (1H, m), 4.55 (1H, m), 4.96 (2H, m), 5.44 (2H, m), 5.81 (1H, d, J 11) and 6.45 (1H, d, J 11); 31 (more polar isomer); needles (from methanol), m. p. 85 - 86°C; δ 0.06 (12H, s), 0.56 (3H, s), 0.87 and 0.90 (each 9H, s), 1.05 (3H, d, J 7), 3.73 (1H, m), 4.2 (1H, m), 4.55 (1H, m), 4.96 (2H, m), 5.41 (2H, m), 5.81 (1H, d, J 11), and 6.45 (1H, d, J 11).

Preparation 32: Compounds 32 and 33.

Method: as Preparation 28; Starting material: 19 (0.5 g); Data: 32 (less polar isomer); needles (from methanol); δ 0.06 (12H, s), 0.57 (3H, s), 0.87 (9H, s), 0.90 (18H, s), 1.05 (3H, d, J 7), 3.7 (1H, m), 4.2 (1H, m), 4.55 (1H, m), 4.96 (2H, m), 5.48 (2H, m), 5.82 (1H, d, J 11) and 6.45 (1H, d, J 11); 33 (more polar isomer); needles (from methanol); δ 0.06 (12H, s), 0.57 (3H, s), 0.87 (9H, s), 0.90 (18H, s), 1.05 (3H, d, J 7), 3.65 (1H, m), 4.2 (1H, m), 4.55

(1H, m), 4.96 (2H, m), 5.45 (2H, m), 5.82 (1H, d, J 11) and 6.45 (1H, d, J 11).

Preparation 33: Compounds 34 and 35.

Method: as Preparation 28; Starting material: 20 (197 mg); Modification: only 2 ml of CeCl_3 solution used; Data: 34 (less polar isomer; δ 0.06 (12H, s), 0.57 (3H, s), 0.87 and 0.91 (each 9H, s), 1.06 (3H, d, J 7), 4.2 (1H, m), 4.55 (1H, m), 4.96 (2H, m), 5.16 (1H, m), 5.63 (2H, m), 5.81 (1H, d, J 11), 6.46 (1H, d, J 11) and 7.34 (5H, m); 35 (more polar isomer); δ 0.06 (12H, s), 0.55 (3H, s), 0.87 and 0.91 (each 9H, s), 1.08 (3H, d, J 7), 4.2 (1H, m), 4.55 (1H, m), 4.96 (2H, m), 5.16 (1H, m), 5.61 (2H, m), 5.81 (1H, d, J 11), 6.46 (1H, d, J 11) and 7.34 (5H, m).

Preparation 34: Compounds 36 and 37.

A stirred solution of 16 (146 mg) in tetrahydrofuran (4 ml) under nitrogen was cooled to about -20°C and treated dropwise with methyl-lithium (ca. 1 M solution in ether) until TLC showed essentially complete consumption of starting material. The reaction mixture was then partitioned between ether and water and the organic layer was washed with water, dried, and concentrated. The residue was crystallised from ether-methanol containing a trace of triethylamine to give 36 and 37 as needles. Compounds 36 and 37 have essentially superimposable NMR spectra: δ 0.06 (12H, s), 0.15 - 0.65 (4H, m), 0.56 (3H, s), 0.87 and 0.90 (each 9H, s), 1.03 (3H, d, J 7), 1.27 (3H, s), 4.2 (1H, m), 4.55 (1H, m), 4.96 (2H, m), 5.31 (1H, d, J 16), 5.54 (1H, dd, J 7, 16), 5.81 (1H, d, J 11) and 6.46 (1H, d, J 11).

Preparation 35: Compound 16 (from recycling of 26 and 27).

A solution of either 26, 27, or a mixture of these two compounds (0.5 g) in dichloromethane (30 ml) was stirred under nitrogen at room temperature with active manganese dioxide (4.0 g) for 6 h. The reaction mixture was filtered, concentrated and the residue purified as in Preparation 19 to give crystalline 16.

Preparation 36: Compound 38.

A solution of starting material 26 (21 mg), anthracene (4 mg) and triethylamine (1 drop) in toluene (5 ml) under N_2 in a Pyrex flask was irradiated with light from a high pressure ultra-violet lamp, type TQ 150Z2 (Hanau) at room temperature for 100 min. The solution was filtered, concentrated in vacuo and the residue purified by chromatography (silica gel; 15 % ethyl acetate in petroleum ether as eluant) to give 38, δ 0.06 (12H, s), 0.15 - 0.65 (4H, m), 0.55 (3H, s), 0.88 (18H, s), 1.05 (3H, d, J 7 Hz), 3.5 (1H, m), 4.2 (1H, m), 4.35 (1H, m), 4.85 (1H, m), 5.17 (1H, m), 5.50 (2H, m), 5.99 (1H, d, J 12 Hz) and 6.24 (1H, d, J 12 Hz).

It should be noted that in the eluant system specified above, 38 is less polar than and distinguishable on TLC from 39.

Preparations 37 - 51: Compounds 39 - 53.

Using the method of Preparation 36, the following starting materials IV (20 - 30 mg) were converted to the corresponding products V, which were each purified by chromatography using the eluant system specified (the entry in the 'Eluant' column indicates the percentage of the more polar component of either an ethyl acetate (EtOAc) or ether (Et_2O) in petroleum ether mixture):

Preparation	V	IV	Eluant	Data (for V)
37	<u>39</u>	<u>27</u>	15 % EtOAc	δ 0.06 (12H, s), 0.15 - 0.65 (4H, m), 0.55 (3H, s); 0.88 (18H, s), 1.05 (3H, d, J 7), 3.45 (1H, m), 4.2 (1H, m), 4.35 (1H, m), 4.85 (1H, m), 5.17 (1H, m), 5.46 (2H, m), 5.99 (1H, d, J 12) and 6.24 (1H, d, J 12).
38	<u>40</u>	<u>22</u>	15 % EtOAc	δ 0.06 (6H, s), 0.15 - 0.65 (4H, m), 0.56 (3H, s), 0.89 (9H, s), 1.05 (3H, d, J 7), 3.5 (1H, m), 3.85 (1H, m), 4.8 (1H, m), 5.0 (1H, m), 5.50 (2H, m), and 6.1 (2H, ABq, J 11).

