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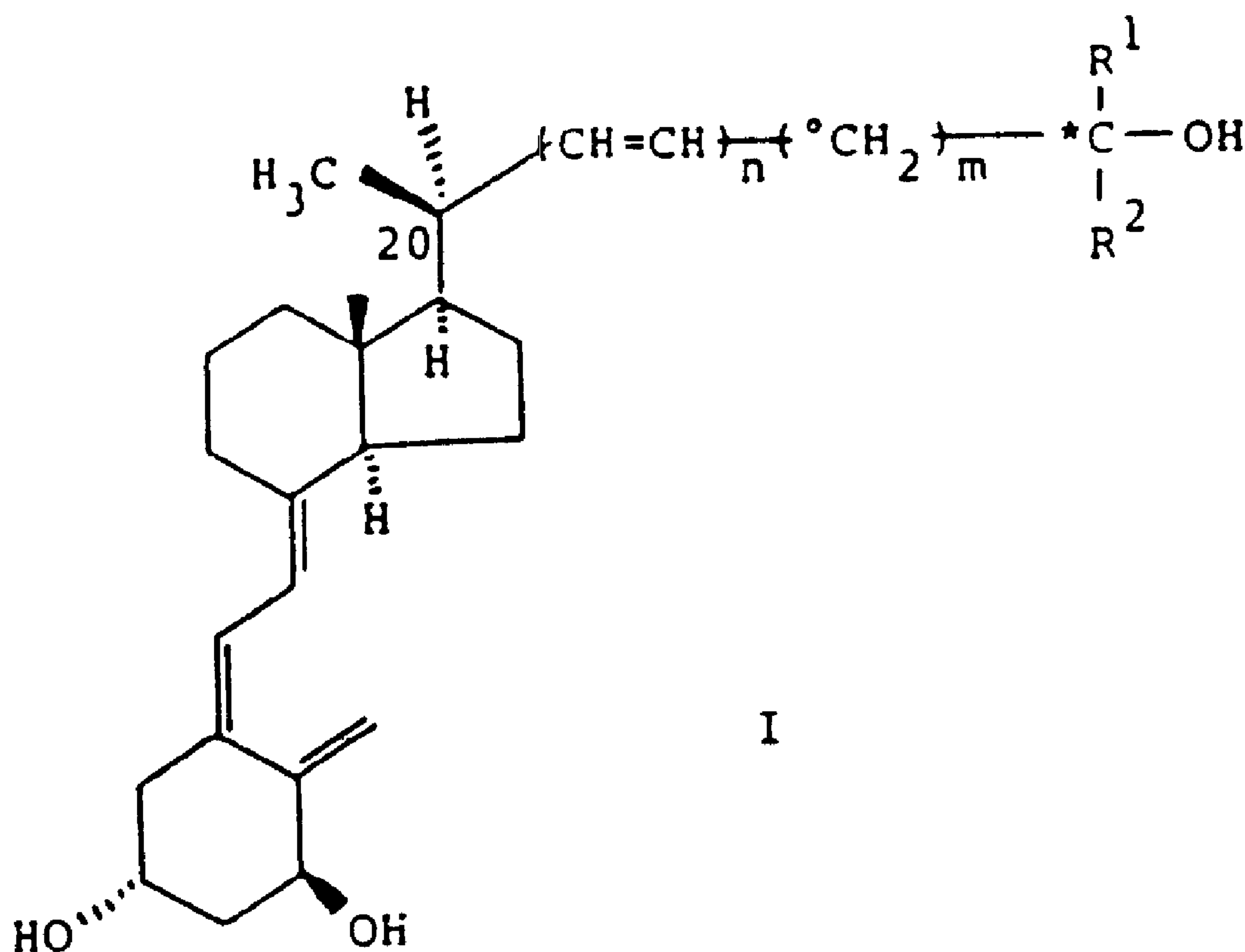
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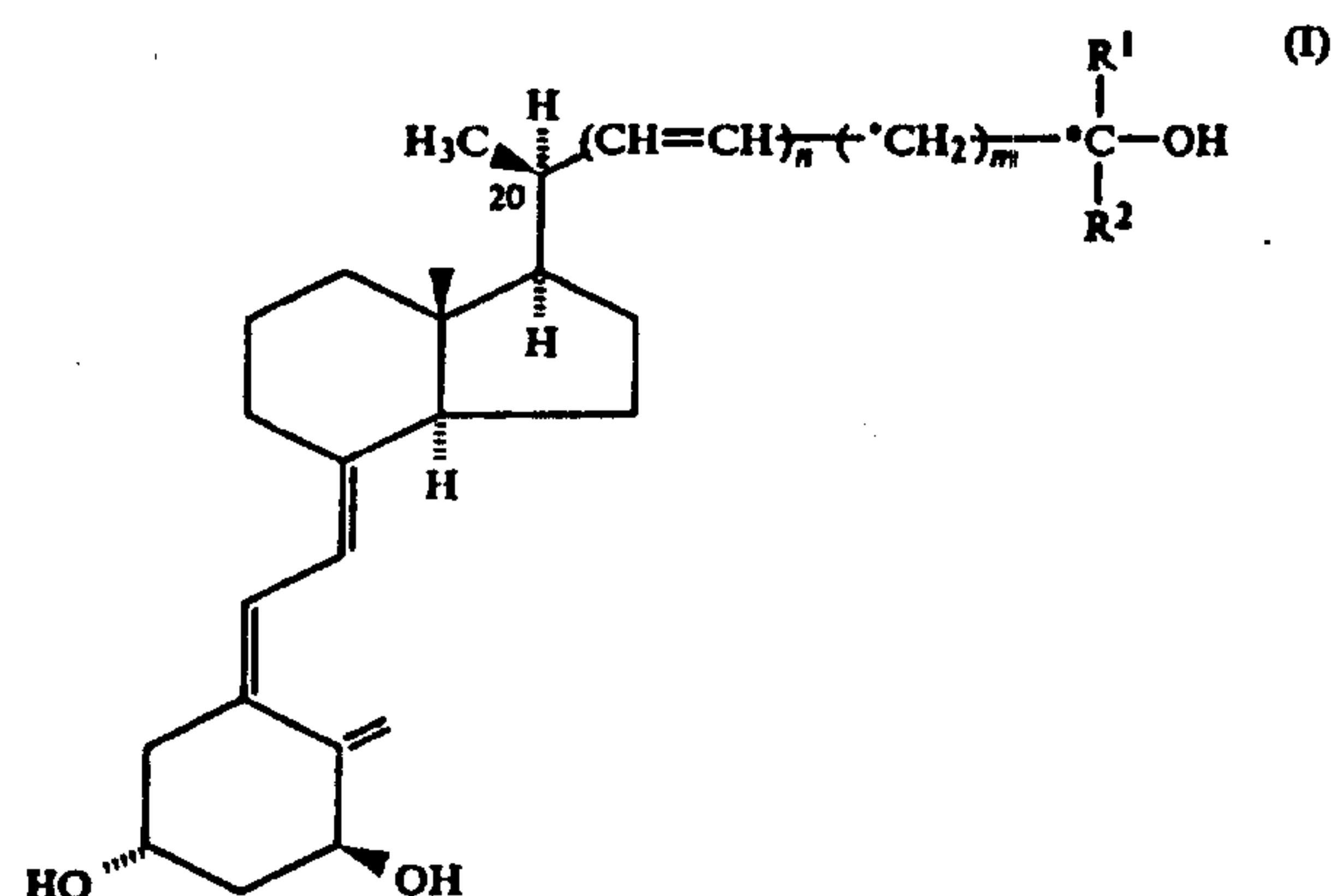
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(57) **Abrégé/Abstract:**

Novel compounds of the following formula are provided in which n, m, R¹ and R² are as defined in the specification. Such compounds find use in both human and veterinary practice in the treatment and prophylaxis of autoimmune diseases (including diabetes mellitus), hypertension, acne, alopecia, skin ageing, imbalance in the immune system, inflammatory diseases, e. g. , rheumatoid arthritis and asthma as well as diseases characterized by abnormal cell differentiation and/or cell proliferation, e.g., psoriasis and cancer.

ABSTRACT

Novel compounds of the following formula are provided.



in which n, m, R¹ and R² are as defined in the specification. Such compounds find use in both human and veterinary practice in the treatment and prophylaxis of autoimmune diseases (including diabetes mellitus), hypertension, acne, alopecia, skin ageing, imbalance in the immune system, inflammatory diseases, e.g., rheumatoid arthritis and asthma as well as diseases characterized by abnormal cell differentiation and/or cell proliferation, e.g., psoriasis and cancer.

5 This invention relates to a hitherto unknown class of compounds which shows antiinflammatory and immunomodulating effects as well as 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 and prophylaxis of a number of disease states including diabetes mellitus, hypertension, acne, alopecia, skin ageing, imbalance in the immune system, inflammatory diseases, e.g., rheumatoid arthritis and asthma, as well as diseases characterized by abnormal cell differentiation and/or cell proliferation, e.g., psoriasis and cancer.

It has recently been shown that $1\alpha,25$ -dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$) influences the effects and/or production of interleukins (Immunol. Lett. 17, 361-366 (1988)), indicating the potential use of this compound in the treatment of diseases characterized by a dysfunction of the immune system, e.g. autoimmune diseases, host versus graft reactions, and rejection of transplants or other conditions characterized by an abnormal interleukin-1 production, e.g. inflammatory diseases such as rheumatoid arthritis and asthma.

It has also been shown that $1,25(OH)_2D_3$ is able to stimulate the differentiation of cells and inhibit excessive cell proliferation (Abe, E. et al, Proc. Natl. Acad. Sci., U.S.A. 78, 4990-4994 (1981)), and it has been suggested that this compound might be useful in the treatment of diseases characterized by abnormal cell proliferation and/or cell differentiation such as leukemia, myelofibrosis and psoriasis.

Also, the use of $1,25(OH)_2D_3$, or its pro-drug 1α -OH- D_3 , for the treatment of hypertension (Lind, L. et al, Acta Med. Scand. 222, 423-427 (1987)) and diabetes mellitus (Inomata, S. et al, Bone Mineral 1, 187-192 (1986)) has been suggested. Another indication for $1,25(OH)_2D_3$ is suggested by the recent observation of an association between hereditary vitamin D resistance and

alopecia: treatment with $1,25(\text{OH})_2\text{D}_3$ may promote hair growth (Lancet, March 4, 1989, p. 478). Also, the fact that topical application of $1,25(\text{OH})_2\text{D}_3$ reduces the size of sebaceous glands in the ears of male Syrian hamsters suggests that this compound might be useful for the treatment of acne (Malloy, V.L. et al., the Tricontinental Meeting for Investigative Dermatology, Washington, 1989). Finally, as thickening of the skin is observed in rats treated topically with $1,25(\text{OH})_2\text{D}_3$, this compound may be useful for treatment or prevention of skin ageing.

However, the therapeutic possibilities in such indications of $1,25(\text{OH})_2\text{D}_3$ are severely limited by the well known potent effect of this hormone on calcium metabolism; elevated blood concentrations will rapidly give rise to hypercalcemia. Thus, this compound and its potent synthetic analogues are not completely satisfactory for use as drugs in the treatment of e.g. psoriasis, leukemia or immune diseases which may require continuous administration of the drug in relatively high doses.

A number of vitamin D analogues have recently been described which show some degree of selectivity in favour of the cell differentiation inducing/cell proliferation inhibiting activity as compared with the effect on calcium metabolism.

Thus, the vitamin D_3 analogue, MC 903, containing a 22,23-double bond, a 24-hydroxy group and in which the carbon atoms 25,26 and 27 are incorporated in a three membered ring, is a potent inducer of cell differentiation and inhibitor of cell proliferation which shows only moderate activity on calcium metabolism in vivo (Binderup, L. and Bramm, E., Biochemical Pharmacology 37, 889-895 (1988)). However, this selectivity is not paralleled by in vitro studies, which show that MC 903 binds equally well as

1,25(OH)₂D₃ to the intestinal vitamin D receptor. It may therefore be that the low in vivo activity on calcium metabolism of MC 903 is due to a rapid metabolism of the compound, thus limiting the potential of this compound for systemic use.

24-Homo-1,25-dihydroxyvitamin D₃ and 26-homo-1,25-dihydroxyvitamin D₃ (together with their 22,23-didehydro-analogues) (Ostrem, V.K.; Tanaka, Y.; Prah1, J.; DeLuca, H.F.; and Ikekawa, N.; Proc. Natl. Acad. Sci. USA 84, 2610-14 (1987)) have been claimed to have the same binding affinity as 1,25(OH)₂D₃ to both the rat and chicken intestinal receptor and the receptor in a human myeloid leukemia cell line (HL-60), and yet to be 10-fold more potent than 1,25(OH)₂D₃ in inducing differentiation of HL-60 cells in vitro. In vivo, these compounds are respectively "significantly less potent" and "more potent" than 1,25(OH)₂D₃ in calcium metabolism assessments.

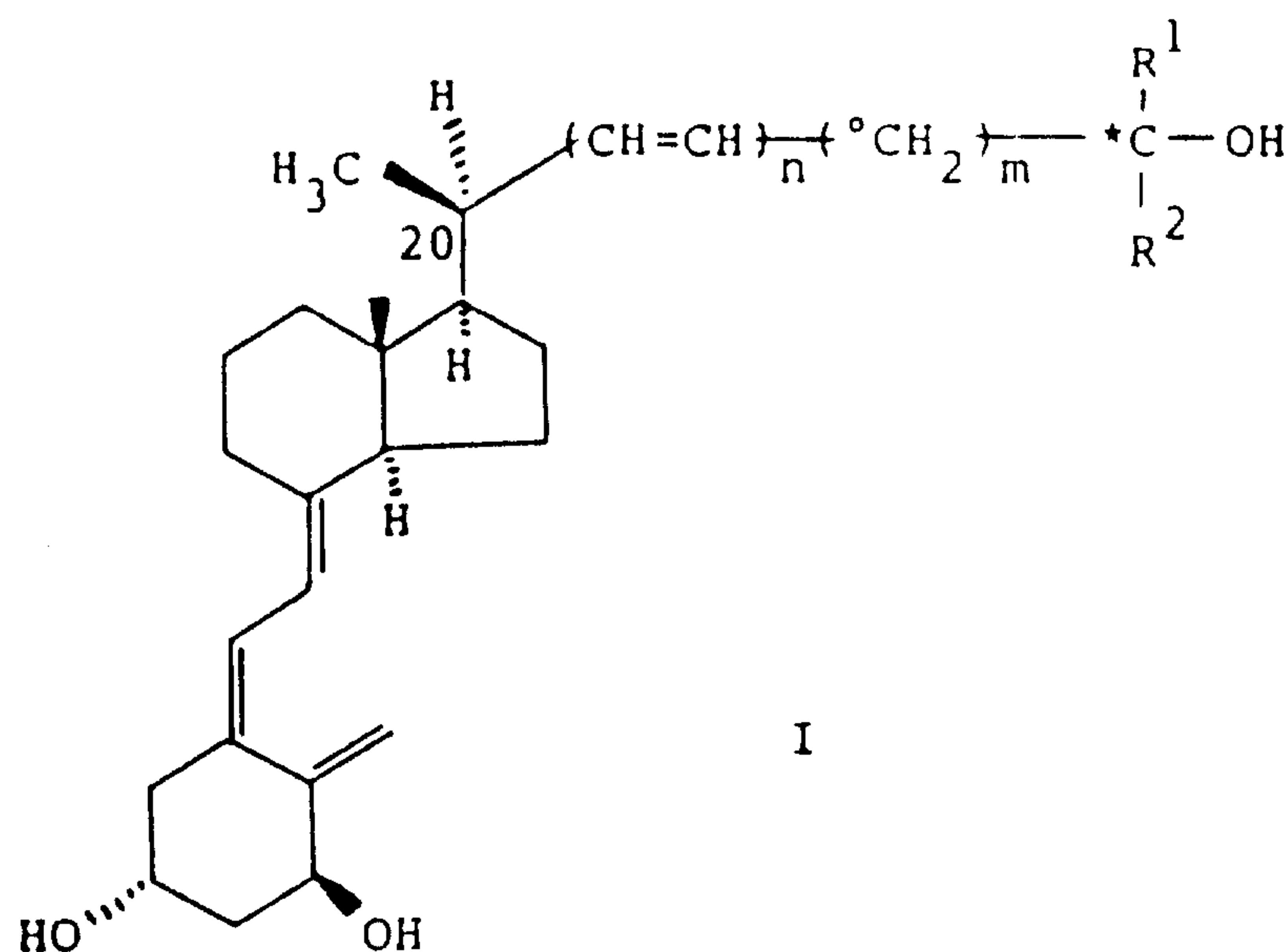
26,27-Dimethyl-1 α ,25-dihydroxyvitamin D₃ has been synthesized, but the published information regarding its biological activities is contradictory. (Sai, H.; Takatsuto, S.; Hara, N.; and Ikekawa, N.; Chem. Pharm. Bull. 33, 878-881 (1985) and Ikekawa, N.; Eguchi, T.; Hara, N.; Takatsuto, S.; Honda, A.; Mori, Y.; and Otomo, S.; Chem. Pharm. Bull. 35, 4362-4365 (1987)). The closely related 26,27-diethyl-1 α ,25-dihydroxyvitamin D₃ is also reported by these authors; in this case as having "almost no vitamin D activity" (i.e. calcium metabolism effects) while being 10-fold more potent than 1,25(OH)₂D₃ in inducing cell differentiation.

The fact that there are only small structural differences between the above compounds indicates that the present state of knowledge does not allow prediction of the structure of vitamin D analogues which will show a favourable degree of selectivity, as reflected by a higher cell

differentiating activity in vitro compared to the binding affinity for intestinal vitamin D receptor in vitro.