39	<u>41</u>	<u>23</u>	15 % EtOAc	δ 0.06 (6H, s), 0.15 - 0.65 (4H, m), 0.56 (3H, s), 0.89 (9H, s), 1.05 (3H, d, J 7), 3.45 (1H, m), 3.85 (1H, m), 4.8 (1H, m), 5.0 (1H, m), 5.47 (2H, m), and 6.1 (2H, ABq, J 11).
5 40	<u>42</u>	<u>28</u>	10 % Et ₂ O	δ 0.06 (12H, s), 0.55 (3H, s), 0.88 (18H, s), 1.04 (3H, d, J 7), 3.81 (1H, m), 4.2 (1H, m), 4.35 (1H, m), 4.85 (1H, m), 5.45 (2H, m), 5.99 (1H, d, J 12) and 6.24 (1H, d, J 12).
41	<u>43</u>	<u>29</u>	10 % Et ₂ O	δ 0.06 (12H, s), 0.55 (3H, s), 0.88 (18H, s), 1.04 (3H, d, J 7), 3.78 (1H, m), 4.2 (1H, m), 4.35 (1H, m), 4.85 (1H, m), 5.41 (2H, m), 5.99 (1H, d, J 12) and 6.24 (1H, d, J 12).
10 42	<u>44</u>	<u>30</u>	10 % Et ₂ O	δ 0.06 (12H, s), 0.55 (3H, s), 0.88 (18H, s), 1.04 (3H, d, J 7), 3.75 (1H, m), 4.2 (1H, m), 4.35 (1H, m), 4.86 (1H, m), 5.16 (1H, m), 5.43 (2H, m), 5.99 (1H, d, J 12) and 6.24 (1H, d, J 12).
43	<u>45</u>	<u>31</u>	10 % Et ₂ O	δ 0.06 (12H, s), 0.55 (3H, s), 0.88 (18H, s), 1.04 (3H, d, J 7), 3.73 (1H, m), 4.2 (1H, m), 4.35 (1H, m), 4.86 (1H, m), 5.16 (1H, m), 5.41 (2H, m), 5.99 (1H, d, J 12) and 6.24 (1H, d, J 12).
15 44	<u>46</u>	<u>32</u>	10 % Et ₂ O	δ 0.06 (12H, s), 0.55 (3H, s), 0.88 (18H, s), 0.90 (9H, s), 1.04 (3H, d, J 7), 3.67 (1H, m), 4.2 (1H, m), 4.35 (1H, m), 4.86 (1H, m), 5.16 (1H, m), 5.47 (2H, m), 5.99 (1H, d, J 12) and 6.24 (1H, d, J 12).
20 45	<u>47</u>	<u>33</u>	10 % Et ₂ O	δ 0.06 (12H, s), 0.55 (3H, s), 0.88 (18H, s), 0.90 (9H, s), 1.04 (3H, d, J 7), 3.63 (1H, m), 4.2 (1H, m), 4.35 (1H, m), 4.86 (1H, m), 5.16 (1H, m), 5.43 (2H, m), 5.99 (1H, d, J 12), and 6.24 (1H, d, J 12).
25 46	<u>48</u>	<u>34</u>	10 % Et ₂ O	δ 0.08 (12H, s), 0.56 (3H, s), 0.90 (18H, s), 4.2 (1H, m), 4.4 (1H, m), 4.87 (1H, m), 5.17 (2H, m), 5.61 (2H, m), 6.02 (1H, d, J 11), 6.26 (1H, d, J 11) and 7.34 (5H, m).
47	<u>49</u>	<u>35</u>	10 % Et ₂ O	δ 0.08 (12H, s), 0.56 (3H, s), 0.90 (18H, s), 4.2 (1H, m), 4.4 (1H, m), 4.87 (1H, m), 5.17 (2H, m), 5.59 (2H, m), 6.02 (1H, d, J 11), 6.26 (1H, d, J 11) and 7.34 (5H, m).
30 48	<u>50</u>	<u>24</u>	30 % Et ₂ O	δ 0.06 (12H, s), 0.15 - 0.65 (4H, m), 0.54 (3H, s), 0.88 (18H, s), 4.18 (1H, m), 4.37 (1H, m), 4.86 (1H, m), 5.17 (1H, m), 6.00 (1H, d, J 12) and 6.24 (1H, d, J 12).
49	<u>51</u>	<u>25</u>	30 % Et ₂ O	δ 0.06 (12H, s), 0.15 - 0.65 (4H, m), 0.54 (3H, s), 0.88 (18H, s), 4.18 (1H, m), 4.37 (1H, m), 4.86 (1H, m), 5.17 (1H, m), 6.00 (1H, d, J 12) and 6.24 (1H, d, J 12).
35 50	<u>52</u>	<u>36</u>	20 % Et ₂ O	δ 0.06 (12H, s), 0.15 - 0.65 (4H, m), 0.55 (3H, s), 0.88 (18H, s), 1.02 (3H, d, J 7), 1.26 (3H, s), 4.2 (1H, m), 4.35 (1H, m), 4.85 (1H, m), 5.17 (1H, m), 5.31 (1H, d, J 16), 5.54 (1H, dd, J 7, 16), 5.99 (1H, d, J 12) and 6.24 (1H, d, J 12).
40 51	<u>53</u>	<u>37</u>	20 % Et ₂ O	δ 0.06 (12H, s), 0.15 - 0.65 (4H, m), 0.55 (3H, s), 0.88 (18H, s), 1.02 (3H, d, J 7), 1.26 (3H, s), 4.2 (1H, m), 4.35 (1H, m), 4.85 (1H, m), 5.17 (1H, m), 5.31 (1H, d, J 16), 5.54 (1H, dd, J 7, 16), 5.99 (1H, d, J 12) and 6.24 (1H, d, J 12).

Preparation 52: Compound 14a (Z = Z' = OSiMe₂But^t).

Method: as Preparation 36; Starting material: 12 (28 mg); Modification: the triethylamine was omitted; Chromatography eluant: 5 % ether in petroleum ether; δ 0.06 (12H, s), 0.59 (3H, s), 0.88 (18H, s), 1.14 (3H, d, J 7), 4.2 (1H, m), 4.4 (1H, m), 4.86 (1H, m), 5.17 (1H, m), 5.99 (1H, d, J 12), 6.24 (1H, d, J 12) and 9.58 (1H, d, J 3).

Preparation 53: Compound 14b (Z = H, Z' = OSiMe₂But^t).

Method: as Preparation 36 ; Starting material: 13 (24 mg); Modification: the triethylamine was omitted; Chromatography eluant: 5 % ether in petroleum ether; δ 0.06 (6H, s), 0.60 (3H, s), 0.88 (9H, s), 1.14 (3H, d, J 7), 3.85 (1H, m), 4.78 (1H, m), 4.99 (1H, m), 6.1 (2H, ABq, J 11) and 9.59 (1H, d, J 3).

Preparation 54: Compound 54.

A solution of starting material 26 (30 mg) and tetrabutylammonium fluoride (60 mg) in tetrahydrofuran (5 ml) was heated at 60°C under N₂ for 60 min. After cooling, the reaction solution was partitioned between ethyl acetate and 2 % sodium hydrogen carbonate solution, and the organic layer was washed with water, dried and concentrated. The residue was purified by chromatography (silica gel, ethyl acetate as eluant) to give 54, $\lambda_{\max}$ (EtOH) 265 nm, δ 0.15 - 0.65 (4H, m), 0.58 (3H, s), 0.8 - 1.1 (1H, m), 1.05 (3H, d, J 7), 3.5 (1H, m), 4.2 (1H, m), 4.5 (1H, m), 4.97 (1H, m), 5.11 (1H, m), 5.51 (2H, m), 5.88 (1H, d, J 11) and 6.57 (1H, d, J 11).