Furthermore, the matter is complicated by the observation that receptor binding affinities in vitro are not always paralleled by in vivo studies, probably reflecting a pharmacokinetic difference between the compounds.

The compounds of aspects of the present invention constitute a novel class of vitamin D analogues and are represented by the general Formula



in which Formula (and also throughout the remainder of this disclosure) n is 0 or 1, m is 0 or an integer from 1 to 7, R¹ and R², (which may be the same or different), stand for hydrogen or an unsubstituted C₁-C₈-hydrocarbyl, hydrocarbyl indicating the residue after removal of a hydrogen atom from a straight saturated hydrocarbon, a straight unsaturated hydrocarbon, a branched saturated hydrocarbon, a branched unsaturated hydrocarbon, a cyclic saturated hydrocarbon, or a cyclic unsaturated hydrocarbon, or, taken with the carbon bearing the hydroxyl group, (starred in Formula I), R¹ and R², can form a saturated C₃-C₈ carbocyclic ring, or an unsaturated C₃-C₈ carbocyclic ring; or in which

at least one of R^1 , R^2 and one of the m carbons designated by the " $\circ$ ", is substituted with a hydroxyl group, or at least one chlorine or fluorine atom; and where one of the carbon atoms designated by the " $\circ$ ", is substituted by one C_1 - C_2 alkyl group or by two C_1 - C_2 alkyl groups; and prodrugs or derivatives of the compounds of Formula I in which at least one hydroxy has been transformed into a masking group which is selected from the group consisting of -O-acyl, -O-glycosyl and a phosphate ester group; wherein the masking groups are hydrolysable in vivo.

By variants of such compound, pure diastereoisomers or a mixture of diastereoisomers, of such compound are provided.

Particularly advantageous species of such compound include: 1(S),3(R)-dihydroxy-20(S)-(4-hydroxy-4-methyl-1-pentyl)-9,10-secopregna-5(Z),7(E),10(19)-triene; or 1(S),3(R)-dihydroxy-20(S)-(5-ethyl-5-hydroxy-1-heptyl)-9,10-secopregna-5(Z),7(E),10(19)-triene; or 1(S),3(R)-dihydroxy-20(S)-(5-ethyl-5-hydroxy-hept-1(E)-en-1-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene.

In the context of various aspects of this invention, the expression "hydrocarbyl radical" indicates the residue after removal of a hydrogen atom from a straight, branched or cyclic saturated or unsaturated hydrocarbon.

Examples of R^1 and R^2 when taken separately include (apart from hydrogen), but are not limited to, methyl, trifluoromethyl, ethyl, vinyl, normal-, iso- and cyclo-propyl, and 1-methylvinyl.

Examples of R^1 and R^2 when taken together include di-, tri-, tetra- and penta-methylene.

As can be seen from Formula I, depending on the meanings of R^1 and R^2 , and n , the compounds of aspects of this invention include diastereoisomeric forms (e.g. E or Z configuration of a side chain double bond; R or S configuration at the starred carbon atom). The invention in its various aspects covers all these diastereoisomers in pure form and also mixtures of diastereoisomers. It should be noted, however, that the investigations conducted herein indicate a notable difference in activity between the stereoisomeric forms. In addition, derivatives of Formula 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 aspects of this invention ("bioreversible derivatives or pro-drugs of Formula I").

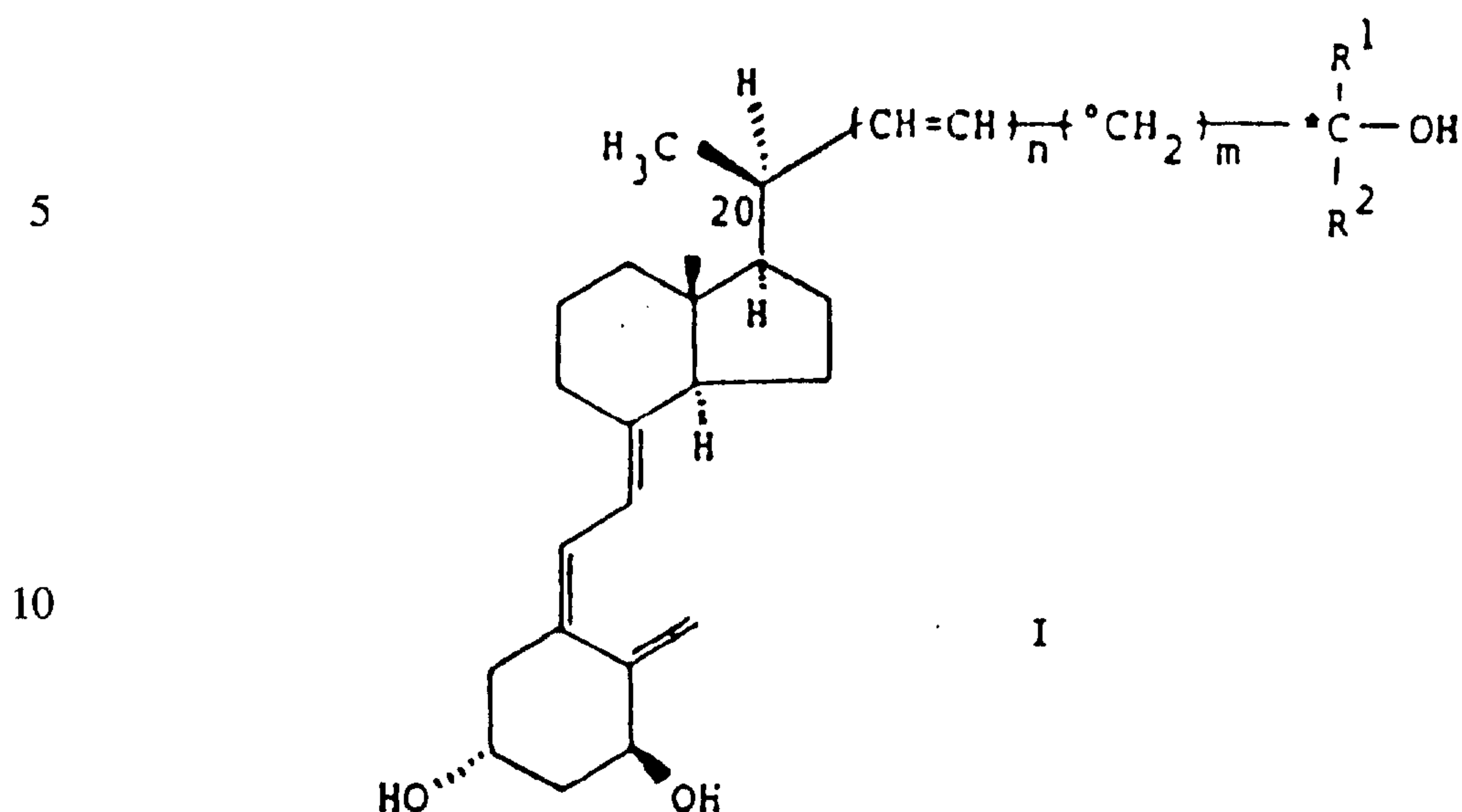
5 The term "bioreversible derivatives or prodrugs of Formula I" includes, but is not limited to, derivatives of the compounds of Formula I in which one or more hydroxy groups have been transformed into -O-acyl or -O-glycosyl or phosphate ester groups, such masked groups being hydrolyzable in vivo.

10 Also within the scope of these aspects of this invention is another type of prodrug of Formula I in which the hydroxyl group at the starred carbon atom is replaced by a hydrogen atom. These compounds are relatively inactive in vitro, but are converted to active compounds of Formula I by enzymatic hydroxylation after administration to the patient.

15 The compounds of aspects of the present invention differ structurally from all vitamin D analogues which have been reported to have potent effects on cell differentiation/proliferation in the configuration of the methyl group at carbon-20. This "unnatural" configuration present in compounds of Formula I has surprisingly been found to have a profound and advantageous biological significance. Thus, a particular compound of Formula I, when compared to the corresponding compound containing the "natural" C-20 configuration (methyl and hydrogen radicals exchanged), is observed to show one or more of the following advantages:

- 20 (a) more potent effects on cell differentiation/proliferation;
- (b) a greater selectivity in favour of the potent effects on cell differentiation/proliferation contra the effects on calcium metabolism;
- (c) more portent effects on the production and action of interleukins;
- 25 (d) a greater selectivity in favour of the effects on interleukin production and action contra the effects on calcium metabolism.

The present invention, in another broad aspect, provides a process for the preparation of a compound of Formula I



in which Formula: n is 0 or 1, m is 0 or an integer from 1 to 7, R¹ and R², (which may be the same or different), stand for hydrogen or an unsubstituted C₁-C₈-hydrocarbyl, hydrocarbyl indicating the residue after removal of a hydrogen atom from a straight saturated hydrocarbon, a straight unsaturated hydrocarbon, a branched saturated hydrocarbon, a branched unsaturated hydrocarbon, a cyclic saturated hydrocarbon, or a cyclic unsaturated hydrocarbon, or, taken with the carbon bearing the hydroxyl group, (starred in Formula I), R¹ and R², can form a saturated C₃-C₈ carbocyclic ring, or an unsaturated C₃-C₈ carbocyclic ring; or in which at least one of R¹, R² and one of the m carbons designated by the "°", is substituted with a hydroxyl group, or at least one chlorine or fluorine atom; and where one of the carbon atoms designated by the "°", is substituted by one C₁-C₂ alkyl group or by two C₁-C₂ alkyl groups; and prodrugs or derivatives of the compounds of Formula I in which at least one hydroxy has been transformed into a masking group which is selected from the group consisting of -O-acyl, -O-glycosyl and a phosphate ester group; wherein the masking groups are hydrolysable in vivo, which process comprises: elaborating the side chain which is attached to C-20,

6b

or of an alcohol which is a protected form thereof, in the compound of Formula I, from 1(S),3(R)-bis-(tert-butyldimethylsilyloxy)-20(R)-formyl-9,10-secopregna-5(E),7(E),10(19)-triene, or its 5(Z) isomer, by one of the following processes: (i) reducing the 1(S),3(R)-bis-(tert-butyldimethyl-silyloxy)-20(R)-formyl-9,10-secopregna-5(E),7(E),10(19)-triene to its corresponding 20(R)-hydroxymethyl derivative, converting the hydroxy group therein to a leaving group, and displacing the leaving group with an organometallic reagent; or (ii) reacting the 1(S),3(R)-bis-(tert-butyldimethyl-silyloxy)-20(R)-formyl-9,10-secopregna-5(E),7(E),10(19)-triene with a Wittig-type reagent, and reacting the ketone so-formed with an organometallic reagent, or with a reducing agent; or (iii) reacting the 1(S),3(R)-bis-(tert-butyldimethyl-silyloxy)-20(R)-formyl-9,10-secopregna-5(E),7(E),10(19)-triene with the carbanion which is derived from the sulphone $\text{PhS(O}_2\text{)CH}_2\text{-(}^\circ\text{CH}_2\text{)}_m\text{-C(OH)R}^1\text{R}^2$ by treatment with a base, and reductively eliminating the product β -hydroxy-sulphone so-formed.

By one variant of process (i) above, the reducing reaction is carried out with sodium borohydride. By a variation of such variant, the conversion of the hydroxy group is carried out by reaction with p-toluenesulphonylchloride and pyridine. By yet another variation of such variant or variation, the displacement of the leaving group is carried out with $\text{BrMg-(}^\circ\text{CH}_2\text{)}_{m-1}\text{-C(OSiMe}_3\text{)R}^1\text{R}^2$ in the presence of Li_2CuCl_4 .

By one variant of process (ii) above, the Wittig-type reagent comprises $\text{Ph}_3\text{P}^+\text{-CH}^-\text{-C(O)-R}^2$. By a variation thereof, the organometallic reagent comprises R^1MgBr . By another variation thereof, the reducing agent comprises NaBH_4 .

By one variant of process (iii) above, the base comprises lithium di-isopropylamide. By a variation thereof, two equivalents of the base are used. By another variation of such variant or variation, the reductive elimination is carried out with sodium amalgam. By one variation thereof, the process further comprises the step of deriving the β -hydroxy group. By a variation thereof, the step of deriving the β -hydroxy group is carried out with benzoyl chloride and a base.

6c

By another variant of the processes, variants or variations described above, the process further comprises the step of separating a diastereoisomer in pure form from a mixture of diastereoisomers so formed. By one variation thereof, the separation step is carried out by chromatography.

By another variant of the processes, variants or variations thereof, the compound so-formed is subjected to a triplet-sensitized photoisomerization to the 5(Z) isomer.

By another variant of the processes, variants or variations thereof, the compound so-formed further undergoes disilylation.

By a variation thereof, the disilylation is carried out with tetrabutyl ammonium fluoride.

By another variant of the processes, variants or variations thereof, the compound so-formed further undergoes deprotection.

By another variant of the processes, variants or variations thereof, the process further comprises the step of recovering the compound so-formed as a diastereoisomer in pure form.

By another variant of the processes, variants or variations thereof, the process further comprises the step of recovering the compound so-formed as a mixture of diastereoisomers.

By another variant of the processes, variants or variations thereof, the compound so-formed is 1(S),3(R)-dihydroxy-20(S)-4-hydroxy-4-methyl-1-pentyl)-9,10-secopregna-5(Z),7(E),10(19)-triene; or is 1(S),3(R)-dihydroxy-20(S)-(5-ethyl-5-hydroxy-1-heptyl)-9,10-secopregna-5(Z),7(E),10(19)-triene; or is 1(S),3(R)-dihydroxy-20(S)-5-ethyl-5-hydroxy-hept-1(E)-en-1-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene.

The compounds of aspects of the invention are therefore especially suited for both local and systemic treatment and prophylaxis of human and veterinary disorders which are characterized by: 1) abnormal cell proliferation and/or cell differentiation, e.g., certain dermatological disorders including psoriasis and certain cancer forms; 2) an imbalance in the immune system, e.g., in autoimmune diseases, including diabetes mellitus, host versus graft

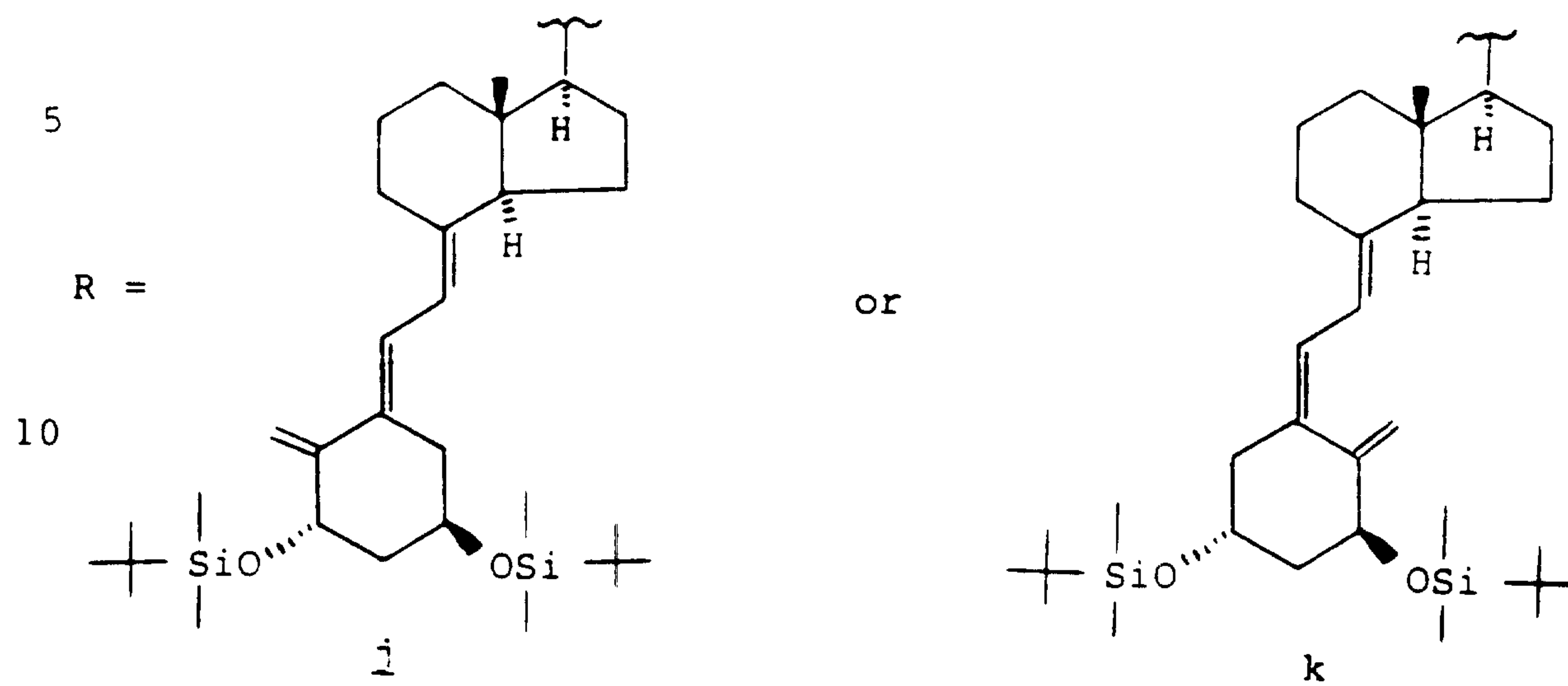
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reaction, and rejection of transplants; and 3) additionally for the treatment of inflammatory diseases, e.g., rheumatoid arthritis and asthma. Acne, alopecia, skin ageing, including photo-ageing, and hypertension are other conditions which may be treated with the compounds of aspects of the invention.