Preparation 55: Compound 55.

Method: as Preparation 54; Starting material: 27 (26 mg); $\lambda_{\max}$ (EtOH) 265 nm, δ 0.15 - 0.65 (4H, m), 0.58 (3H, s), 0.8 - 1.1 (1H, m), 1.05 (3H, d, J 7), 3.45 (1H, m), 4.5 (1H, m), 4.97 (1H, m), 5.11 (1H, m), 5.48 (2H, m), 5.88 (1H, d, J 11) and 6.57 (1H, d, J 11).

Preparation 56: Equilibration of compounds 59 and 73.

A solution of 59 (73 mg) in ethanol (20 ml) was heated under reflux under nitrogen for 40 min. After cooling, the solvent was removed in vacuo, and the residue purified by chromatography (silica gel, ethyl acetate as eluant) to return 59 followed by the more polar 73, δ 0.15 - 0.65 (4H, m), 0.72 (3H, s), 0.8 - 1.1 (1H, m), 1.05 (3H, d, J 7), 3.45 (1H, m), 4.2 (2H, m), 5.47 (3H, m) and 5.83 (2H, m).

Example 1: (1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-cyclopropyl-3'-hydroxyprop-1'-enyl)-3-hydroxypregna-5,7,10(19)-triene, isomer A (Compound 56).

A solution of starting material 40 (37 mg) and tetrabutylammonium fluoride (90 mg) in tetrahydrofuran (4 ml) was heated under reflux under N₂ for 1 h. After cooling, the reaction solution was partitioned between ethyl acetate and 2 % sodium hydrogen carbonate solution, and the organic layer was washed with water, dried and concentrated. The residue was purified by chromatography (silica gel; 50 % ethyl acetate in petroleum ether as eluant) to give 56, $\lambda_{\max}$ (EtOH) 265 nm, δ 0.15 - 0.65 (4H, m), 0.55 (3H, s), 1.05 (3H, d, J 7), 3.5 (1H, m), 3.94 (1H, m), 4.81 (1H, m), 5.02 (1H, m), 5.50 (2H, m), 6.01 (1H, d, J 11) and 6.24 (1H, d, J 11).

Example 2: (1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-cyclopropyl-3'-hydroxyprop-1'-enyl)-3-hydroxypregna-5,7,10(19)-triene, isomer B (compound 57).

Method: as Example 1; Starting material: 41 (40 mg); Data: $\lambda_{\max}$ (EtOH) 265 nm, δ 0.15 - 0.65 (4H, m), 0.55 (3H, s), 1.05 (3H, d, J 7), 3.45 (1H, m), 3.94 (1H, m), 4.81 (1H, m), 5.02 (1H, m), 5.47 (2H, m), 6.01 (1H, d, J 11) and 6.24 (1H, d, J 11).

Example 3: (1S,1'E,3R,5Z,7E,20R)-(9,10)-seco-20-(3'-cyclopropyl-3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene, isomer A (compound 58).

Method: as Example 1; Starting material: 38 (15 mg); Chromatography eluant: ethyl acetate; Data: T_R 10.4 min, $\lambda_{\max}$ (EtOH) 265 nm, δ 0.15 - 0.65 (4H, m), 0.56 (3H, s), 0.75 - 1.1 (1H, m), 1.05 (3H, d, J 7 Hz), 3.47, (1H, m), 4.2 (1H, m), 4.4 (1H, m), 4.99 (1H, m), 5.31 (1H, m), 5.50 (2H, m), 5.99 (1H, d, J 11 Hz), and 6.36 (1H, d, J 11 Hz); m/z 412 (M⁺) and 134.

Example 4: Compound 58 (alternative method)

A solution of 54 (15 mg), anthracene (4 mg) and triethylamine (20 mg) in toluene (5 ml) under N₂ in a Pyrex flask was irradiated with light from a high pressure ultraviolet lamp, type TQ 150Z2 (Hanau) at room temperature for 100 min. The solution was concentrated in vacuo and the residue purified by chromatography (silica gel; ethyl acetate as eluant) to give 58.

Example 5: (1S,1'E,3R,5Z,7E,20R)-(9,10)-seco-20-(3'-cyclopropyl3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene, isomer B (compound 59).

A solution of 39 (45 mg) and tetrabutylammonium fluoride (90 mg) in tetrahydrofuran (4 ml) was heated under reflux under N₂ for 60 min. After cooling, the reaction solution was partitioned between ethyl acetate and 2 % sodium hydrogen carbonate solution, and the organic layer was washed with water, dried and concentrated. The residue was purified by chromatography (silica gel; ethyl acetate as eluant) followed by crystallisation from methyl formate to give 59 as needles, m. p. 166 - 168°C, T_R 9.2 min, λ_{max} (EtOH) 265 nm, δ 0.15 - 0.65 (4H, m), 0.56 (3H, s), 0.75 - 1.1 (1H, m), 1.05 (3H, d, J 7 Hz), 3.45 (1H, m), 4.2 (1H, m), 4.4 (1H, m), 4.99 (1H, m), 5.31 (1H, m), 5.47 (2H, m), 5.99 (1H, d, J 11 Hz), and 6.36 (1H, d, J 11 Hz); m/z 412 (M⁺) and 134.

Example 6: Compound 59 (alternative method)

A solution of 55 (15 mg), anthracene (4 mg) and triethylamine (20 mg) in toluene (5 ml) under N₂ in a Pyrex flask was irradiated with light from a high pressure ultraviolet lamp, type TQ 150Z2 (Hanau) at room temperature for 100 min. The solution was concentrated in vacuo and the residue purified by chromatography (silica gel; ethyl acetate as eluant) to give 59.

Example 7: Compound 59 (alternative method).

A solution of 73 (125 mg) in ether (9 ml) was kept under nitrogen in the dark at about 20°C for 10 days. The solvent was removed in vacuo and the residue purified by chromatography (silica gel; ethyl acetate as eluant) followed by crystallisation from methyl formate to give 59.

Example 8: (1S,1'E,3R,5Z,7E,20R)-(9,10)-seco-20-(3'-cyclopentyl3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene, isomer A (compound 60).

Method: as Example 1; Starting material 42 (49 mg); Chromatography eluant: ethyl acetate; Data: λ_{max} (EtOH) 265 nm; δ 0.56 (3H, s), 1.03 (3H, d, J 7), 3.8 (1H, m), 4.2 (1H, m), 4.4 (1H, m), 4.98 (1H, m), 5.31 (1H, m), 5.45 (2H, m), 5.99 (1H, d, J 12) and 6.36 (1H, d, J 12); m/z 440 (M⁺) and 134; T_R 8.2 min.

Example 9: (1S,1'E,3R,5Z,7E,20R)-(9,10)-seco-20-(3'-cyclopentyl3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene, isomer B (compound 61).