The compounds of aspects of the invention may be used in combination with other pharmaceuticals. In the prevention of graft rejection and graft versus host reaction, a treatment with the compounds of aspects of the present invention may advantageously be combined with, e.g., a cyclosporin treatment.

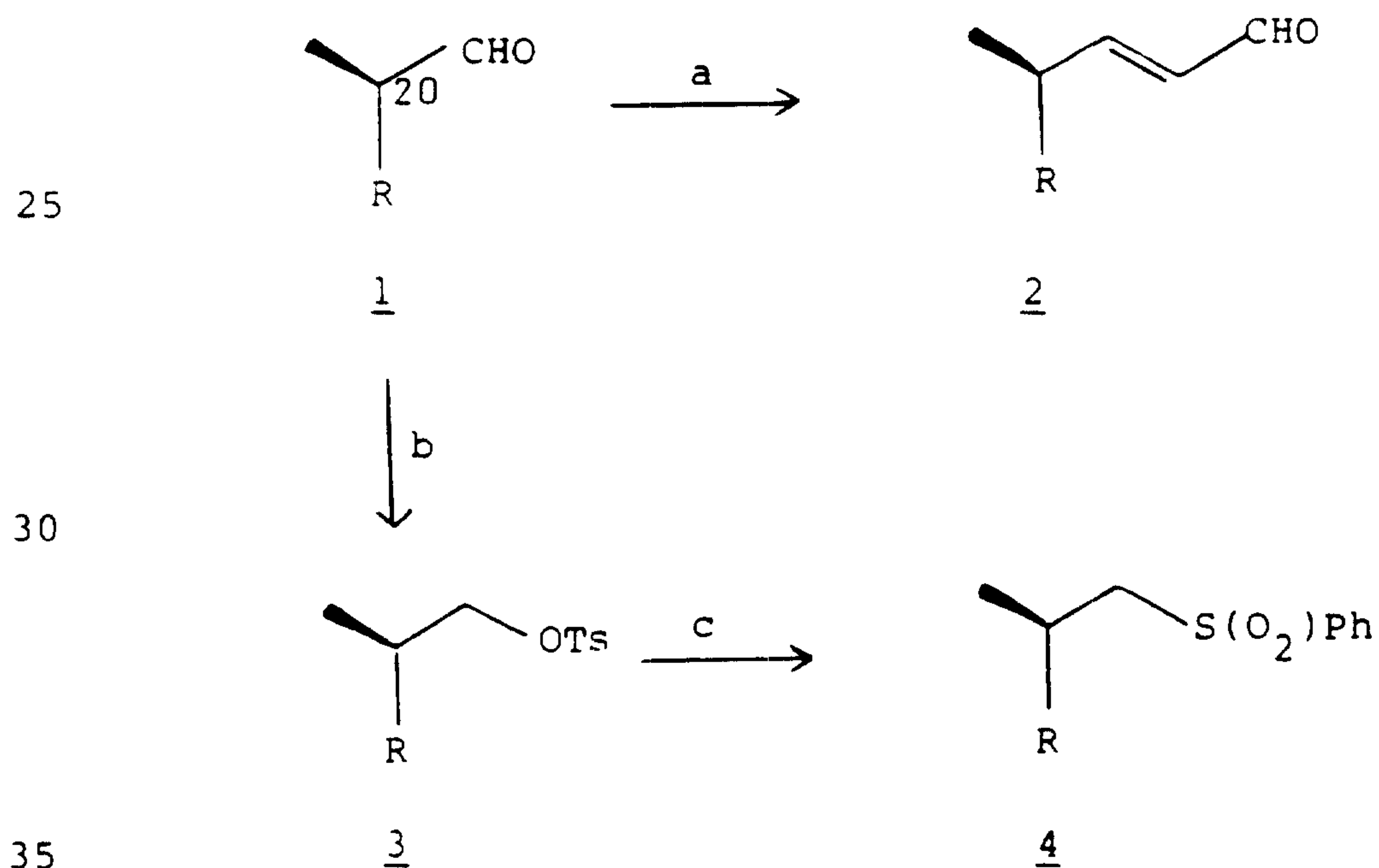
Compounds of Formula I can be prepared from the vitamin D-derived aldehyde 1j; a synthesis of which has been reported (M.J. Calverley, Tetrahedron 43, 4609 (1987)), optionally via the compounds 2j, 3j or 4j, (Scheme 1), or from the compounds 1k, 2k, 3k or 4k, which may be obtained by triplet-sensitized photoisomerization of the corresponding compound j. Schemes 2 to 6 illustrate reactions for the conversion of these key intermediates to compounds I in which n, m, R¹ and R² have various meanings.

In Schemes 1-6, the following abbreviation is used:



In the Notes to Schemes 1-7, appropriate aqueous work-up steps are implicit. For explanation of the expression "side chain fragment," see following text.

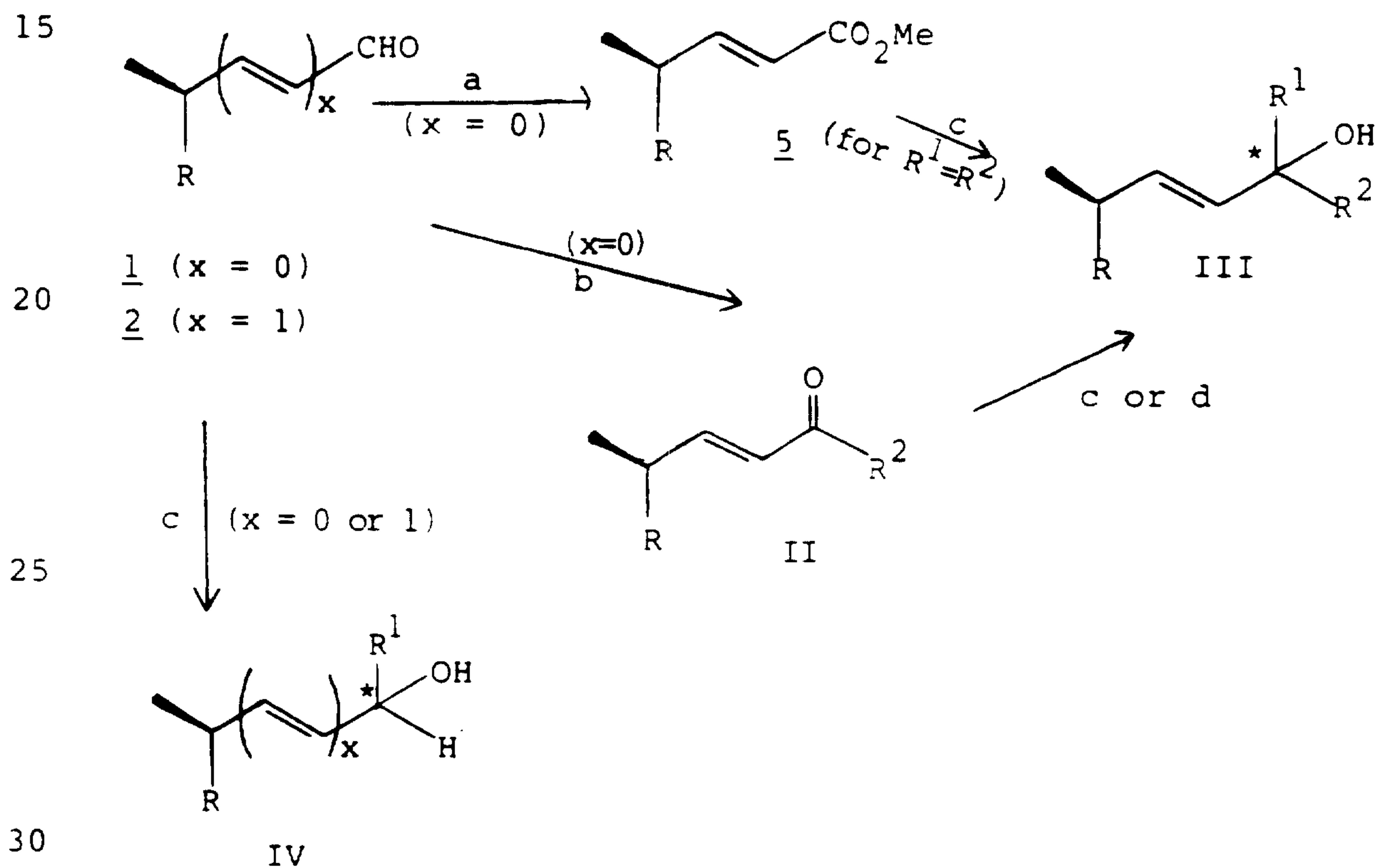
20 Scheme 1



Notes to Scheme 1

$R=j \rightarrow R=k$ at any stage: $h\nu$ -anthracene (toluene or CH_2Cl_2 containing Et_3N).

- 5 a. $\underline{1} \rightarrow \underline{2}$: (i) $\text{Ph}_3\text{P}^+\text{CHCO}_2\text{Me}$ (toluene) (gives compound $\underline{5}$ of Scheme 2); (ii) $i\text{-Bu}_2\text{AlH}$ (THF) (gives compound III, $R^1 = R^2 = \text{H}$, of Scheme 2 (compound $\underline{111}$)); (iii) pyridinium dichromate (CH_2Cl_2);
- b. (i) NaBH_4 (EtOH-THF); (ii) TsCl -pyridine (CH_2Cl_2);
- 10 c. (i) PhS^-K^+ (THF-DMF); (ii) H_2O_2 - NaWO_4 (MeCO_2Et -EtOH- H_2O).

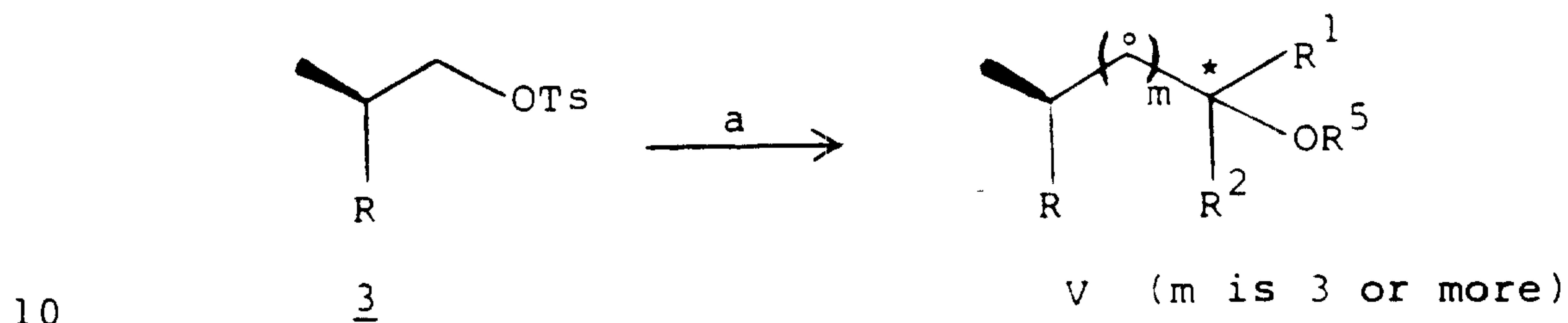
Scheme 2Notes to Scheme 2

- 35 a. $\text{Ph}_3\text{P}^+\text{CHCO}_2\text{Me}$ (toluene);
- b. Metallated derivative, anion or ylide (C') from side chain fragment C (anhydrous solvent or phase transfer conditions);

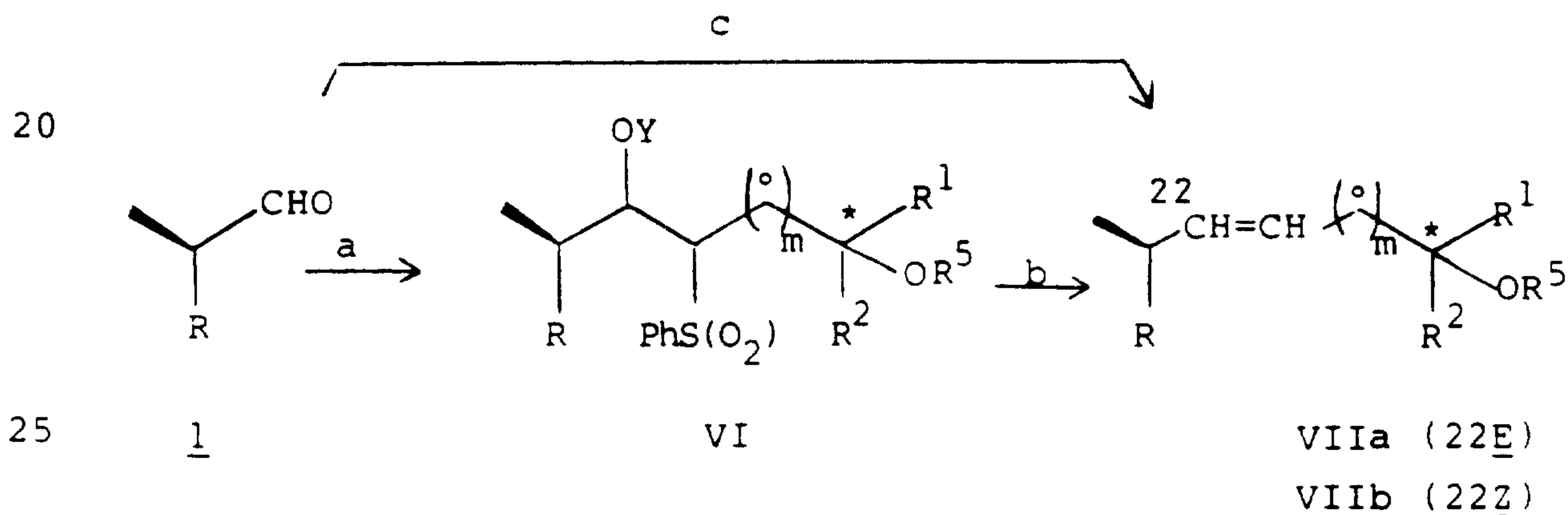
- c. R^1MgBr (R^1MgI) or R^1Li (THF);
 d. $NaBH_4-CeCl_3$ (THF-MeOH) (for $R^1=H$).

Scheme 3

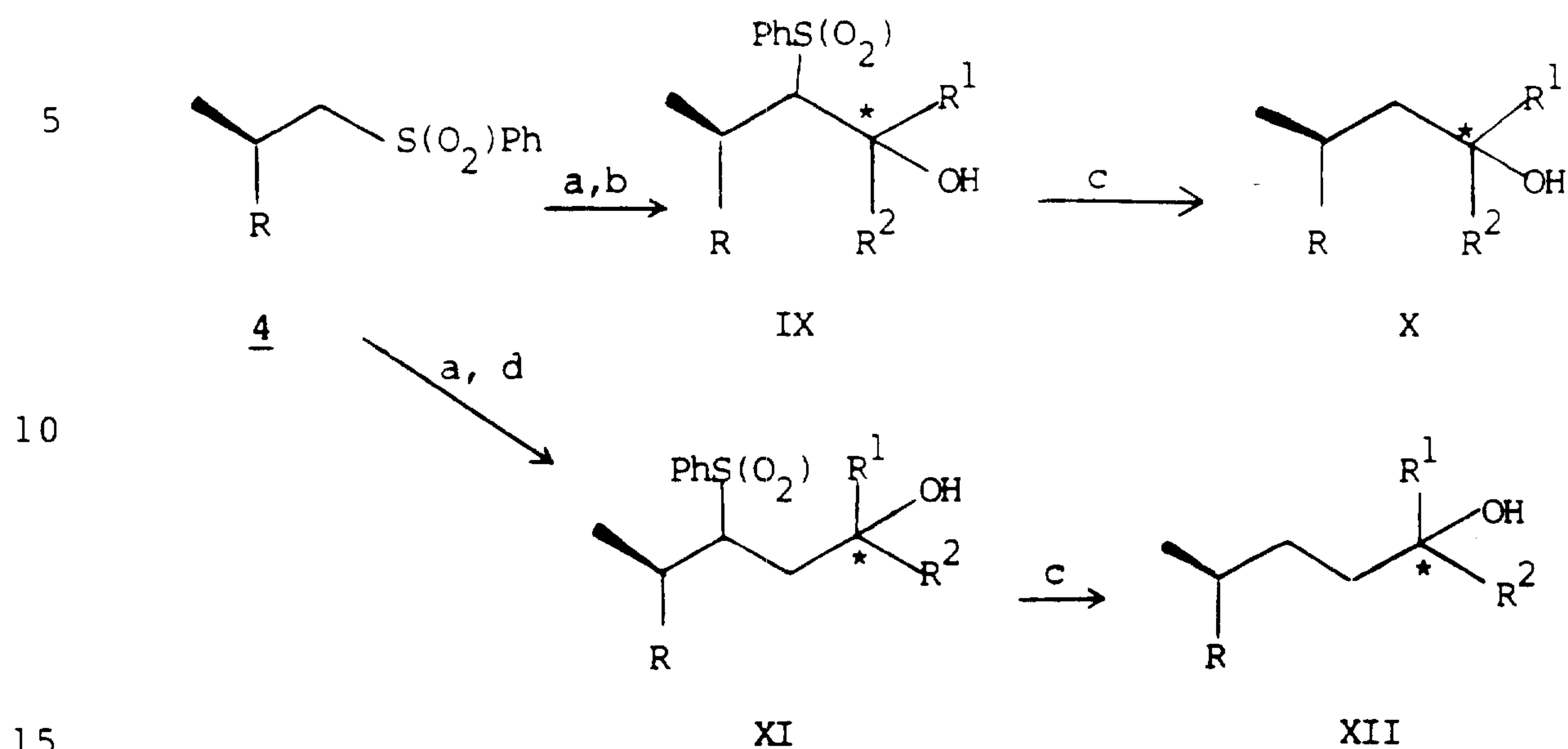
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Note to Scheme 3