Method: as Example 1; Starting material 43 (31 mg); Chromatography eluant: ethyl acetate; Data: λ_{max} (EtOH) 265 nm; δ 0.55 (3H, s), 1.03 (3H, d, J 7), 3.77 (1H, m), 4.2 (1H, m), 4.4 (1H, m), 4.98 (1H, m), 5.31 (1H, m), 5.41 (2H, m), 5.99 (1H, d, J 12) and 6.36 (1H, d, J 12); m/z 440 (M⁺) and 134; T_R 6.6 min.

Example 10: 1S,1'E,3R,5Z,7E,20R)-(9,10)-seco-20-(3'-cyclohexyl3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene, isomer A (compound 62).

Method: as Example 1; Starting material: 44 (40 mg); Chromatography eluant: ethyl acetate; Data: λ_{max} (EtOH) 265 nm; δ 0.56 (3H, s), 1.04 (3H, d, J 7), 3.75 (1H, m), 4.2 (1H, m), 4.4 (1H, m), 4.98 (1H, m), 5.31 (1H, m), 5.43 (2H, m), 5.99 (1H, d, J 12), 6.36 (1H, d, J 12); m/z 454 (M⁺) and 134; T_R 7.2 min.

Example 11: (1S,1'E,3R,5Z,7E,20R)-(9,10)-seco-20-(3'-cyclohexyl3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene, isomer B (compound 63).

Method: as Example 1; Starting material: 45 (41 mg); Chromatography eluant: ethyl acetate; Data: λ_{max} (EtOH) 265 nm; δ 0.56 (3H, s), 1.04 (3H, d, J 7), 3.73 (1H, m), 4.2 (1H, m), 4.4 (1H, m), 4.98 (1H, m), 5.31 (1H, m), 5.40 (2H, m), 5.99 (1H, d, J 12), 6.36 (1H, d, J 12); m/z 454 (M⁺) and 134; T_R 5.8 min.

Example 12: (1S,1'E,3R,5Z,7E,20R)-(9,10)-seco-20-(4',4'-dimethyl3'-hydroxybut-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene, isomer A (compound 64).

Method: as Example 1; Starting material: 46 (29 mg); Chromatography eluant: ethyl acetate; Data: T_R 8.2 min, λ_{max} (EtOH) 265 nm, δ 0.56 (3H, s), 0.89 (9H, s), 1.04 (3H, d, J 7), 3.67 (1H, m), 4.2 (1H, m), 4.41 (1H, m), 4.99 (1H, br s), 5.31 (1H, m), 5.47 (2H, m), 6.00 (1H, d, J 11) and 6.37 (1H, d, J 11).

10 **Example 13: (1S,1'E,3R,5Z,7E,20R)-(9,10)-seco-20-(4',4'-dimethyl3'-hydroxybut-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene, isomer B (compound 65).**

Method: as Example 1; Starting material: 47 (27 mg); Chromatography eluant: ethyl acetate; Data: T_R 6.8 min, λ_{max} (EtOH) 265 nm, δ 0.56 (3H, s), 0.88 (9H, s), 1.04 (3H, d, J 7), 3.63 (1H, m), 4.2 (1H, m), 4.40 (1H, m), 4.99 (1H, br s), 5.31 (1H, m), 5.43 (2H, m), 6.00 (1H, d, J 11) and 6.36 (1H, d, J 11).

20 **Example 14: (1S,1'E,3R,5Z,7E,20R)-(9,10)-seco-20-(3'-hydroxy3-phenylprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene, isomer A (compound 66).**

Method: as Example 1; Starting material: 48 (29 mg); Chromatography eluant: ethyl acetate; Data: T_R 8.2 min., λ_{max} (EtOH) 265 nm, δ 0.56 (3H, s), 1.04 (3H, d, J 7), 4.2 (1H, m), 4.40 (1H, m), 4.98 (1H, m), 5.12 (1H, m), 5.31 (1H, m), 5.60 (2H, m), 6.00 (1H, d, J 11), 6.36 (1H, d, J 11) and 7.33 (5H, m).

30 **Example 15: (1S,1'E,3R,5Z,7E,20R)-(9,10)-seco-20-(3'-hydroxy3-phenylprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene, isomer B (compound 67).**

Method: as Example 1; Starting material: 49 (42 mg); Chromatography eluant: ethyl acetate; Data: T_R 7.2 min., λ_{max} (EtOH) 265 nm, δ 0.54 (3H, s), 1.06 (3H, d, J 7), 4.2 (1H, m), 4.42 (1H, m), 4.97 (1H, m), 5.13 (1H, m), 5.30 (1H, m), 5.59 (2H, m), 5.99 (1H, d, J 11), 6.36 (1H, d, J 11) and 7.33 (5H, m).

35 **Example 16: (1'S,3R,5Z,7E,20R)-(9,10)-cyclopropyl3'-hydroxypropyl)-1,3-dihydroxypregna-5,7,10(19)-triene, isomer A (compound 68).**

40 **Method: as Example 1; Starting material: 50 (40 mg); Chromatography eluant: ethyl acetate; Data: λ_{max} (EtOH) 265 nm, δ 0.15 - 0.65 (4H, m), 0.54 (3H, s), 0.93 (3H, d, J 7), 4.2 (1H, m), 4.4 (1H, m), 4.99 (1H, m), 5.31 (1H, m), 5.99 (1H, d, J 12) and 6.36 (1H, d, J 12).**

45 **Example 17: (1S,3R,5Z,7E,20R)-(9,10)-seco-20-(3'-cyclopropyl3'-hydroxypropyl)-1,3-dihydroxypregna-5,7,10(19)-triene, isomer B (compound 69).**

50 **Method: as Example 1; Starting material: 51 (22 mg); Chromatography eluant: ethyl acetate; Data: λ_{max} (EtOH) 265 nm, δ 0.15 - 0.65 (4H, m), 0.54 (3H, s), 0.93 (3H, d, J 7), 4.2 (1H, m), 4.4 (1H, m), 4.99 (1H, m), 5.31 (1H, m), 5.99 (1H, d, J 12) and 6.36 (1H, d, J 12).**

55 **Example 18: (1S,1'E,3R,5Z,7E,20R)-(9,10)-seco-20-(3'-cyclopropyl3'-hydroxy-but-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene, isomer A (compound 70).**

60 **Method: as Example 1; Starting material: 52 (19 mg); Chromatography eluant: ethyl acetate; Data: λ_{max} (EtOH) 265 nm, δ 0.15 - 0.65 (4H, m), 0.55 (3H, s), 1.02 (3H, d, J 7), 1.26 (3H, s), 4.2 (1H, m), 4.4 (1H, m), 5.31 (1H, d, J 16), 5.31 (1H, m), 5.54 (1H, dd, J 7 and 16), 5.99 (1H, d, J 12) and 6.36 (1H, d, J 12).**

Example 19: (1S,1'E,3R,5Z,7E,20R)-(9,10)-seco-20-(3'-cyclopropyl3'-hydroxy-but-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene, isomer B (compound 71).