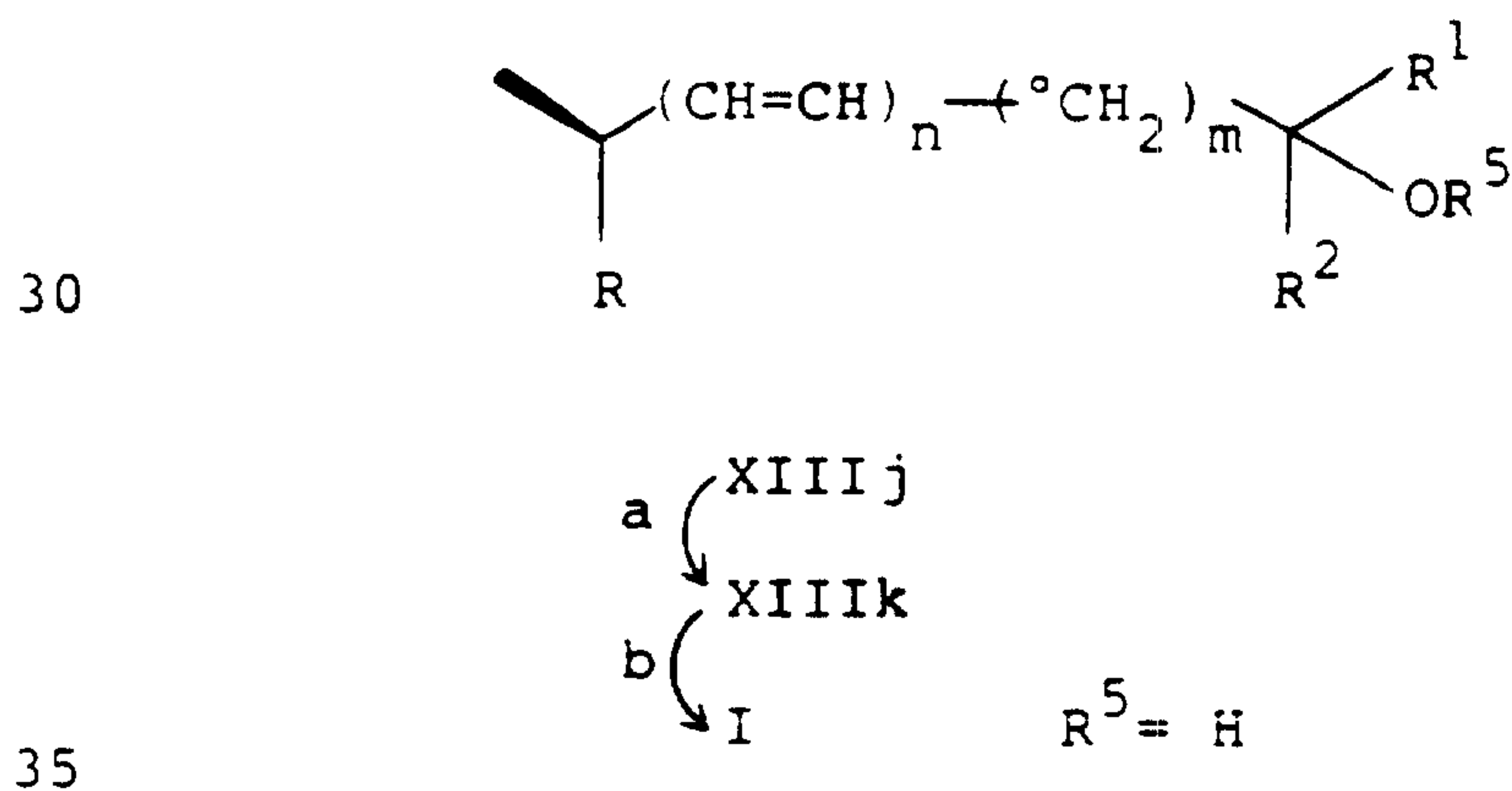
- 15 a. Grignard reagent (A') [derived from side chain fragment A ($y=m-2$)] in the presence of Li_2CuCl_4 (THF).

Scheme 4Notes to Scheme 4

- 30 a. (i) Metallated derivative (B') of side chain fragment B ($y=m$) (THF); (ii) Optional derivatisation of the intermediate alkoxide ($Y=M$) or the isolated $Y=H$ compound, e.g. with benzoyl chloride;
 b. Reductive elimination mediated by e.g. Na-Hg [for $Y=H$, $MeC(O)-$, $PhC(O)-$ or $MeS(O_2)-$];
 35 c. Metallated derivative, anion or ylide (W') from side chain fragment W.

Scheme 5Notes to Scheme 5

- 20
- a. $\text{LiN}(\text{Pr}^1)_2$ (THF);
- b. $\text{R}^1\text{C}(\text{O})\text{R}^2$ (THF);
- c. Na-Hg (MeOH-EtOAc - Na_2HPO_4);
- d. $\text{CH}_2\text{C}(\text{R}^1)(\text{R}^2)$ (THF).

25 Scheme 6

Notes to Scheme 6

R^5 = H or alcohol protective group

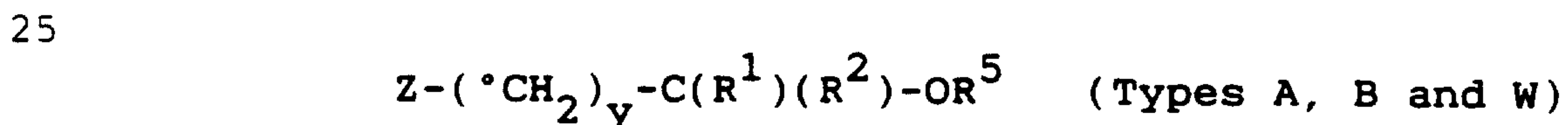
- a. anthracene - h ν (toluene or CH_2Cl_2 containing Et_3N);
 5 b. (i) $n-Bu_4N^+F^-$ (THF) or HF ($MeCN-H_2O$);
 (ii) any necessary reaction (sequence) for deprotecting
 OR^5 - OH.

Compounds XIII correspond to the compounds of the type
 10 III, IV, V, VII, X or XII described in Schemes 2 - 5, and
 appear as these in Table 3 and the Preparations.

A key step in the syntheses as described is the
 15 reaction with an intermediate (of type A', B', W' or C')
 which is obtained by treatment of a side chain fragment of
 type A, B, W or C respectively) either by conversion to an
 organometallic agent or to an ylide, as appropriate.

All these types of reactions are well known in the
 20 art of carbon-carbon bond formation in synthetic organic
 chemistry, and have in fact been applied in syntheses of
 other vitamin D-type compounds.

In general, the side chain fragments have the
 structure:



30 with the following meanings (the following standard abbreviations are used throughout this disclosure: Bu = butyl; Et = ethyl; Hep = heptyl; Me = methyl; Ph = phenyl; Pr = propyl; THP = tetrahydro-4H-pyran-2-yl; THF = tetrahydro-furan; Ts = p-toluenesulphonyl; DMF = N,N-dimethylform-
 35 amide):

For type A, $Z = X-^{\circ}CH_2-$, where X is Cl, Br or I, and corresponding A' has $Z = XMg-^{\circ}CH_2-$.

For type B, $Z = PhS(O_2)-CH_2-$, and the corresponding

B' has $Z = \text{PhS}(\text{O}_2)\text{-CHM-}$, where M = metal, e.g. Li.

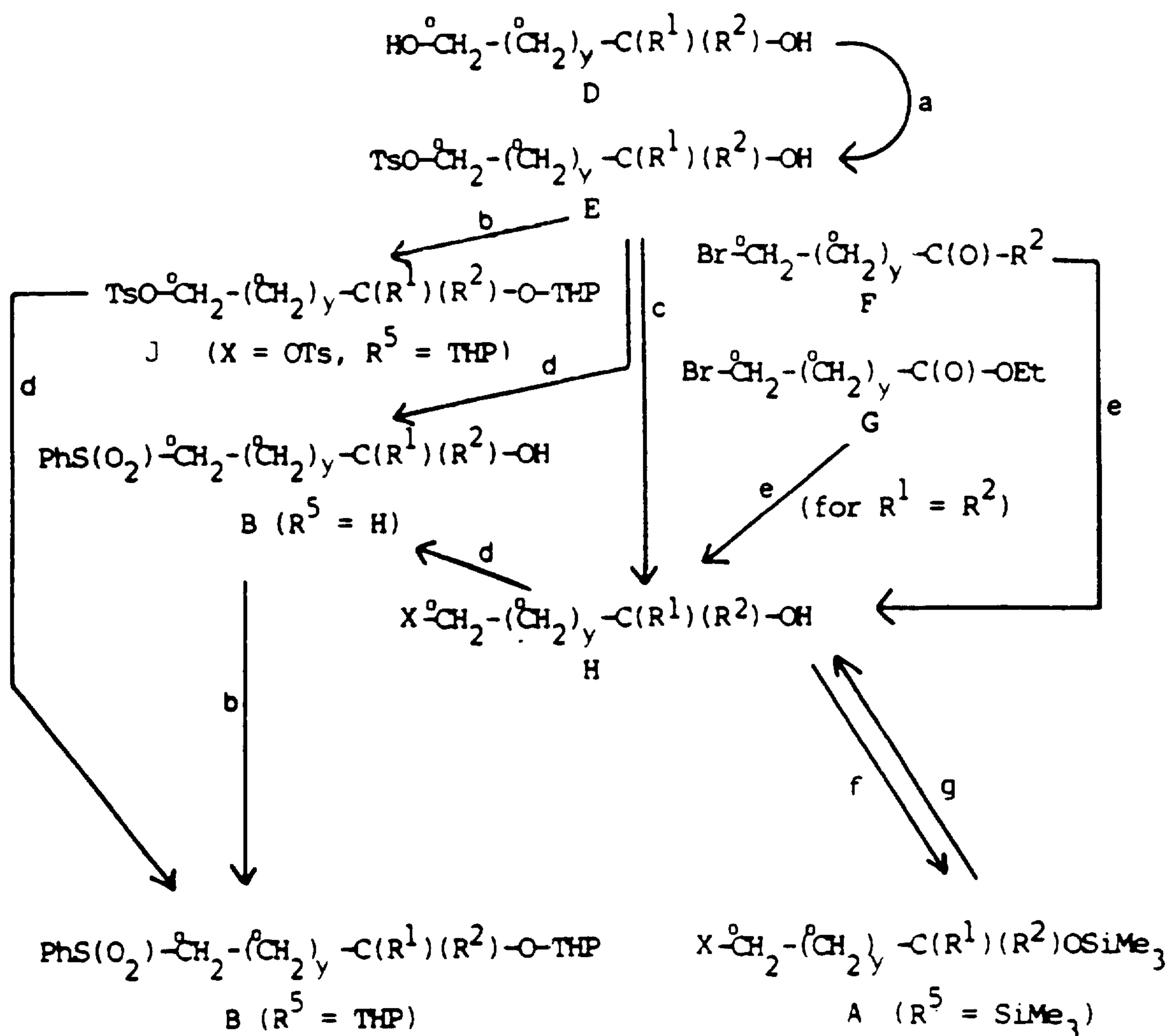
For types C and W, $Z = \text{Ph}_3\text{P}^+\text{-CH}_2\text{-}$ or $Z = \text{Q}_2\text{P}(\text{O})\text{-CH}_2\text{-}$, where Q = methoxy, ethoxy or phenyl, and the corresponding C' (W') has $Z = \text{Ph}_3\text{P}^+\text{-CH}^-\text{-}$ or $\text{Q}_2\text{P}(\text{O})\text{-CHM-}$ (M = metal e.g.

5 Li or metal equivalent, e.g. Bu_4N).

R^5 is optionally hydrogen or an alcohol protective group such as tri(loweralkyl)silyl or THP. In the case where $\text{R}^5 = \text{H}$ in A, B, or W, then $\text{R}^5 = \text{M}$ (M = metal, e.g. XMg or Li) in the derived A', B' or W'.

10 The syntheses of the particular fragments of types A and B can be varied greatly, but solely for the purpose of exemplification, the syntheses of the specific compounds shown in Table 1 using the routes summarized in Scheme 7 are described in the Preparations. It should be noted that
15 the fragments of type B, with γ , R^1 and R^2 corresponding to exemplified type A compounds, but which are not exemplified themselves, are readily obtained from the corresponding described intermediates by analogous reactions. Fragments of type C or C' are known compounds or readily available as
20 described for example in international patent application No. PCT/DK86/00081, international filing date 14th July, 1986, Publication No. WO 87/00834. Some Examples are listed in Table 2.

Some of these side chain fragments are converted (see
25 Preparations and Examples) to the appropriate compounds I via the intermediates indicated in the Schemes. Parallel reactions can be used to convert other side chain fragments to the corresponding compounds I.

Scheme 7Notes to Scheme 7

30

a. TsCl - base; b. dihydropyran - acid; c. LiBr (for X = Br) or NaI (for X = I); d. (i) PhSH - base, (ii) H_2O_2 - NaWO_4 ; e. Grignard reagent R^1MgBr or R^1MgI ; f. Me_3SiCl - base; g. MeOH - acid;

35

Table 1: Some Specific Side Chain Fragments (Types A and B
 $[Z-(\text{CH}_2)_y-C(R^1)(R^2)OR^5]$

Compound Number	Type *	y	Formula				Z
			R ¹	R ²	R ⁵		
6 ++	A	1	Me	H	SiMe ₃		ICH ₂
7 **	A	1	H	Me	SiMe ₃		ICH ₂
8 **	A	1	H	Hep	SiMe ₃		ICH ₂
9	A	1	Me	Me	SiMe ₃		BrCH ₂
10 10	A	1	-(CH ₂) ₂ -		SiMe ₃		BrCH ₂
11	A	1	-(CH ₂) ₄ -		SiMe ₃		BrCH ₂
13	A	2	-(CH ₂) ₂ -		SiMe ₃		BrCH ₂
14	A	2	Et	Et	SiMe ₃		BrCH ₂
15 15	A	2	Pr	Pr	SiMe ₃		BrCH ₂
16	A	3	Me	Me	SiMe ₃		BrCH ₂
18	A	3	Pr	Pr	SiMe ₃		BrCH ₂
17	A	3	Et	Et	SiMe ₃		BrCH ₂
19	A	4	Me	Me	SiMe ₃		BrCH ₂
20 20	A	5	Me	Me	SiMe ₃		BrCH ₂
21	B	1	Me	Me	H		PhS(O ₂)CH ₂
22	B	1	-(CH ₂) ₂ -		THP		PhS(O ₂)CH ₂
23	B	2	Et	Et	H		PhS(O ₂)CH ₂
24	B	3	Me	Me	H		PhS(O ₂)CH ₂
25 25	B	4	Me	Me	H		PhS(O ₂)CH ₂

Table 1 (continued):

Compound Number ⁺	Formula					
	Type*	† y	R ¹	R ²	R ⁵	Z
26 ⁺⁺	A	1 (CH(Me))	Me	Me	SiMe ₃	BrCH ₂
27 ^{**}	A	1 (CH(Me))	Me	Me	SiMe ₃	BrCH ₂
28 ⁺⁺	B	1 (CH(Me))	Me	Me	H	PhS(O ₂)CH ₂
29 ^{**}	B	1 (CH(Me))	Me	Me	H	PhS(O ₂)CH ₂

- 10
- +

As referred to in the Preparations
- *

See text
- ++

S-Form
- **

R-Form
- †

Unsubstituted CH₂ unless otherwise indicated by specifying an alternative meaning of "(°CH₂)".

15

Table 2: Some Specific Side Chain Fragments (Type C and C')
[Z-C(O)R²]

Compound Number	R ²	Z
30	] -CHMe ₂ [	Ph ₃ [⊕] PCH [⊖]
30a		(EtO) ₂ P(O)CH ₂
31a y=1	$\overline{-CH(CH_2)_yCH_2}$	Ph ₃ [⊕] PCH [⊖]
31b y=2		
31c y=3		
31d y=4		
32	$\overline{-CCl-CH_2-CH_2}$	Ph ₃ [⊕] PCH [⊖]
33	$\overline{-CF-CH_2-CH_2}$	(EtO) ₂ P(O)CH ₂
34	-CMe ₃	Ph ₃ [⊕] PCH [⊖]
35	-CHEt ₂	Ph ₃ [⊕] PCH [⊖]
36	-CH(n-Pr) ₂	Ph ₃ [⊕] PCH [⊖]

For the synthesis of compounds of Formula I in which the starred carbon atom is chiral ($R^1 \neq R^2$), the compound D in Scheme 7 is conveniently used as the stereoisomer with largely or exclusively the required configuration, to give largely or exclusively the required diastereoisomer(s) of I.

5 Alternatively, the compound D may be used as the stereoisomer having the opposite configuration, and the configuration may be then inverted at a later stage in the synthesis.

10 In other cases where ($R^1 \neq R^2$) in compounds of Formula I, the isomers in the corresponding intermediates XIII can be separated (e.g., by chromatography), and the configuration at the starred carbon atom can be inverted or equilibrated at this stage by application of standard reactions.

The synthesis of the prodrugs of compounds of Formula I which lack the side chain hydroxyl (at the starred carbon atom) may follow the routes of Schemes 3 and 4, using the appropriate side chain fragment of structure $Z-(^{\circ}\text{CH}_2)_y\text{-CH}(R^1)(R^2)$.

15 By other aspects of this invention, a pharmaceutical composition is provided containing an effective amount of at least one of the compounds as described more fully hereinabove, together with a pharmaceutically-acceptable, non-toxic carrier.

By one variant thereof, the pharmaceutical composition is for topical use and contains from 0.1 to 100 $\mu\text{g/g}$ of the compound as described more fully hereinabove.
20 By a variation thereof, the pharmaceutical composition is in dosage unit form. By another variation thereof, such dosage unit form of the pharmaceutical composition contains from 0.025 to 100 μg for oral and parenteral formulations.

By yet another aspect of this invention, the use is provided of at least one of the compounds as described more fully hereinabove, for the preparation of a pharmaceutical
25 composition for the treatment and/or prophylaxis of autoimmune diseases including diabetes mellitus, hypertension, acne, alopecia, skin aging including photoageing, inflammatory diseases, rheumatoid arthritis and asthma, as well as diseases which are characterized by abnormal cell differentiation and/or cell proliferation and/or imbalance in the immune system.

By yet another aspect of this invention, the use is provided of at least one of the compounds as described more fully hereinabove, for the treatment and/or prophylaxis of autoimmune diseases including diabetes mellitus, hypertension, acne, alopecia, skin aging including photoageing, inflammatory diseases, rheumatoid arthritis and asthma, as well as diseases which are characterized by abnormal cell differentiation and/or cell proliferation and/or imbalance in the immune system.

By yet another aspect of this invention, the use is provided of at least one of the pharmaceutical compositions as fully described above, for the treatment and/or prophylaxis of autoimmune diseases including diabetes mellitus, hypertension, acne, alopecia, skin aging including photoageing, inflammatory diseases, rheumatoid arthritis and asthma, as well as diseases which are characterized by abnormal cell differentiation and/or cell proliferation and/or imbalance in the immune system.

By yet another aspect of this invention, the use is provided of at least one of the compounds as described more fully hereinabove, or of at least one of the pharmaceutical compositions as fully described above, inclusive, for the treatment or prophylaxis of cancer, or for the treatment or prophylaxis of psoriasis.

Thus, as specified above, the compounds of aspects of this invention are intended for use in pharmaceutical compositions which are useful in the treatment of human and veterinary disorders as described above.

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 disease state which is to be treated, the route of administration and the mammal under treatment. The compounds of aspects of this invention can be administered by the parenteral, intra-articular, 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.

Conveniently, the active ingredient comprises from 0.1 - 100 $\mu\text{g/g}$ for topical formulations and 0.05 - 100 $\mu\text{g/g}$ for oral and parenteral formulations.

By the term "dosage unit" is meant a unitary, i.e., a single dose which is capable of being administered to a patient as a physically and chemically stable unit dose

comprising either the active material as such or a mixture of it with solid or liquid pharmaceutically-acceptable diluents or carriers.

5 The formulations, both for veterinary and for human medical use, of aspects 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.

10 The formulations include, e.g., those in a form suitable for oral, rectal, parenteral (including transdermal, subcutaneous, intramuscular and intravenous), intraarticular 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 additional 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.

20 Formulations of aspects 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; or may be in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or may be in the form of an oil-in-water emulsion or a water-in-oil emulsion.

25 A tablet may be made by compressing or moulding the active ingredient optionally with one or more additional ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form, e.g., 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 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, e.g., cocoa butter, or may be in the form of an enema.

5 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.

10 Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the active ingredient which may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the active ingredient for both intra-articular and ophthalmic administration.

15 Formulations suitable for topical administration may include liquid or semi-liquid preparations, e.g., liniments, lotions, applicants, oil-in-water or water-in-oil emulsions, e.g., creams, ointments or pastes; or may include solutions or suspensions, e.g., drops; or may include sprays.

For asthma treatment, inhalation of powder, self-propelling or spray formulations, dispensed with a spray can, a nebulizer or an atomizer can be used. The formulations, when dispensed, preferably have a particle size in the range of 10 to 100 μ .

20 Such formulations are most preferably in the form of a finely comminuted powder for pulmonary administration from a powder inhalation device or self-propelling powder-dispensing formulations. In the case of self-propelling solution and spray formulations, the effect may be achieved either by choice of a valve having the desired spray characteristics (i.e., being capable of producing a spray having the desired particle size) or by incorporating the active ingredient as a suspended powder in controlled particle size. These self-propelling formulations may be either powder-dispensing formulations
25 or formulations dispensing the active ingredient as droplets of a solution or suspension.

Self-propelling powder-dispensing formulations preferably comprise dispersed particles of solid active ingredients, and a liquid propellant having a boiling point below 18° at atmospheric pressure. The liquid propellant may be any propellant known to be suitable for medicinal administration and may comprise one or more C₁-C₆-alkyl hydrocarbons or halogenated C₁-C₆-alkyl hydrocarbons or mixtures thereof; chlorinated and fluorinated C₁-C₆-alkyl hydrocarbons are especially preferred. Generally, the propellant constitutes 45 to 99.9% w/w of the formulation whilst the active ingredient constitutes 1 ppm to 0.1% w/w, of the formulation.

In addition to the aforementioned ingredients, the formulations of aspects of this invention may include one or more additional ingredients, e.g., 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 of aspects of this invention may further contain other therapeutically-active compounds which are usually applied in the treatment of the above mentioned pathological conditions.

The present invention in still further aspects further concerns the use of compounds and/or compositions of aspects of this invention useful for treating patients suffering from one of the above pathological conditions. The use involves administering to a patient in need of treatment, an effective amount of one or more compounds of Formula I, alone or in combination with one or more other therapeutically-active compounds usually applied in the treatment of the pathological conditions. The use of the compounds of aspects of this invention and/or with further therapeutically-active compounds may be simultaneous or may be used spaced by intervals.

In the treatment of systemic disorders, daily doses of from 0.05-100 µg, preferably from 0.1-50 µg, of a compound

of formula I are administered. In the topical treatment of dermatological disorders, ointments, creams or lotions containing from 0.1-100 µg/g, and preferably from 1-10 µg/g, of a compound of formula I are administered. The oral compositions are formulated, preferably as tablets, capsules, or drops, containing from 0.025-100 µg, preferably from 0.05-50 µg, of a compound of formula I, per dosage unit.

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

Preparations and Examples

General

The exemplified compounds I are listed in Table 4. The intermediates of Schemes 1-6 referred to in the Preparations are to be identified by numbers with the corresponding formulae in Table 3. These are used to illustrate typical syntheses of the exemplified compounds I.

The compound of Example 19 (not listed in Table 4) corresponds to compound 122 in which the hydroxyl group at the starred carbon atom of formula I is replaced by a hydrogen atom.

For nuclear magnetic resonance spectra (300 MHz) chemical shift values (δ) are quoted for deuteriochloroform solutions relative to internal tetramethylsilane ($\delta = 0$) or chloroform ($\delta = 7.25$). The value for a multiplet, either defined (doublet (d), triplet (t), quartet (q)) or not (m) at the approximate mid point is given unless a range is quoted (s = singlet, b = broad). Coupling constants (J) are given in Hertz, and are sometimes approximated to the nearest unit.

Ether is diethyl ether, and was dried over sodium. THF was dried over sodium-benzophenone. Petroleum ether refers to the pentane fraction. Reactions were run at room temperature unless otherwise noted. The work-up procedure referred to involves dilution with the specified solvent (otherwise the organic reaction solvent), extraction with water and then brine, drying over anhydrous $MgSO_4$, and concentration in vacuo to give a residue. Chromatography

was performed on silica gel.

Table 3: Compounds of Schemes 2-6 which are Intermediates in the Preparation of Compounds I of Scheme 6

Compound Number (R=j or k)	Type	Scheme	x	m ⁺	R ¹	R ²	R ⁵
101j	II	2	-	-	-	$\overline{\text{CHCH}_2\text{CH}_2}$	-
102j	III	2	-	-	H	$\overline{\text{CHCH}_2\text{CH}_2}$	-
103j		2					
102k		6					
103k		6					
104j	IV	2	0	-	$\text{-(CH}_2\text{)}_2\text{CMe}_2$ OSiMe ₃	-	-
105j		2					
104k		6					
105k		6					
106j	V	3	-	3	Me	Me	SiMe ₃
106k		6					
107j		3		4	Et	Et	SiMe ₃
107k		6					
108j	V	3	-	5	Me	Me	SiMe ₃
108k		6					
109j	VIIa	4	-	2	Et	Et	H
109k		6					
110j	VIIb	4	-	2	Et	Et	H
110k		6					

Table 3 (continued):

Compound Number (R=j or k)	Type	Scheme	x	m [†]	R ¹	R ²	R ⁵
111j 111k	III	[1,2 6]	-	-	H	H	-
112j 113j							
112k 113k	IV	2	0	-	Me	-	-
114j 115j							
114k 115k	IV	6	0	-	Me	-	-
116j 116k							
117j 117k	VIIa	[4 6]	-	1 [(<u>S</u>)-CH(Me)]	Me	Me	H
118j 118k							
119j 119k	VIIb	[4 6]	-	1 [(<u>R</u>)-CH(Me)]	Me	Me	H

† Note as for Table 1

NB (i) Where identical descriptions for two numbered compounds are given (e.g. 102j and 103j) the compounds are distinguished only in their configuration at the starred carbon atom. These configurations give rise to two series of compounds, referred to as "isomer A" and "isomer B" in the Preparations and Examples.

(ii) Where a hydroxyl group is present in R^1 , R^2 or one of the "*" carbons of formula I, then this may optionally be protected in the corresponding intermediates (e.g. 104 and 105).

5 Table 4: Exemplified Compounds I

Compound Number	m^+	n	R^1	R^2
120 } 121 }	0	1*	H	$\overline{-CHCH_2}CH_2$
122	3	0	Me	Me
10 123	4	0	Et	Et
124	2	1*	Et	Et
125	2	1+	Et	Et
126	1	1*	H	H
127 } 15 128 }	0	0	Me	H
129 } 130 }	0	0	$(CH_2)_2 \begin{array}{c} CMe_2 \\ \\ OH \end{array}$	H
131 } 132 }	0	0	$(CH_2)_4 \begin{array}{c} CMe_2 \\ \\ OH \end{array}$	H
20 133	5	0	Me	Me
134 } 135 }	$\begin{array}{c} 1 \\ [(S)-CH(Me)] \end{array}$	$\begin{bmatrix} 1* \\ 1+ \end{bmatrix}$	Me	Me
136 } 137 }	$\begin{array}{c} 1 \\ [(R)-CH(Me)] \end{array}$	$\begin{bmatrix} 1* \\ 1+ \end{bmatrix}$	Me	Me

25 Notes as for Table 3;

* 22(E);

+ 22(Z) (The carbon in the side chain connected to C-20 apart from the methyl group is C-22)

Preparation 1: 4-Bromo-2-methyl-2-trimethylsilyl-oxybutane (Compound 9)

To a stirred, ice-cooled solution of ethyl 3-bromopropionate (G, $y=1$) (15.0 ml) in dried ether (100 ml) was
5 added dropwise over 1 hour a filtered solution of Grignard reagent, prepared from magnesium (10 g) and methyl iodide (25 ml) in dried ether (200 ml). After a further 30 minutes on the ice bath, the reaction mixture was allowed to warm to room temperature over 30 minutes before being poured
10 onto a stirred, ice-cooled solution of ammonium chloride (30 g) in water (200 ml). After the vigorous reaction had subsided, the ether layer was separated, and the aqueous layer was extracted with more ether. The combined ether layers were washed consecutively with water and brine,
15 dried, and concentrated in vacuo to give the crude intermediate carbinol H ($y = 1$, $R^1 = R^2 = \text{Me}$) as a pale yellow oil. This was dissolved in dichloromethane (130 ml) and triethylamine (40 ml) and 4-dimethylaminopyridine (0.2 g) added. The stirred solution was ice-cooled during the
20 addition of trimethylsilyl chloride (27 ml) dropwise over 30 minutes. The reaction mixture was then stirred at room temperature for 2 hours before being partitioned between ether (500 ml) and water (500 ml). The ether layer was washed four times with water, once with brine, and dried.
25 After removing the solvent in vacuo, the residue was distilled to give a product, b.p. 75-77°C/11 mmHg. A portion (5 g) of the product was purified by chromatography (150 g silica gel; 1% ether in petroleum ether as eluant) and redistilled to give the pure bromide (9) as an oil, δ (300
30 MHz) 0.10 (9 H, s), 1.23 (6 H, s), 2.02 (2 H, m) and 3.44 (2 H, m).

Preparation 2 3-Hydroxy-3-methylbutyl phenyl sulphone (Compound 21)

35 To a solution of 4-bromo-2-methyl-2-trimethylsilyloxybutane (9) (12 g) in methanol (55 ml) at room temperature was added ethanolic hydrogen chloride (ca. 1 M, 0.2 ml). After 10 minutes the solution was concentrated in

vacuo (at room temperature) to constant weight. The residue was taken up in chloroform and reconcentrated to constant weight to give 4-bromo-2-methyl-2-butanol ($H, y = 1, R^1 = R^2 = Me$) as a chromatographically homogenous oil. The product was dissolved in THF (10 ml) and added to a premixed, stirred solution of potassium tert-butoxide (3.7 g) and thiophenol (3.6 ml) in N,N-dimethylformamide (50 ml) at room temperature. After a few minutes a precipitate started forming, and after 30 minutes the mixture was partitioned between ethyl acetate (300 ml) and water (200 ml). The organic layer was washed consecutively with 2 N sodium hydroxide solution, water and brine. Drying and concentration in vacuo gave 3-hydroxy-3-methylbutyl phenyl sulphide as a chromatographically homogenous oil. This was dissolved in methanol (60 ml), and to the stirred solution was added sodium hydrogen carbonate (4.7 g), aqueous sodium tungstate solution (2%, 5 ml) and hydrogen peroxide (100 vol, 11.8 ml). The initial exothermic reaction which ensued was checked by momentary ice-cooling. The reaction mixture was then stirred at 50°C for 1 hour. After cooling, the mixture was partitioned between dichloromethane (200 ml) and water. The aqueous layer was extracted with more dichloromethane, and the combined dichloromethane layers were washed with water, brine, and dried. Concentration in vacuo gave a crude product which was purified by chromatography (150 g silica gel; ether as eluant) to give the sulphone (21) as a viscous oil, δ (300 MHz) 1.22 (6H, s), 1.64 (1H, bs), 1.88 (2H, m), 3.25 (2H, m), 7.55-7.70 (3H, m), 7.93 (2H, m).

Preparation 3: 4-Hydroxy-4-ethylhexyl phenyl-sulphone (Compound 23)

The compound was prepared using the procedure of Preparation 2, except using 6-bromo-3-methyl-3-trimethylsilyloxyhexane (compound 14) as starting material, via the corresponding intermediates 6-bromo-3-methyl-3-hexanol ($H, y = 2, R^1 = R^2 = Et$) and 4-hydroxy-4-ethylhexyl phenyl sulphide. 23; δ (300 MHz) 0.82 (6H, t, J 7.5), 1.31 (1H,

s), 1.43 (4H, q, J 7.5), 1.48 (2H, m), 1.74 (2H, m), 3.13 (2H, m), 7.57 (2H, m), 7.66 (1H, m) and 7.92 (2H, m).

Preparation 4: Compound 26

5 The compound was prepared from 1-p-toluenesulphonyloxy-2(S),3-dimethyl-3-hydroxybutane (J. Org. Chem. 53, 3457-3465 (1988)) by tosylate exchange with LiBr followed by trimethylsilylation using a procedure analogous to the relevant section of Preparation 5 of our international
10 published patent application No. WO 89/10351.

Preparation 5: Compound 27

The compound was prepared analogously to Compound 26
15 (Preparation 4), from 1-p-toluenesulphonyloxy-2(R),3-dimethyl-3-hydroxybutane. This compound was prepared analogously to the 2(S)-isomer as described in J. Org. Chem. 53, 3457-3465 (1988), but using methyl (S)-(+)-3-hydroxy-2-methylpropionate as starting material instead of the
20 (R)-(-)-isomer.

Preparation 6: Compound 29

The compound was prepared analogously to Compound 28 as described in J. Org. Chem. 53, 3457-3465 (1988), but
25 using methyl (S)-(+)-3-hydroxy-2-methylpropionate as starting material instead of the (R)-(-)-isomer. M.p. 67-68°C, $[\alpha]_D$ -35° (c 1, CHCl₃).

All other compounds of Table 1, except compound 28
30 (prepared as described in J. Org. Chem. 53, 3457-3465 (1988), were prepared as described in international published patent application No. WO 89/10351.

As indicated in M.J. Calverley, Tetrahedron 43, 4609
35 (1987), Compound 1j was prepared by base-catalysed equilibration of its C-20 epimer and separated by chromatography (5% Et₂O in petroleum ether as eluant). The compound has now been obtained crystalline (from

Et₂O-MeOH).

Preparation 7a: Compound 31b

The compound was prepared as described for the
5 corresponding compound 31a [M.J. Calverley, Tetrahedron 43,
4609 (1987)] except using cyclobutyl methyl ketone instead
of cyclopropyl methyl ketone. 31b: δ (300 MHz) 1.70-2.00
(2H, m), 2.05-2.35 (4H, m), 3.21 (1H, m), 3.66 (1H, d, J
26), 7.4-7.7 (15H, m).

10

Preparation 7b: Compound 32

The compound was prepared as described for the
corresponding compound 31a [M.J. Calverley, Tetrahedron 43,
4609 (1987)] except using 1-chlorocyclopropyl methyl ketone
15 instead of cyclopropyl methyl ketone. 32: δ (300 MHz) 1.11
and 1.57 (each 2H, m), 4.58 (1H, d, J 25), 7.4-7.7 (15H,
m).