Method: as Example 1; Starting material: 53 (17 mg); Chromatography eluant: ethyl acetate; Data: $\lambda_{\max}$ (EtOH) 265 nm, δ 0.15 - 0.65 (4H, m), 0.55 (3H, s), 1.02 (3H, d, J 7), 1.26 (3H, s), 4.2 (1H, m), 4.4 (1H, m), 5.31 (1H, d, J 16), 5.31 (1H, m), 5.54 (1H, dd, J 7 and 16), 5.99 (1H, d, J 12) and 6.36 (1H, d, J 12).

10 Example 20: Dermatological Cream Containing 59.

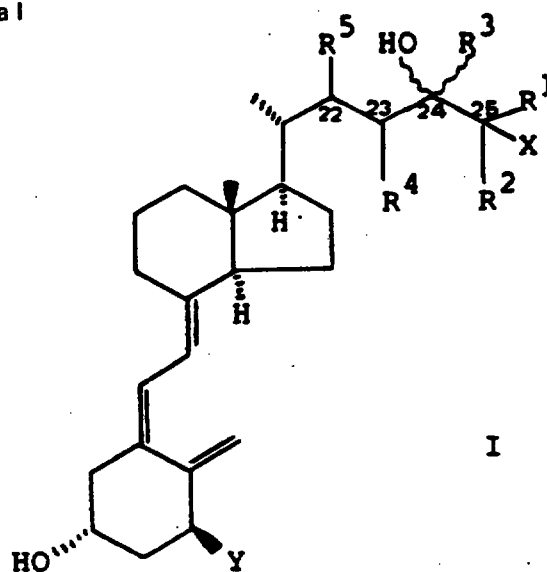
In 1 g almond oil was dissolved 1 mg 59. To this solution was added 40 g of mineral oil and 20 g of self emulsifying beeswax. The mixture was heated to liquify. After the addition of 40 ml hot water, the mixture was mixed well. The resulting cream contains approximately 10 μ g of 59 per gram of cream.

Example 21: Capsules containing 59.

59 was dissolved in a triglyceride of a medium chain fatty acid to a final concentration of 50 μ g 59/ml oil. 10 Parts by weight of gelatine, 5 parts by weight glycerine, 0.08 parts by weight potassium sorbate, and 14 parts by weight distilled water were mixed together with heating and formed into soft gelatine capsules. These were then filled each with 100 μ l of the 59 in oil solution, such that each capsule contained 5 μ g 59.

Claims

1. A compound of the formula I



in which formula X stands for hydrogen, C₁-C₆-alkyl, halogen or hydroxy; Y stands for hydrogen or hydroxy; R¹ and R², which may be the same or different, stand for C₁-C₆-alkyl, optionally substituted with halogen or hydroxy, with the proviso that R¹ and R² cannot both be methyl when X is other than C₁-C₆-alkyl, or R¹ and R², taken together with the carbon atom numbered 25, can form a saturated or unsaturated C₃-C₉ carbocyclic ring including an aromatic ring which may optionally be substituted at any possible position(s) with C₁-C₆-alkyl, halogen or hydroxy; R³ stands for hydrogen or C₁-C₆-alkyl; R⁴ and R⁵ represent either each hydrogen, or when taken together constitute a bond with the result that a double bond connects carbon atoms numbered 22 and 23; and derivatives thereof, wherein one or more hydroxy groups are transformed into O-acyl or O-glycosyl groups which are hydrolysable in vivo.

2. A compound according to claim 1, in crystalline form.

3. A compound according to claim 1, which is a compound of formula I in which R³ is hydrogen or methyl.

4. A compound according to claim 3, in which R⁴ and R⁵ taken together represent a bond, the resulting 22, 23 double bond having the trans configuration.

5. A compound according to claim 1, selected from the groups consisting of the 3'R and 3'S isomers of:

Example 19: (1S,1'E,3R,5Z,7E,20R)-(9,10)-seco-20-(3'-cyclopropyl3'-hydroxy-but-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene, isomer B (compound 71).

Method: as Example 1; Starting material: 53 (17 mg); Chromatography eluant: ethyl acetate; Data: $\lambda_{\max}$ (EtOH) 265 nm, δ 0.15 - 0.65 (4H, m), 0.55 (3H, s), 1.02 (3H, d, J 7), 1.26 (3H, s), 4.2 (1H, m), 4.4 (1H, m), 5.31 (1H, d, J 16), 5.31 (1H, m), 5.54 (1H, dd, J 7 and 16), 5.99 (1H, d, J 12) and 6.36 (1H, d, J 12).

Example 20: Dermatological Cream Containing 59.

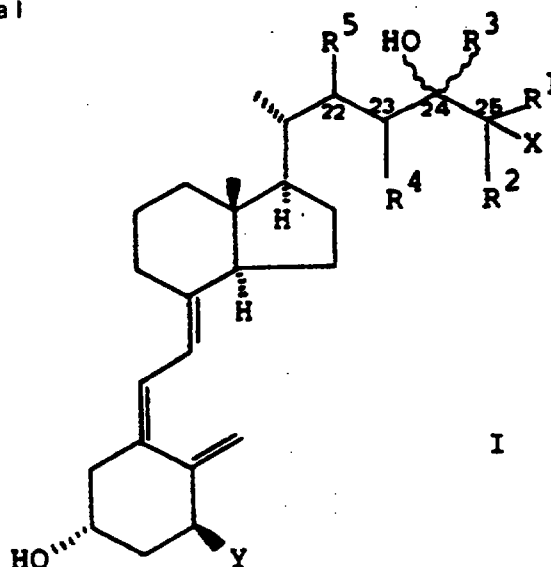
In 1 g almond oil was dissolved 1 mg 59. To this solution was added 40 g of mineral oil and 20 g of self emulsifying beeswax. The mixture was heated to liquify. After the addition of 40 ml hot water, the mixture was mixed well. The resulting cream contains approximately 10 μ g of 59 per gram of cream.

Example 21: Capsules containing 59.

59 was dissolved in a triglyceride of a medium chain fatty acid to a final concentration of 50 μ g 59/ml oil. 10 Parts by weight of gelatine, 5 parts by weight glycerine, 0.08 parts by weight potassium sorbate, and 14 parts by weight distilled water were mixed together with heating and formed into soft gelatine capsules. These were then filled each with 100 μ l of the 59 in oil solution, such that each capsule contained 5 μ g 59.

Claims

1. A compound of the formula I



in which formula X stands for hydrogen, C₁-C₆-alkyl, halogen or hydroxy; Y stands for hydrogen or hydroxy; R¹ and R², which may be the same or different, stand for C₁-C₆-alkyl, optionally substituted with halogen or hydroxy, with the proviso that R¹ and R² cannot both be methyl when X is other than C₁-C₆-alkyl, or R¹ and R², taken together with the carbon atom numbered 25, can form a saturated or unsaturated C₃-C₉ carbocyclic ring including an aromatic ring which may optionally be substituted at any possible position(s) with C₁-C₆-alkyl, halogen or hydroxy; R³ stands for hydrogen or C₁-C₆-alkyl; R⁴ and R⁵ represent either each hydrogen, or when taken together constitute a bond with the result that a double bond connects carbon atoms numbered 22 and 23; and derivatives thereof, wherein one or more hydroxy groups are transformed into O-acyl or O-glycosyl groups which are hydrolysable in vivo.