Preparation 8: Compound 33

20 This compound was prepared using a procedure
analogous to that described for the preparation of the
corresponding compound 30a (J. Org. Chem., 1982, 47, 2163),
except using 1-fluorocyclopropyl methyl ketone as starting
material. 33; b.p. 90-93°C/0.2 mmHg, δ (inter alia) 3.47
25 (1H, J 3.7 and 22.6).

Preparation 9 1(S),3(R)-bis-tert-butyldimethyl-
silyloxy-20(R)-hydroxymethyl-9,10-
secopregna-5(E),7(E),10(19)-triene

30 A stirred, ice-cooled solution of the aldehyde 1j (5
g) in THF (20 ml) and ethanol (70 ml) was treated with
sodium borohydride (0.35 g). After 10 minutes the reaction
mixture was partitioned between ethylacetate and water, and
the organic layer was washed with brine and dried.
35 Concentration in vacuo gave the title compound, δ (300 MHz)
0.05 (12H, bs), 0.56 (3H, s), 0.86 (9H, s), 0.89 (9H, s),
0.96 (3H, d, J 7), 1.1-2.1 (15H, m), 2.31 (1H, bd), 2.55
(1H, dd, J 14 and 5), 2.86 (1H, bd), 3.48 (1H, dd, J 10 and

7), 3.71 (1H, dd, $\underline{J}$ 11 and 4), 4.21 (1H, m), 4.52 (1H, m), 4.93 (1H, bs), 4.98 (1H, bs), 5.82 (1H, d, $\underline{J}$ 11.5), and 6.44 (1H, d, $\underline{J}$ 11.5).

5 Preparation 10 1(S),3(R)-bis-tert-butyl-dimethyl-
silyloxy-20(R)-p-toluenesulphonyloxy-
methyl-9,10-secopregna-5(E),7(E),
10(19)-triene (Compound 3j)

The compound from Preparation 9, 1(S),3(R)-bis-tert-butylldimethylsilyloxy-20(R)-hydroxymethyl-9,10-secopregna-5(E),7(E),10(19)-triene (5 g) was dissolved in dichloromethane (25 ml) and pyridine (3 ml), and the solution was stirred and ice-cooled during the addition of p-toluene-sulphonyl chloride (2.5 g). The reaction mixture was allowed to stand at 5°C overnight before being partitioned between ethyl acetate and water. The organic layer was washed consecutively with saturated copper sulphate solution (twice), water, 5% sodium hydrogen carbonate solution, and brine, and then dried and concentrated in vacuo. The residue was purified by chromatography (200 g silica gel; 5% ether in petroleum ether as eluant) to give title compound, δ (300 MHz) 0.035 (3H, s), 0.044 (3H, s), 0.051 (3H, s), 0.056 (3H, s), 0.45 (3H, s), 0.85 (9H, s), 0.88 (9H, s), 0.89 (3H, d, J 6), 1.15-2.05 (14H, m), 2.28 (1H, bd), 2.44 (3H, s), 2.52 (1H, dd, J 14 and 5), 2.84 (1H, bd), 3.81 (1H, m), 4.11 (1H, m), 4.20 (1H, m), 4.51 (1H, m), 4.93 (1H, bs), 4.97 (1H, bs), 5.79 (1H, d, J 11), 6.42 (1H, d, J 11), 7.33 (2H, bd) 7.78 (2H, bd).

30 Preparation 11: 1(S),3(R)-bis-tert-butyldimethyl-
silyloxy-20(R)-formyl-9,10-seco-
pregna-5(Z),7(E),10(19)-triene
 (Compound 1k)

The compound was prepared analogously to Procedure 4 (see below) in which the starting material was 1j. 5% Ether in petroleum ether was used as eluant. 1k δ (300 MHz) 0.05 (12H, bs), 0.52 (3H, s), 0.86 (18H, s), 1.03 (3H, d, J 6), 1.1-2.5 (16H, m), 2.82 (1H, bd), 4.17 (1H, m), 4.36 (1H,

m), 4.84 (1H, bd), 5.16 (1H, m), 6.00 and 6.20 (each 1H, d, J 11), and 9.56 (1H, d, J 8).

5 Procedure 1a Reaction of aldehyde 1 with stable
 ylide C'(Z = Ph₃P⁺-CH⁻) to give II
 (Scheme 2)

 A stirred mixture of 1 and a molar excess of C' in
toluene (10 ml per gram 1) was heated under reflux under an
N₂ atmosphere until a reasonable or complete conversion of
10 1 was obtained (4 to 16 hours). After cooling, the mixture
was filtered, and the filtrate concentrated and purified by
chromatography (5 - 10% ether in petroleum ether for the
examples of Table 2) to give II.

 Compound 101j (obtained thus from 1j and 31a) is
15 described in Tetrahedron 43, 4609 (1987).

20 Procedure 1b Reaction of aldehyde 1 with C'(W')-
 formed in situ from side chain
 fragment C(W)

 An equivalent amount of 1 (dissolved in THF) was
added to an ice-cooled solution of C'(W') in THF [prepared
by adding base (BuLi or NaH, 1 equivalent) to a solution of
C or W (2 equivalents base for W with R⁵ = H)]. After stir-
25 ring overnight, the reaction mixture was worked up (ether),
and the residue purified by chromatography to give the
compound II (from C) or VII (from W).

30 Preparation 12 Compounds 102j and 103j

 Sodium borohydride (0.29 g) was added to an ice-
cooled, stirred solution of 101j (2.5 g) in tetrahydro-
furan (8 ml) and 0.4 M CeCl₃.7H₂O in ethanol (11.5 ml).
Methanol (6 ml) was added over 10 minutes, and after stir-
ring for a further 20 minutes the mixture was partitioned
35 between ethyl acetate and water. The organic layer was
washed with water, dried and concentrated in vacuo. The
residue was purified by chromatography (silica gel;
toluene:acetone 97:3 as eluant) to give the title com-

pounds. The first eluted product was isomer A (102j); δ (100 MHz) 0.06 (12H, s), 0.53 (3H, s), 0.13-0.68 (4H, m), 0.87 (9H, s), 0.90 (9H, s), additionally 0.70-2.70 (21H, m), 2.85 (1H, m), 3.44 (1H, m), 4.20 (1H, m), 4.51 (1H, m), 4.95 (2H, m), 5.52 (2H, m), 5.80 (1H, d, $\underline{J}$ 12 and 6.45 (1H, d, $\underline{J}$ 12); λ_{max} 270 nm (ϵ = 24900) (crystallized from methanol).

The second eluted product was isomer B (103j). M.p. 104-5°C (from methanol); δ (100 MHz) 0.06 (12H, s), 0.53 (3H, s), 0.15-0.65 (4H, m), 0.87 (9H, s), 0.90 (9H, s), additionally 0.67-2.70 (21H, m), 2.85 (1H, m), 3.40 (2H, m), 4.21 (1H, m), 4.52 (1H, m), 4.95 (2H, m), 5.50 (2H, m), 5.80 (1H, d, $\underline{J}$ 12 and 6.45 (1H, d, $\underline{J}$ 12); $\lambda_{\max}$ 270 nm (ϵ = 24500).

15 Procedure 2 Reaction of aldehyde 1 or 2 with
 (a) R¹MgBr (R¹MgI) or (b) R¹Li to
 give IV (Scheme 2)

(a) An aliquot (2 ml) of the Grignard reagent obtained from R^1Br (R^1I) (20 mmol) (in the event that R^1 contains a hydroxy group in the compound I, this may be protected for example as a trimethylsilyl ether for the reaction of Procedure 2. The unmasking of this hydroxyl then occurs during the reaction of Procedure 5), and magnesium (20 mmol) in dry THF (15 ml) was added dropwise to a stirred solution of 1 or 2 (1 mmol) in dry THF (5 ml) at 0°C. After 30 min., the reaction mixture was partitioned between water and ether, and the ether layer was washed with brine, dried and concentrated in vacuo. Purification of the residue by chromatography gave IV.

30 (b) The organo-lithium reagent (1.5 M in ether or hexanes, 1 ml) was substituted for the aliquot of Grignard reagent in (a), running the reaction at -40°C instead of 0°C .

35 **Preparation 13 Compounds 104j and 105j**

Using Procedure 2a, starting with compounds 9 and 1j, and using 5% ethyl acetate in petroleum ether for the chromatography, the title compounds as were obtained as

isomer A (less polar isomer) and B, respectively.

Procedure 2c Conversion of tosylate 3 to V
Scheme 3)

5 This procedure is illustrated in Preparations 14 and 51.

Preparation 14 Compound 106j

The stirred Grignard reagent obtained from Compound 9
10 (5.0 g) and magnesium (0.53 g) in dry THF (15 ml) was treated at 0°C with a solution of lithium chloride (68 mg) and anhydrous cupric chloride (108 mg) in dry THF (8 ml) followed by a solution of Compound 3j (1.0 g) in dry THF (5 ml). After 5 hours, the reaction mixture was partitioned
15 between water and ether, and the ether layer was washed with brine, dried and concentrated in vacuo. Purification of the residue by chromatography (150 g silica gel, petroleum ether to 2% ether in petroleum ether as eluant) followed by crystallisation from ether-methanol gave the
20 title compound, δ (300 MHz) 0.05 (12H, bs), 0.09 (9H, s), 0.54 (3H, s), 0.85 (3H, d, J 6), 0.85 (9H, s), 0.89 (9H, s), 1.19 (6H, s), additionally 1.2-2.05 (20H, m), 2.30 (1H, bd), 2.55 (1H, dd), 2.86 (1H, bd), 4.21 (1H, m), 4.52 (1H, m), 4.93 (1H, bs), 4.98 (1H, bs), 5.82 (1H, d, J 11.6),
25 6.45 (1H, d, J 11.6).

Preparation 15 Compound 107j

The compound was prepared using the method of Preparation 14, except that the Grignard reagent was
30 prepared from Compound 14 (5.9 g).
107j: δ (300 MHz) 0.05 (12H, bs), 0.08 (9H, s), 0.53 (3H, s), 0.80 (9H, m), 0.86 (9H, bs), 0.89 (9H, bs), [1.05-2.05 (26H, m, including 1.43 (4H, q)], 2.30 (1H, m), 2.56 (1H, m), 2.86 (1H, m), 4.21 (1H, m), 4.52 (1H, m), 4.93 (1H, m),
35 4.98 (1H, m), 5.82 (1H, d, J 11.5), 6.45 (1H, d, J 11.5).

Preparation 16 Compound 108j

The compound was prepared using the method of

Preparation 14, except that the Grignard reagent was prepared from Compound 16 (5.5 g).

Procedure 3

Preparation of Compounds VII from
Aldehyde (1) and Side Chain
Fragment B (Scheme 4)

5
10
15
20
25
30
A solution of lithium di-iso-propylamide (0.4 M in THF-hexanes, 3:1) was added dropwise via a syringe (10 minutes) to a solution of the side chain fragment B in dry THF (8 ml), stirred at -25°C under nitrogen. The resulting yellow solution was then cooled to -40°C, and a solution of the aldehyde (1) (1.21 g) in dry THF (8 ml) was added dropwise (5 minutes). After stirring for 30 minutes, benzoyl chloride (0.6 ml) was added dropwise, and the mixture was allowed to warm to 0°C for a further 30 minutes. The reaction mixture was treated with ether (10 ml) and water (1 ml) and partitioned between ethyl acetate (100 ml) and water (50 ml). The organic layer was washed with brine, dried, and concentrated in vacuo to give a crude oil containing compound VI (Y = PhC(O)) as a mixture of diastereoisomers. This was dissolved in ethyl acetate (5 ml) and diluted with methanol (50 ml, saturated with and containing suspended disodium hydrogen phosphate). To the ice-cooled mixture was added sodium amalgam (ca. 5% Na, 15 g), and the reaction mixture was stirred at 5°C under nitrogen for 15 hours. The mixture was then partitioned between ethyl acetate (200 ml) and water (200 ml) (decanting from the mercury), and the organic layer was washed with brine, dried and concentrated in vacuo. Purification of the residue by chromatography gave VII.

Preparation 17 Compounds 109j and 110j

35
This compound was prepared from 1j using Procedure 3 in which the side chain fragment B was compound 23 (0.66 g) and 12 ml of the lithium di-iso-propylamide solution was used. The intermediate VIj has $R^5 = OH$. The chromatography was performed using 10% ethyl acetate in petroleum ether as eluant. The major product (more polar) 109j was

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PCT/DK90/00156

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recrystallized from Et₂O-MeOH. 109j; δ (300 MHz) 0.05 (12H, bs), 0.50 (3H, s), 0.85 (6H, t, $\underline{J}$ 7.5), 0.86 (9H, s), 0.89 (9H, s), 0.90 (3H, d, $\underline{J}$ 6.6), 1.1-2.1 (23H, m), 2.30 (1H, bd, $\underline{J}$ 14), 2.55 (1H, dd, $\underline{J}$ 14 and 5), 2.86 (1H, bd, $\underline{J}$ 12),
 5 4.21 (1H, m), 4.53 (1H, m), 4.93 (1H, bs), 4.98 (1H, bs), 5.30 (2H, m), 5.80 (1H, d, $\underline{J}$ 12), and 6.45 (1H, d, $\underline{J}$ 12);
 $\lambda_{\max}$ 270 nm. 110j; δ (300 MHz) 0.05 (12H, bs), 0.47 (3H, s), 0.85 (6H, t), 0.86 (9H, s), 0.89 (9H, s), 0.9 (3H, d),
 10 $\underline{J}$ 14 and 5), 2.30 (1H, m), 2.35 (1H, m), 2.55 (1H, dd, $\underline{J}$ 14 and 5), 2.86 (1H, bd, $\underline{J}$ 12), 4.21 (1H, m), 4.53 (1H, m), 4.93 (1H, bs), 4.98 (1H, bs), 5.2 (2H, m), 5.80 (1H, d, $\underline{J}$ 12), and 6.45 (1H, d, $\underline{J}$ 12); $\lambda_{\max}$ 270 nm.

15 Procedure 4 Preparation of Compound XIV from the
 Corresponding Compound XIII
 (Scheme 6)

A mixture of anthracene (0.10 g), triethylamine (20 mg), and the compound
 20 XIII (0.20 g) in toluene (15 ml), stirred under an atmosphere of nitrogen in a
 PYREX_{TM} flask immersed in a water bath at 20°C, was illuminated with radiation
 from a high pressure Hg lamp (type known by the trade-mark HANAU TQ_{TM}
 718Z2) for 30 minutes. The reaction mixture was filtered and concentrated in vacuo
 to give a residue. This was purified by chromatography (30 g silica gel) to give
 25 XIV.

Preparation 18 Compound 102k

The compound was prepared using Procedure 4 in which
 starting material XIII was compound 102j. (Eluant: toluene-
 30 acetone, 97:3) 102k; δ (300 MHz) 0.06 (12H, s), 0.15-0.38
 (2H, m), 0.52 (3H, s), 0.40-0.57 (2H, m), 0.87 (18H, s),
 0.94 (3H, d, $\underline{J}$ 7), 0.65-2.15 (16H, m), 2.20 (1H, dd), 2.44
 (1H, dd), 2.80 (1H, bd), 3.44 (1H, t), 4.18 (1H, m), 4.36
 (1H, m), 4.85 (1H, d, $\underline{J}$ 2), 5.17 (1H, m), 5.46 and 5.58
 35 (each 1H, dd, $\underline{J}$ 16 and 9), 6.00 (1H, d, $\underline{J}$ 11), 6.22 (1H, d,
 $\underline{J}$ 11); $\lambda_{\max}$ 265 nm.

Preparation 19 Compound 103k

The compound was prepared using Procedure 4 in which starting material XIII was compound 103j. (Eluant: toluene-acetone, 97:3) 103k; δ (300 MHz) 0.06 (12H, s), 0.15-0.38 (2H, m), 0.52 (3H, s), 0.40-0.57 (2H, m), 0.87 (18H, s), 0.94 (3H, d, $\underline{J}$ 7), 0.65-2.15 (16H, m), 2.20 (1H, dd), 2.44 (1H, dd), 2.80 (1H, bd), 3.38 (1H, t), 4.18 (1H, m), 4.36 (1H, m), 4.85 (1H, d, $\underline{J}$ 2), 5.17 (1H, m), 5.48 (2H, m), 6.00 (1H, d, $\underline{J}$ 11), 6.22 (1H, d, $\underline{J}$ 11); $\lambda_{\max}$ 265 nm.

10

Preparation 20 Compound 106k

The compound was prepared using Procedure 4 in which starting material XIII was compound 106j. (Eluant: petroleum ether to 2% ether in petroleum ether) 106k; δ (300 MHz) 0.05 (12H, bs), 0.09 (9H, s), 0.52 (3H, s), 0.83 (3H, d, $\underline{J}$ 6), 0.88 (18H, s), 1.1-2.05 (26H, m, including 1.19 (6H, s)), 2.20 (1H, dd, $\underline{J}$ 13 and 7), 2.43 (1H, dd, $\underline{J}$ 13 and 4), 2.81 (1H, m), 4.18 (1H, m), 4.36 (1H, m), 4.86 (1H, bd), 5.17 (1H, bd), 6.01 (1H, d, $\underline{J}$ 11), 6.22 (1H, d, $\underline{J}$ 11); $\lambda_{\max}$ 265 nm.

20

Preparation 21 Compound 107k

The compound was prepared using Procedure 4 in which starting material XIII was compound 107j. (Eluant: petroleum ether to 2% ether in petroleum ether) 107k; δ (300 MHz) 0.05 (12 H, bs), 0.08 (9H, s), 0.52 (3H, s), 0.80 (9H, m), 0.87 (18H, s), 1.05-2.0 (26H, m, including 1.43 (4H, q), 2.21 (1H, dd), 2.43 (1H, bd), 2.82 (1H, bd), 4.16 (1H, m), 4.37 (1H, m), 4.85 (1H, m), 5.17 (1H, m), 6.01 (1H, d, $\underline{J}$ 11), 6.23 (1H, d, $\underline{J}$ 11); $\lambda_{\max}$ 265 nm.

30

Preparation 22: Compound 109k

The compound was prepared using Procedure 4 in which starting material XIII was compound 109j. (Eluant: 20% ether in petroleum ether).

35

Preparation 23: Compound 5

A stirred solution of 1j (3.9 g), and methoxy-

carbonylmethylene-triphenylphosphorane (4.6 g) in toluene (40 ml) was heated under reflux for 3 hours. The reaction mixture was cooled, filtered, and concentrated in vacuo. Purification of the residue by chromatography (200 g silica gel; 5% ether in petroleum ether as eluant) followed by recrystallization from ether-methanol gave the title compound as needles; δ (300 MHz) 0.05 (12H, m), 0.49 (3H, s), 0.86 (9H, s), 0.89 (9H, s), 1.00 (3H, d), 1.03-2.05 (13H, m), 2.24 (1H, m), 2.31 (1H, bd), 2.54 (1H, dd), 2.85 (1H, dd), 3.73 (3H, s), 4.21 (1H, m), 4.52 (1H, m), 4.93 (1H, m), 4.97 (1H, m), 5.76 (1H, d, J 15.6), 5.80 (1H, d), 6.43 (1H, d), 6.88 (1H, dd, J 15.6 and 9.9).

Preparation 24: Compound 111j

To a stirred solution of 5 (3.3 g) in dry THF (35 ml) at -70°C under N_2 was added di-isobutylaluminium hydride (1 M solution in hexanes (15 ml) for compound 2; 8 ml for compound 3) dropwise. After stirring for 30 minutes, methanol (3 ml) was added dropwise, and the reaction mixture was allowed to warm up to room temperature. EtOAc and water were added, and after stirring for an additional 30 minutes, the organic phase was separated, washed with brine, dried and concentrated to give the title compound. δ (300 MHz) 0.05 (12H, m), 0.51 (3H, s), 0.86 (9H, s), 0.89 (9H, s), 0.94 (3H, d), 1.00-2.20 (15H, m), 2.30 (1H, bd), 2.55 (1H, dd), 2.85 (1H, bd), 4.08 (2H, bs), 4.21 (1H, m), 4.52 (1H, m), 4.93 (1H, m), 4.97 (1H, m), 5.56 (2H, m), 5.82 (1H, d), 6.44 (1H, d).

Preparation 25: Compound 2j

Pyridinium dichromate (0.5 g) was added at room temperature to a stirred solution of compound 111j (0.53 g) in dichloromethane (10 ml). After stirring for 3 hours the mixture was diluted with ether and filtered. The filtrate was concentrated in vacuo and purified by chromatography (silica gel, hexane:ether 4:1 as eluant) to give 2j; δ (300 MHz) 0.06 (12H, m), 0.50 (3H, s), 0.85 (9H, s), 0.89 (9H, s), 1.05 (3H, d), 1.06-2.10 (13H, m), 2.30 (1H, bd), 2.40

(1H, m), 2.54 (1H, dd), 2.86 (1H, bd), 4.21 (1H, m), 4.52 (1H, m), 4.93 (1H, m), 4.97 (1H, m), 5.81 (1H, d), 6.06 (1H, dd, $\underline{J}$ 15.6 and 7.9), 6.43 (1H, d), 6.76 (1H, dd, $\underline{J}$ 15.6 and 9.8), 9.52 (1H, d, $\underline{J}$ 7.9).

5

Preparation 26 1(S),3(R)-bis-tert-butyldimethyl-
silyloxy-20(R)-phenylthiomethyl-
-9,10-secopregna-5(E),7(E),10(19)-
-triene

10 A solution of potassium thiophenoxide in DMF [prepared by adding potassium tert-butoxide (0.35 g) to thiophenol (0.35 g) dissolved in DMF (5 ml)] was added to a solution of 3j (1 g) in THF (5 ml). After 30 minutes, the reaction mixture was worked up (ether) and purified by
15 chromatography (2% ether in petroleum ether as eluant) to give the title compound. δ (300 MHz) 0.05 (12H, m), 0.51 (3H, s), 0.86 (9H, s), 0.89 (9H, s), 1.04 (3H, d), 1.20-2.0 (13H, m), 2.04 (1H, bt), 2.30 (1H, bd), 2.54 (1H, dd), 2.75 (1H, dd), 2.85 (1H, bd), 3.24 (1H, dd), 4.21 (1H,
20 m), 4.52 (1H, m), 4.93 (1H, bs), 4.97 (1H, bs), 5.71 (1H, d), 6.44 (1H, d), 7.10-7.4 (5H, m).

Preparation 27 1(S),3(R)-bis-tert-butyldimethyl-
silyloxy-20(R)-phenylsulphonylmethyl-
25 -9,10-secopregna-5(E),7(E),10(19)-
-triene (Compound 4j)

To a solution of 1(S),3(R)-bis-tert-butyldimethyl-silyloxy-20(R)-phenylthiomethyl-9,10-secopregna-5(E),7(E),-10(19)-triene (Preparation 26) (0.9 g) in ethyl acetate (8
30 ml) and ethanol (15 ml) was added sodium hydrogen carbonate (0.5 g), aqueous sodium tungstate (3%, 0.5 ml) and hydrogen peroxide (30%, 2 ml). The stirred mixture was heated at 60°C for 8 hours, cooled and worked-up (ethyl acetate). Purification by chromatography (40% ether in petroleum
35 ether as eluant) gave 4j. δ (300 MHz) 0.05 (12H, m), 0.36 (3H, s), 0.86 (9H, s), 0.89 (9H, s), 1.10 (3H, d), 1.5-2.15 (m, 13H), 2.29 (1H, bd), 2.52 (1H, dd), 2.83 (1H, bd), 2.86 (1H, dd), 3.43 (1H, dd), 4.20 (1H, m), 4.51 (1H, m), 4.93

(1H, m), 4.96 (1H, m), 5.78 (1H, d), 6.41 (1H, d), 7.57 (3H, m), 7.92 (2H, m).

5 Preparation 28, 29, and 30 Compounds 2k, 3k, and 4j

Each compound was prepared analogously to Procedure 4 in which the starting material was the corresponding compound j. The eluant used was that used in the purification of the compound j.

10

Preparation 31: Compounds 112j and 113j

Using Procedure 2(b) as follows: To a solution of Compound 1j (0.8 g) in dry THF (7 ml), cooled to -40°C and stirred under N₂, was added dropwise a solution of
15 methyl-lithium (1.5 M in ether, 1.2 ml). After 15 minutes, ether (50 ml) was added and the reaction mixture was worked up. The residue was purified by chromatography (10% ethyl acetate in petroleum ether as eluant) to give the less polar isomer (isomer A) 112j; NMR: δ = 0.05 (m, 12H), 0.54
20 (s, 3H), 0.85 (d, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.13 (d, 3H, J = 6.3), 1.00-2.10 (m, 15H), 2.31 (bd, 1H), 2.54 (dd, 1H), 2.88 (bd, 1H), 4.06 (m, 1H), 4.21 (m, 1H), 4.52 (m, 1H), 4.93 (m, 1H), 4.98 (m, 1H), 5.82 (d, 1H, J = 11.4), 6.44 (d, 1H, J = 11.4), and the more polar isomer 113j
25 (isomer B); NMR: δ = 0.05 (m, 12H), 0.56 (s, 3H), 0.86 (d, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.07 (d, 3H, J = 6.3), 1.00-2.10 (m, 15H), 2.31 (bd, 1H), 2.54 (dd, 1H), 2.88 (bd, 1H), 4.10 (m, 1H), 4.21 (m, 1H), 4.52 (m, 1H), 4.93 (m, 1H), 4.98 (m, 1H), 5.82 (d, 1H, J = 11.4), 6.44 (d, 1H, J =
30 11.4).

Preparation 32 Compound 114j and 115j

Using Procedure 2a, starting with compounds 19 and 1j, and using 5% ethyl acetate in petroleum ether as eluant
35 for the chromatography, the title compounds were obtained. Major isomer (114j); δ (300 MHz) 0.05 (12H, m), 0.08 (9H, s), 0.54 (3H, s), 0.83 (3H, d), 0.86 (9H, s), 0.89 (9H, s), 1.18 (6H, s), 1.00-2.12 (23H, m), 2.31 (1H, bd), 2.55 (1H,

dd) 2.88 (1H, bd), 3.85 (1H, m), 4.21 (1H, m), 4.53 (1H, m), 4.93 (1H, m), 4.98 (1H, m), 5.83 (1H, d), and 6.45 (1H, m). The minor isomer (115j) was the more polar isomer, δ (300 MHz) in agreement with assigned structure.

5

Preparation 33 Compounds 116j and 117j

These compounds were prepared from 1j using procedure 3 in which the side chain fragment B was compound 29 (0.6 g) and 12 ml of the lithium di-iso-propylamide solution was used. The intermediate VIj has $R^5 = OH$. The chromatography was performed using 10% ethyl acetate in petroleum ether as eluant to give the less polar 22Z isomer (117j); δ (300 MHz) 0.05 (12H, m), 0.47 (3H, s), 0.86 (9H, s), 0.89 (9H, s), 0.91 (3H, d), 0.97 (3H, d), 1.15 (3H, s), 1.18 (3H, s), 1.07-2.20 (14H, m), 2.31 (1H, bd), 2.39 (1H, m), 2.54 (2H, m), 2.85 (1H, bd), 4.21 (1H, m), 4.52 (1H, m), 4.92 (1H, m), 4.97 (1H, m), 5.07 (1H, t, J 10.9), 5.35 (1H, t, J 10.9), 5.81 (1H, d), and 6.45 (1H, d); λ_{max} 270 nm; and the more polar 22E isomer (116j); δ (300 MHz) 0.05 (12H, m), 0.51 (3H, s), 0.86 (9H, s), 0.89 (9H, s), 0.93 (3H, d), 0.99 (3H, d), 1.13 (3H, s), 1.16 (3H, s), 1.05-2.22 (16H, m), 2.30 (1H, bd), 2.54 (1H, dd), 2.85 (1H, bd), 4.21 (1H, m), 4.52 (1H, m), 4.92 (1H, m), 4.97 (1H, m), 5.40 (2H, m), 5.81 (1H, d), and 6.44 (1H, d).

25

Preparation 34 Compounds 118j and 119j

This compound was prepared from 1j using procedure 3 in which the side chain fragment B was compound 28 (0.6 g) and 12 ml of the lithium di-iso-propylamide solution was used. The intermediate VIj has $R^5 = OH$. The chromatography was performed using 10% ethyl acetate in petroleum ether as eluant to give the 22Z isomer (119j) and the 22E isomer (118j).

35

Preparation 35-47 Compounds 104k, 105k, 108k, 110k, 111k, 112k, 113k, 114k, 115k, 116k, 117k, 118k and 119k

Each compound was prepared using Procedure 4 in which

the starting material XIII was the corresponding compound j. (Eluant: the same eluant as used in the preparation of the corresponding compound j).

5 Preparation 48 1(S),3(R)-bis-tert-butyldimethyl-
 silyloxy-20(R)-p-toluenesulphonyloxy-
 methyl-9,10-secopregna-5(Z),7(E),
 10(19)-triene (Compound 3k)

 The compound was prepared analogously to Procedure 4
10 in which the starting material was 3j. 5% Ether in
 petroleum ether was used as eluant.

Preparation 49 1(S),3(R)-bis-tert-butyldimethyl-
 silyloxy-20(R)-phenylsulphonylmethyl-
15 -9,10-secopregna-5(Z),7(E),10(19)-
 -triene (Compound 4k)

 The compound was prepared analogously to Procedure 4
 in which the starting material was 4j. 40% Ether in
 petroleum ether was used as eluant.

20 Preparation 50 1(S),3(R)-bis-tert-butyldimethyl-
 silyloxy-20(R)-hydroxymethyl-
 -9,10-secopregna-5(Z),7(E),10(19)-
 -triene

25 The compound was prepared analogously to Procedure 4
 in which the starting material was 1(S),3(R)-bis-tert-but-
 yldimethylsilyloxy-20(R)-hydroxymethyl-9,10-secopregna-
 -5(E),7(E),10(19)-triene (Preparation 9). 40% Ether in
 petroleum ether was used as eluant.

30 Preparation 51 1(S),3(R)-bis-tert-butyldimethyl-
 silyloxy-20(S)-(4-methyl-1-pentyl)-
 -9,10-secopregna-5(Z),7(E),10(19)-
 -triene

35 The stirred Grignard reagent obtained from isoamyl
 bromide (3.0 g) and magnesium (0.53 g) in dry THF (15 ml)
 was treated at 0°C with a solution of lithium chloride (68
 mg) and anhydrous cupric chloride (108 mg) in dry THF (8

ml) followed by a solution of Compound 3k (1.0 g) in dry THF (5 ml). After 5 hours, the reaction mixture was partitioned between water and ether, and the ether layer was washed with brine, dried and concentrated in vacuo.

5 Purification of the residue by chromatography (150 g silica gel, petroleum ether to 2% ether in petroleum ether as eluant) gave the title compound; δ (300 MHz) in agreement with assigned structure.

10 Procedure 5 Preparation of Compound I from the
 Corresponding Compound XIV
 (Scheme 6)

A solution of the compound XIV (0.2 g) and tetra-
n-butylammonium fluoride trihydrate (0.4 g) in THF (10 ml)
15 was heated at 60°C under an atmosphere of nitrogen for 50
minutes. After cooling, the reaction solution was parti-
tioned between ethyl acetate (40 ml) and 2% sodium hydrogen
carbonate solution (30 ml), and the organic layer was
washed with water and brine, dried and concentrated. The
20 residue was purified by chromatography (30 g silica gel,
ethyl acetate as eluant) to give I.

The compounds of Examples 1 to 18 were prepared using
procedure 5 in which starting material XIV was respectively
25 compounds 102k, 103k, 106k, 107k, 109k, 110k, 111k, 112k,
113k, 104k, 105k, 114k, 115k, 108k, 116k, 117k, 118k, and
119k.

The starting material for Example 19 was the compound
of Preparation 51. All exemplified compounds showed $\lambda_{\max}$
30 (EtOH) 264-265 nm.

Example 1 20(S)-(3'-Cyclopropyl-3'-hydroxyprop-
 -1'(E)-enyl)-1(S),3(R)-Dihydroxy-
 -9,10-secopregna-5(Z),7(E), 10(19)-
35 -triene (Isomer A) (Compound 120)

δ (300 MHz) 0.15-0.36 (2H, m), 0.40-0.60 (2H, m), 0.51 (3H, s), 0.92 (3H, m, J 6.6), 0.80-2.15 (18H, m), 2.29 (1H, dd), 2.57 (1H, dd), 2.79 (1H, dd), 3.43 (1H, t), 4.20 (1H, m),

4.41 (1H, m), 4.98 (1H, m), 5.31 (1H, m), 5.45 (1H, dd, $\underline{J}$ 15.5 and 6), 5.56 (1H, dd, $\underline{J}$ 15.5 and 9), 5.99 (1H, d, $\underline{J}$ 11), and 6.35 (1H, d, $\underline{J}$ 11).

5 Example 2 20(S)-(3'-Cyclopropyl-3'-hydroxyprop-
 -1'(E)-enyl)-1(S),3(R)-Dihydroxy-
 -9,10-secopregna-5(Z),7(E), 10(19)-
 -triene (Isomer B) (Compound 121)

10 δ (300 MHz) 0.15-0.40 (2H, m), 0.41-0.60 (2H, m), 0.53 (3H, s), 0.95 (3H, m, $\underline{J}$ 6.6), 0.80-2.15 (18H, m), 2.31 (1H, dd), 2.60 (1H, dd), 2.81 (1H, dd), 3.40 (1H, m), 4.23 (1H, m), 4.43 (1H, m), 5.00 (1H, m), 5.33 (1H, m), 5.50 (1H, m), 6.01 (1H, d, $\underline{J}$ 11), and 6.37 (1H, d, $\underline{J}$ 11).

15 Example 3 1(S),3(R)-Dihydroxy-20(S)-(4-hydroxy-
 -4-methyl-1-pentyl)-9,10-secopregna-
 5(Z),7(E),10(19)-triene
 (Compound 122)

20 δ (300 MHz) 0.53 (3H, s), 0.83 (6H, t, $\underline{J}$ 6), 1.1-2.1 (29H, m, including 1.20 (6H, s)), 2.30 (1H, dd), 2.58 (1H, bd), 2.81 (1H, bd), 4.22 (1H, m), 4.42 (1H, m), 4.99 (1H, bs), 5.32 (1H, bs), 6.00 (1H, d, $\underline{J}$ 11), 6.36 (1H, d, $\underline{J}$ 11).

25 Example 4 1(S),3(R)-Dihydroxy-20(S)-(5-ethyl-
 -5-hydroxy-1-heptyl)-9,10-secopregna-
 5(Z),7(E),10(19)-triene
 (Compound 123)

30 δ (300 MHz) 0.54 (3H, s), 0.82 (3H, d), 0.84 (6H, t), 1.0-2.0 [29H, m, including 1.47 (4H, q)], 2.31 (1H, m), 2.59 (1H, bd), 2.83 (1H, bd), 4.23 (1H, m), 4.43 (1H, m), 5.00 (1H, bs), 5.32 (1H, bs), 6.01 (1H, d, $\underline{J}$ 11) and 6.38 (1H, d, $\underline{J}$ 11).