2. A compound according to claim 1, in crystalline form.

3. A compound according to claim 1, which is a compound of formula I in which R³ is hydrogen or methyl.

4. A compound according to claim 3, in which R⁴ and R⁵ taken together represent a bond, the resulting 22, 23 double bond having the *trans* configuration.

5. A compound according to claim 1, selected from the groups consisting of the 3'R and 3'S isomers of.



(1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-cyclopropyl-3'-hydroxyprop-1'-enyl)-3-hydroxypregna-5,7,10(19)-triene;
 (1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-cyclopropyl-3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene;

(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-cyclopentyl-3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene;

(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-cyclohexyl-3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene;

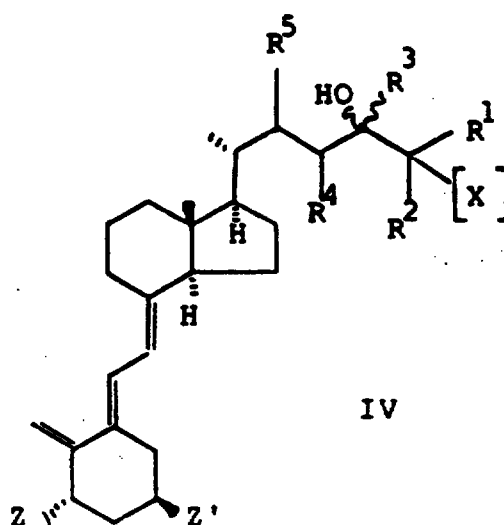
(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(4',4'-dimethyl-3'-hydroxypent-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene;

(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-phenyl-3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene;

(1S,3R,5Z,7E,20R)-9,10-seco-(3'-cyclopropyl-3'-hydroxypropyl)-1,3-dihydroxypregna-5,7,10(19)-triene;

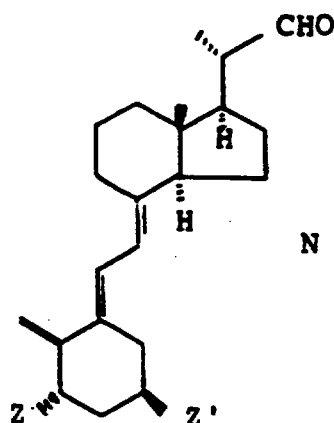
(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-cyclopropyl-3'-hydroxybut-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene.

6. A method for producing a compound of claim 1, in which a compound of formula IV:



in which R¹, R², R³, R⁴ and R⁵ are as defined above, [X] is X, as defined above, or a protected or masked derivative which can later be converted to X, Z' is an optionally protected hydroxy group, and Z is either H or an optionally protected hydroxy group, is subjected to a triplet-sensitized photoisomerisation and, if necessary, deprotection of the hydroxy group(s), the sequence of these reactions being arbitrary.

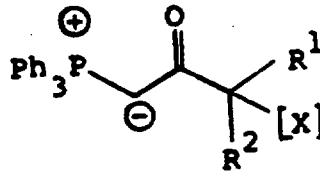
7. A method for producing a compound of formula IV of claim 6, in which compound N



in which Z' and Z are as defined above, is reacted with a compound of formula D



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D

optionally followed by a reduction of the 22, 23-double bond, and conversion of the 24-oxo compound into the 24-hydroxy compound of formula IV by treatment with a reducing agent (R^3 = hydrogen) or an organometallic reagent (R^3 = alkyl).

8. A method for producing a compound of formula I of claim 1, in which the corresponding pre-vitamin, optionally with one or more protected hydroxy groups, is subjected to thermal isomerization, if necessary followed by deprotection of the hydroxy group(s).

9. A compound of formula N of claim 7, which is (3R,5E,7E,20S)-9,10-seco-20-formyl-3-(tertbutyldimethylsilyloxy)pregna-5,7,10(19)-triene; or (1S,3R,5E,7E,20S)-9,10-seco-20-formyl-1,3-bis(tertbutyldimethylsilyloxy)pregna-5,7,10(19)-triene.

10. A pharmaceutical Preparation, containing an effective amount of one or more of the compounds of formula I of claim 1, together with pharmaceutically acceptable, non-toxic carriers and/or auxiliary agents.

11. A pharmaceutical Preparation according to claim 10, in topical form.

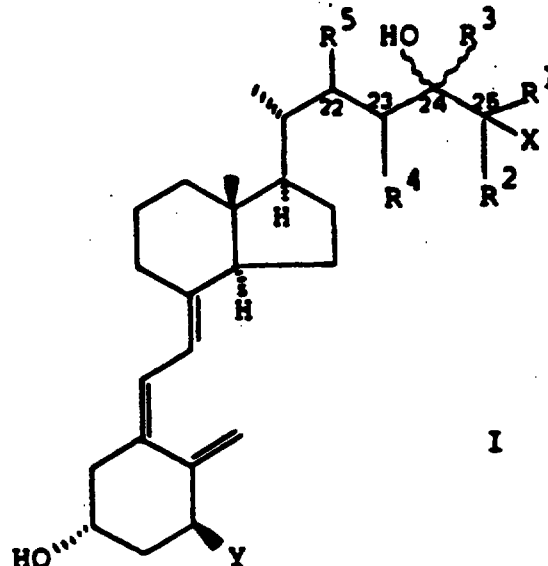
12. A pharmaceutical Preparation according to claim 10, in oral form.

13. The use of one or more compounds of formula I for preparing a pharmaceutical Preparation for the treatment of patients suffering from disorders characterized by abnormal cell-proliferation and/or cell-differentiation.

14. The use according to claim 13 for preparing the Preparation according to claim 11 for the treatment of patients suffering from psoriasis.

Patentansprüche

1. Verbindungen der Formel I



I

worin

X für ein Wasserstoffatom, eine C_1 - C_6 -Alkylgruppe, ein Halogenatom oder eine Hydroxygruppe steht,

Y für ein Wasserstoffatom oder eine Hydroxygruppe steht;

R^1 und R^2 gleich oder verschieden sein können und für eine gegebenenfalls mit einem Halogenatom oder einer Hydroxygruppe substituierte C_1 - C_6 -Alkylgruppe stehen, unter der Bedingung, daß R^1 und R^2 nicht für eine Methylgruppe stehen, wenn X eine andere Bedeutung als C_1 - C_6 -Alkyl besitzt, oder R^1 und R^2 zusammen mit dem Kohlenstoffatom 25 einen gegebenenfalls in jeder möglichen Position mit einer C_1 - C_6 -Alkylgruppe, einem Halogenatom oder einer Hydroxygruppe substituierten gesättigten oder ungesättigten carbocyclischen Ring mit 3 bis 9 Kohlenstoffatomen einschließlich eines aromatischen Ringes bilden können.



R³ für ein Wasserstoffatom oder eine C₁-C₆-Alkyl-gruppe steht;
 R⁴ und R⁵ jeweils entweder für ein Wasserstoffatom stehen oder zusammen eine Bindung bilden, so daß zwischen dem Kohlenstoffatom 22 und 23 eine Doppelbindung vorliegt;
 und Derivate davon, in welchen eine oder mehrere Hydroxygruppen in O-Acyl- oder O-Glycosylgruppen umgewandelt sind, die in vivo hydrolysierbar sind.

2. Verbindungen nach Anspruch 1 in kristalliner Form.

3. Verbindung nach Anspruch 1, wobei es sich um eine Verbindung der Formel I handelt, worin R³ für ein Wasserstoffatom oder eine Methylgruppe steht.

4. Verbindung nach Anspruch 3, worin R⁴ und R⁵ zusammen für eine Bindung stehen, nämlich die 22, 23-Doppelbindung mit Transkonfiguration.

5. Verbindung nach Anspruch 1, ausgewählt unter den aus 3'R- und 3'S-Isomeren bestehenden Verbindungen:

(1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-Cyclopropyl-3'-hydroxyprop-1'-enyl)-3-hydroxypregna-5,7,10(19)-trien;

(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-Cyclopropyl-3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-trien;

(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-Cyclopentyl-3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-trien;

(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-Cyclohexyl-3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-trien;

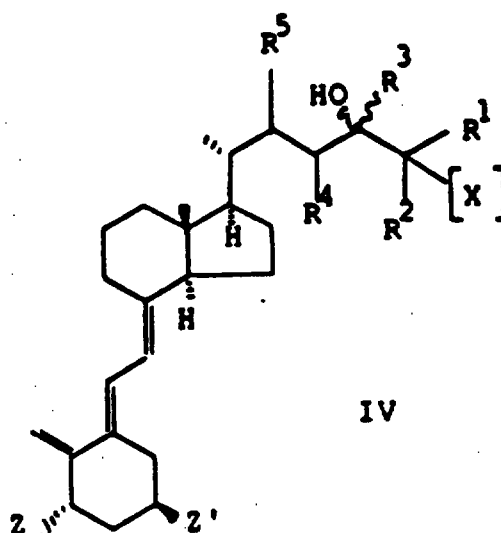
(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(4',4'-Dimethyl-3'-hydroxypent-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-trien;

(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-Phenyl-3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-trien;

(1S,3R,5Z,7E,20R)-9,10-seco-(3'-Cyclopropyl-3'-hydroxypropyl)-1,3-dihydroxypregna-5,7,10(19)-trien;

(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-Cyclopropyl-3'-hydroxybut-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-trien.

6. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, in welchem eine Verbindung der Formel IV:



worin

R¹, R², R³, R⁴ und R⁵ wie oben definiert sind,

[X] für X wie oben definiert steht, oder für ein geschütztes oder maskiertes Derivat steht, das später in X überführt werden kann,

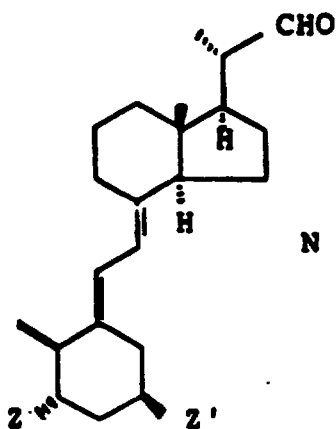
Z' für eine gegebenenfalls geschützte Hydroxygruppe steht, und

Z entweder für H oder eine gegebenenfalls geschützte Hydroxygruppe steht,

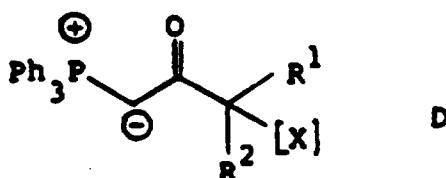
einer triplett-sensibilisierten Photoisomerisierung unterworfen wird, wobei, wenn notwendig, die Hydroxygruppe(n) entfernt wird (werden) und die Reihenfolge dieser Reaktionen willkürlich ist.

7. Verfahren zur Herstellung einer Verbindung der Formel IV nach Anspruch 6, in welchem die Verbindung N

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worin Z' und Z wie oben definiert sind, mit einer Verbindung der Formel D



umgesetzt wird und sich gegebenenfalls eine Reduktion der 22, 23-Doppelbindung und die Umwandlung der 24-Oxo-verbindung in die 24-Hydroxyverbindung der Formel IV durch Behandlung mit einem Reduktionsmittel (R^3 = Wasserstoff) oder einem metallorganischen Reagenz (R^3 = Alkyl) anschließt.

8. Verfahren zur Herstellung einer Verbindung der Formel I nach Anspruch 1, in welchem das entsprechende Provitamin gegebenenfalls mit einer oder mehreren geschützten Hydroxygruppen einer thermischen Isomerisierung unterzogen wird, wobei, wenn nötig, die Hydroxygruppe(n) anschließend entfernt wird (werden).

9. Verbindung der Formel N nach Anspruch 7, nämlich (3R,5E,7E,20S)-9,10-seco-20-Formyl-3-(tertbutyldimethylsilyloxy)pregna-5,7,10(19)-trien; oder (1S,3R,5E,7E,20S)-9,10-seco-20-Formyl-1,3-bis(tertbutyldimethylsilyloxy)pregna-5,7,10(19)-trien.

10. Pharmazeutisches Präparat, das eine wirksame Menge einer oder mehrerer Verbindungen der Formel I nach Anspruch 1 zusammen mit pharmazeutisch verträglichen, nicht-toxischen Trägern und/oder Hilfsmitteln enthält.

11. Pharmazeutisches Präparat nach Anspruch 10 in topischer Form.

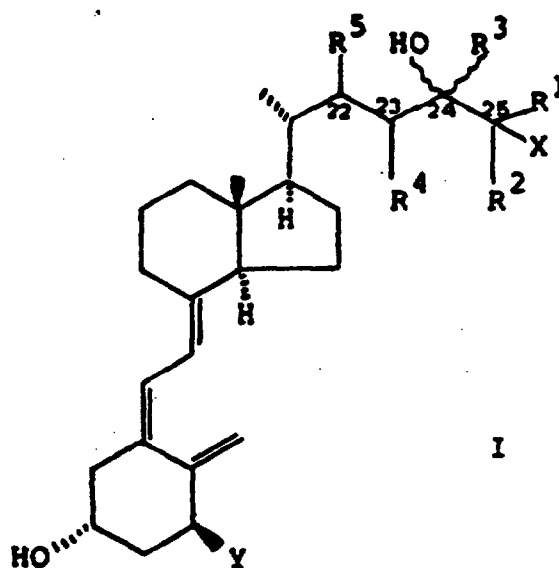
12. Pharmazeutisches Präparat nach Anspruch 10 in oraler Form.

13. Verwendung einer oder mehrerer Verbindungen der Formel I zur Herstellung eines pharmazeutischen Präparats zur Behandlung von Patienten, die an Störungen leiden, die durch abnormale Zellproliferation und/oder Zelldifferenzierung gekennzeichnet sind.

14. Verwendung nach Anspruch 13 zur Herstellung des Präparats gemäß Anspruch 11 zur Behandlung von Patienten, die an Psoriasis leiden.

Revendications

1. Composé de formule I



dans laquelle formule X représente l'hydrogène, un alkyle en C₁-C₆, un halogène ou un hydroxy; Y représente l'hydrogène ou un hydroxy; R¹ et R², qui peuvent être identiques ou différents, représentent un alkyle en C₁-C₆, éventuellement substitué par un halogène ou un hydroxy, à la condition que R¹ et R² ne puissent pas être en même temps méthyle lorsque X est différent d'un alkyle en C₁-C₆, ou R¹ et R² pris ensemble avec l'atome de carbone numéroté 25, peuvent former un noyau carbocyclique en C₃-C₉ saturé ou insaturé y compris un noyau aromatique qui peut être éventuellement substitué en toute(s) position(s) possible(s) par un alkyle en C₁-C₆, un halogène ou un hydroxy; R³ représente l'hydrogène ou un alkyle en C₁-C₆; R⁴ et R⁵ représentent soit chacun l'hydrogène ou, lorsqu'ils sont pris ensemble, constituent une liaison, ce qui a pour résultat qu'une double liaison relie les atomes de carbone numéros 22 et 23; et ses dérivés, dans lesquels un ou plusieurs groupes hydroxy sont transformés en des groupes O-acyle ou O-glycosyle qui sont hydrolysables in vivo.

2. Composé selon la revendication 1 sous forme cristalline.

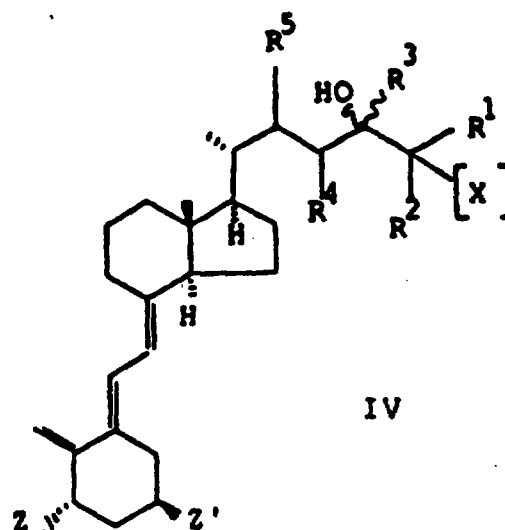
3. Composé selon la revendication 1 qui est un composé de formule I, dans lequel R³ est l'hydrogène ou un méthyle.

4. Composé selon la revendication 3, dans lequel R⁴ et R⁵ pris ensemble représentent une liaison, la double liaison 22, 23 résultante ayant la configuration trans.

5. Composé selon la revendication 1 choisi parmi les groupes consistant en les isomères 3'R et 3'S de:

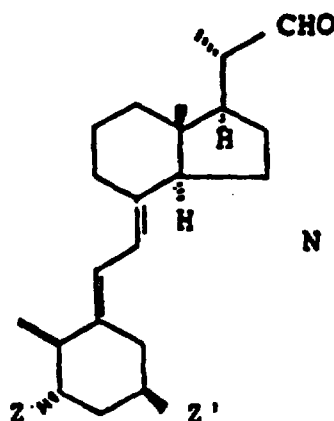
- (1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-cyclopropyl-3'-hydroxyprop-1'-enyl)-3-hydroxypregna-5,7,10(19)-triène;
(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-cyclopropyl-3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triène;
(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-cyclopentyl-3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triène;
(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-cyclohexyl-3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triène;
(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(4',4'-diméthyl-3'-hydroxypent-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triène;
(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-phényl-3'-hydroxyprop-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triène;
(1S,3R,5Z,7E,20R)-9,10-seco-(3'-cyclopropyl-3'-hydroxypropyl)-1,3-dihydroxypregna-5,7,10(19)-triène;
(1S,1'E,3R,5Z,7E,20R)-9,10-seco-20-(3'-cyclopropyl-3'-hydroxybut-1'-enyl)-1,3-dihydroxypregna-5,7,10(19)-triène.

6. Procédé de préparation d'un composé selon la revendication 1, dans lequel un composé de formule IV:

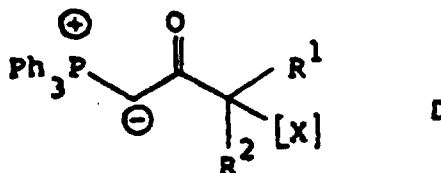


dans laquelle R^1 , R^2 , R^3 , R^4 et R^5 sont tels que définis ci-dessus, $[X]$ est X , tel que défini ci-dessus, ou un dérivé protégé ou masqué qui peut être converti ultérieurement en X , Z' est un groupe hydroxy éventuellement protégé, et Z est H ou un groupe hydroxy éventuellement protégé, est soumis à une photoisomérisation sensibilisée par triplets et, si nécessaire, à une déprotection du ou des groupe(s) hydroxy, la séquence de ces réactions étant arbitraire.

7. Procédé de préparation d'un composé de formule IV selon la revendication 6, dans lequel le composé N



dans lequel Z' et Z sont tels que définis ci-dessus, est mis à réagir avec un composé de formule D



après quoi a lieu éventuellement une réduction de la double liaison 22, 23 et la conversion du composé oxo 24 en le composé hydroxy 24 de formule IV par traitement avec un agent réducteur (R^3 = hydrogène) ou un réactif organométallique (R^3 = alkyle).

8. Procédé de préparation d'un composé de formule I selon la revendication 1, dans lequel la pré-vitamine correspondante, éventuellement avec un ou plusieurs groupes hydroxy protégés, est soumise à une isomérisation thermique, si nécessaire suivie par une déprotection du ou des groupe(s) hydroxy.

9. Composé de formule N selon la revendication 7, qui est le (3R,5E,7E,20S)-9,10-seco-20-formyl-3-(terbutyl-diméthylsilyloxy)-pregna-5,7,10(19)-triène; ou le (1S,3R,5E,7E,20S)-9,10-seco-20-formyl-1,3-bis(tert-butyl-dimé-



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thylsilyloxy)pregna-5,7,10(19)-triène.

10. Préparation pharmaceutique contenant une quantité efficace d'un ou plusieurs des composés de formule I selon la revendication 1, en même temps que des véhicules et/ou des agents auxiliaires non toxiques acceptables du point de vue pharmaceutique.

5 11. Préparation pharmaceutique selon la revendication 10 sous forme topique.

12. Préparation pharmaceutique selon la revendication 10 sous forme orale.

13. Utilisation d'un ou plusieurs composés de formule I pour la préparation d'une préparation pharmaceutique pour le traitement des patients souffrant de troubles caractérisés par une prolifération cellulaire et/ou une différenciation cellulaire anormale.

10 14. Utilisation selon la revendication 13 pour préparer la préparation selon la revendication 11 pour le traitement de patients souffrant de psoriasis.

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