35 Example 5 1(S),3(R)-Dihydroxy-20(S)-(5-ethyl-5-
 -hydroxy-hept-1(E)-en-1-yl)-9,10-
 -secopregna-5(Z),7(E),10(19)-triene
 (Compound 124)

δ (300 MHz) 0.51 (3H, s), 0.85 (6H, t), 0.91 (3H, d),

1.1-2.2 [25H, m, including 1.47 (4H, q)], 2.31 (1H, m),
2.59 (1H, bd), 2.82 (1H, bd), 4.23 (1H, m), 4.43 (1H, m),
4.99 (1H, bs), 5.30 (2H, m), 5.33 (1H, bs), 6.02 (1H, d, J
11) and 6.37 (1H, d, J 11).

5

Example 6

1(S),3(R)-Dihydroxy-20(S)-(5-ethyl-5-
-hydroxy-hept-1(Z)-en-1-yl)-9,10-
-secopregna-5(Z),7(E),10(19)-triene
(Compound 125)

10 δ (300 MHz) in agreement with assigned structure.

Example 7

1(S),3(R)-Dihydroxy-20(S)-(3-hydroxy-
prop-1(E)-enyl)-9,10-secopregna-
-5(Z),7(E),10(19)-triene
(Compound 126)

15

δ (300 MHz) in agreement with assigned structure.

Example 8

1(S),3(R)-Dihydroxy-20(R)-(1-hydroxy-
-1-ethyl)-9,10-secopregna-
-5(Z),7(E),10(19)-triene (Isomer A)
(Compound 127)

20

δ (300 MHz) in agreement with assigned structure.

Example 9

1(S),3(R)-Dihydroxy-20(R)-(1-hydroxy-
-1-ethyl)-9,10-secopregna-
-5(Z),7(E),10(19)-triene (Isomer B)
(Compound 128)

25

δ (300 MHz) in agreement with assigned structure.

Example 10

1(S),3(R)-Dihydroxy-20(R)-(1,4-di-
hydroxy-4-methyl-1-pentyl)-9,10-seco-
pregna-5(Z),7(E),10(19)-triene
(Isomer A) (Compound 129)

30

δ (300 MHz) in agreement with assigned structure.

35

Example 11

1(S),3(R)-Dihydroxy-20(R)-(1,4-di-
hydroxy-4-methyl-1-pentyl)-9,10-seco-
pregna-5(Z),7(E),10(19)-triene
(Isomer B) (Compound 130)

5 δ (300 MHz) in agreement with assigned structure.

Example 12

1(S),3(R)-Dihydroxy-20(R)-(1,6-di-
hydroxy-6-methyl-1-heptyl)-9,10-seco-
pregna-5(Z),7(E),10(19)-triene
(Isomer A) (Compound 131)

10

δ (300 MHz) 0.55 (3H, s), 0.83 (3H, d), 1.20 (6H, s),
1.20-2.10 (26H, m), 2.31 (1H, dd), 2.57 (1H, dd), 2.83 (1H,
dd), 3.84 (1H, m), 4.22 (1H, m), 4.43 (1H, m), 4.99 (1H,
bs), 5.33 (1H, bs), 6.02 (1H, d), 6.37 (1H, d).

15

Example 13

1(S),3(R)-Dihydroxy-20(R)-(1,6-di-
hydroxy-6-methyl-1-heptyl)-9,10-seco-
pregna-5(Z),7(E),10(19)-triene
(Isomer B) (Compound 132)

20 δ (300 MHz) 0.56 (3H, s), 0.85 (3H, d), 1.21 (6H, s),
1.20-2.10 (26H, m), 2.31 (1H, dd), 2.57 (1H, dd), 2.83 (1H,
dd), 3.78 (1H, m), 4.22 (1H, m), 4.43 (1H, m), 4.99 (1H,
bs), 5.33 (1H, bs), 6.02 (1H, d), 6.37 (1H, d).

25

Example 14

1(S),3(R)-Dihydroxy-20(S)-(6-hydr-
oxy-6-methyl-1-heptyl)-9,10-seco-
pregna-5(Z),7(E),10(19)-triene
(Compound 133)

δ (300 MHz) in agreement with assigned structure.

30

Example 15

1(S),3(R)-Dihydroxy-20(S)-(4-hydr-
oxy-3(S),4-dimethylpent-1(E)-enyl-
-9,10-secopregna-5(Z),7(E),10(19)-
-triene (Compound 134)

35 δ (300 MHz) 0.50 (3H, s), 0.91 (3H, d), 0.97 (3H, d), 1.13
(3H, s), 1.15 (3H, s), 1.15-2.20 (18H, m), 2.29 (1H, dd),
2.57 (1H, dd), 2.79 (1H, bd), 4.20 (1H, m), 4.40 (1H, m),
4.98 (1H, bs), 5.31 (1H, bs), 5.38 (2H, m), 5.98 (1H, d),

6.35 (1H, d).

5 Example 16 1(S),3(R)-Dihydroxy-20(S)-(4-hydroxy-3(S),4-dimethylpent-1(Z)-enyl-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 135)

δ (300 MHz) 0.36 (3H, s), 0.91 (3H, d), 0.97 (3H, d), 0.97 (3H, d), 1.2-2.65 (20H, m). 2.82 (1H, bd), 4.23 (1H, m), 4.41 (1H, m), 5.00 (1H, s), 5.08 (1H, t), 5.33 (1H, s), 10 5.36 (1H, t), 6.01 (1H, d), 6.37 (1H, d), 1.15 (3H, s), 1.24 (3H, s).

15 Example 17 1(S),3(R)-Dihydroxy-20(S)-(4-hydroxy-3(R),4-dimethylpent-1(E)-enyl-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 136)

δ (300 MHz) in agreement with assigned structure.

20 Example 18 1(S),3(R)-Dihydroxy-20(S)-(4-hydroxy-3(R),4-dimethylpent-1(Z)-enyl-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 137)

δ (300 MHz) in agreement with assigned structure.

25 Example 19 1(S),3(R)-Dihydroxy-20(S)-(4-methyl-1-pentyl-9,10-secopregna-5(Z),7(E),10(19)-triene (Compound 138)

δ (300 MHz) in agreement with assigned structure.

30 Example 20 Dermatological Cream Containing Compound 122

In 1 g almond oil was dissolved 0.1 mg 122. To this solution was added 40 g of mineral oil and 20 g of self-emulsifying beeswax. The mixture was heated to 35 liquify. After the addition of 40 ml hot water, the mixture was mixed well. The resulting cream contains approximately 1 µg of 122 per gram of cream.

Example 21 Capsules containing Compound 122

122 was suspended in arachis oil to a final concentration of 5 μ g 122/ml oil. 10 Parts by weight of gelatine, 5 parts by weight glycerine, 0.08 parts by weight
5 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 122 in oil suspension, such that each capsule contained 0.5 μ g 122.

10

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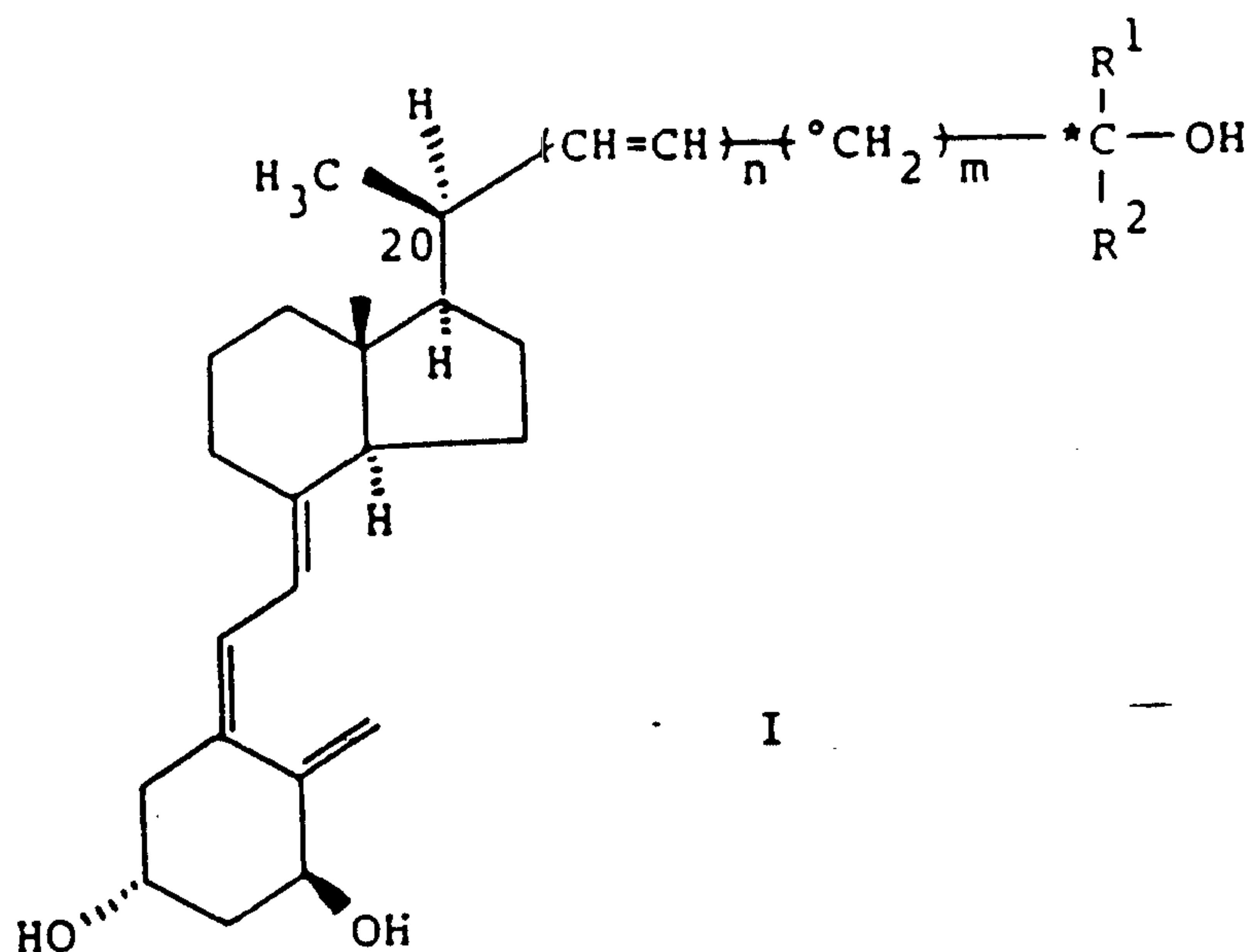
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Claims

1. A compound of Formula I



in which Formula: n is 0 or 1, m is 0 or an integer from 1 to 7, R^1 and R^2 , (which may be the same or different), stand for hydrogen or an unsubstituted C_1 - C_8 -hydrocarbyl, hydrocarbyl indicating the residue after removal of a hydrogen atom from a straight saturated hydrocarbon, a straight unsaturated hydrocarbon, a branched saturated hydrocarbon, a branched unsaturated hydrocarbon, a cyclic saturated hydrocarbon, or a cyclic unsaturated hydrocarbon, or, taken with the carbon bearing the hydroxyl group, (starred in Formula I), R^1 and R^2 , can form a saturated C_3 - C_8 carbocyclic ring, or an unsaturated C_3 - C_8 carbocyclic ring; or in which at least one of R^1 , R^2 and one of the m carbons designated by the " $^{\circ}$ ", is substituted with a hydroxyl group, or at least one chlorine or fluorine atom; and where one of the carbon atoms designated by the " $^{\circ}$ ", is substituted by one C_1 - C_2 alkyl group or by two C_1 - C_2 alkyl groups; and prodrugs or derivatives of said compounds of Formula I in which at least one hydroxy has been transformed into a masking group which is selected from the group consisting of -O-acyl, -O-glycosyl and a phosphate ester group; wherein said masking groups are hydrolysable in vivo.

2. A diastereoisomer of a compound according to claim 1 in pure form.
3. A mixture of diastereoisomers of a compound according to claim 1.

been transformed into a masking group which is selected from the group consisting of -O-acyl, -O-glycosyl and a phosphate ester group; wherein said masking groups are hydrolysable *in vivo*, which process comprises elaborating the side chain which is attached to C-20, or of an alcohol which is a protected form thereof, in said compound of Formula I, from 1(S),3(R)-bis-(tert-butyldimethylsilyloxy)-20(R)-formyl-9,10-secopregna-5(E),7(E),10(19)-triene, or its 5(Z) isomer, by one of the following processes:

(i) reducing said 1(S),3(R)-bis-(tert-butyldimethyl-silyloxy)-20(R)-formyl-9,10-secopregna-5(E),7(E),10(19)-triene to its corresponding 20(R)-hydroxymethyl derivative; converting the hydroxy group therein to a leaving group, displacing said leaving group with an organometallic reagent and desilylating the compound so-formed; or

(ii) reacting said 1(S),3(R)-bis-(tert-butyldimethyl-silyloxy)-20(R)-formyl-9,10-secopregna-5(E),7(E),10(19)-triene with a Wittig-type reagent, reacting the ketone so-formed with an organometallic reagent, or with a reducing agent and desilylating the compound so-formed; or

(iii) reacting said 1(S),3(R)-bis-(tert-butyldimethyl-silyloxy)-20(R)-formyl-9,10-secopregna-5(E),7(E),10(19)-triene with the carbanion which is derived from the sulphone $\text{PhS(O}_2\text{)CH}_2\text{-(}^\circ\text{CH}_2\text{)}_m\text{-C(OH)R}^1\text{R}^2$ by treatment with a base, reductively eliminating the product β -hydroxy-sulphone so-formed and desilylating the compound so-formed.

8. The process of claim 7(i), wherein said reducing reaction is carried out with sodium borohydride.

9. The process of claim 7(i) or claim 8, wherein said conversion of said hydroxy group is carried out by reaction with p-toluenesulphonylchloride and pyridine.

10. The process of claim 7(i), claim 8 or claim 9, wherein said displacement of said leaving group is carried out with $\text{BrMg-(}^\circ\text{CH}_2\text{)}_{m-1}\text{-C(OSiMe}_3\text{)R}^1\text{R}^2$ in the presence of Li_2CuCl_4 .

11. The process of claim 7(ii), wherein said Wittig-type reagent comprises $\text{Ph}_3\text{P}^+\text{-CH-C(O)-R}^2$.

12. The process of claim 7(ii) or claim 11, wherein said organometallic reagent comprises R^1MgBr .

13. The process of claim 7(ii) or claim 11, wherein said reducing agent comprises NaBH_4 .

14. The process of claim 7(iii), wherein said base comprises lithium diisopropylamide.
15. The process of claim 14, wherein two equivalents of said base are used.
16. The process of claim 7(iii), claim 14 or claim 15, wherein said reductive elimination is carried out with sodium amalgam.
17. The process of claim 16, further comprising the step of deriving the β -hydroxy group.
18. The process of claim 17, wherein said step of deriving said β -hydroxy group is carried out with benzoyl chloride and a base.
19. The process of any one of claims 7 to 18, further comprising the step of separating a diastereoisomer in pure form from the mixture of diastereoisomers so formed.
20. The process of claim 19, wherein said separation step is carried out by chromatography.
21. The process of any one of claims 7 to 18, wherein said compound so-formed is subjected to a triplet-sensitized photoisomerization to the 5(Z) isomer.
22. The process of any one of claims 7 to 18, wherein said desilylating step is carried out with tetrabutyl ammonium fluoride.
23. The process of any one of claims 7 to 18, wherein said compound so-formed further undergoes deprotection.
24. The process of any one of claims 7 to 23, further comprising the step of recovering said compound so-formed as a diastereoisomer in pure form.
25. The process of any one of claims 7 to 18 or 20 to 23, further comprising the step of recovering said compound so-formed as a mixture of diastereoisomers.
26. The process of any one of claims 7 to 24, wherein said compound so-formed is 1(S),3(R)-dihydroxy-20(S)-(4-hydroxy-4-methyl-1-pentyl)-9,10-secopregna-5(Z),7(E),10(19)-triene.
27. The process of any one of claims 7 to 24, wherein said compound so-formed is 1(S),3(R)-dihydroxy-20(S)-(5-ethyl-5-hydroxy-1-heptyl)-9,10-secopregna-5(Z),7(E),10(19)-triene.
28. The process of any one of claims 7 to 24, wherein said compound so-formed is 1(S),3(R)-dihydroxy-20(S)-(5-ethyl-5-hydroxy-hept-1(E)-en-1-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene.

29. A pharmaceutical composition containing an effective amount of at least one of the compounds of any one of claims 1 to 6, together with a pharmaceutically-acceptable, non-toxic carrier.

30. The pharmaceutical composition according to claim 29, for topical use containing from 0.1 to 100 $\mu\text{g/g}$ of said compound of any one of claims 1 to 6.

31. The pharmaceutical composition according to claim 29, in dosage unit form.

32. The dosage unit form of the pharmaceutical composition according to claim 31, containing from 0.025 to 100 μg for oral and parenteral formulations of said compound of any one of claims 1 to 6.

33. The use of at least one of the compounds of any one of claims 1 to 6, for the preparation of a pharmaceutical composition for the treatment and/or prophylaxis of autoimmune diseases, diabetes mellitus, hypertension, acne, alopecia, skin aging, photoageing, inflammatory diseases, rheumatoid arthritis and asthma, as well as diseases which are characterized by abnormal cell differentiation and/or cell proliferation and/or imbalance in the immune system.

34. The use of at least one of the compounds of any one of claims 1 to 6, for the treatment and/or prophylaxis of autoimmune diseases, diabetes mellitus, hypertension, acne, alopecia, skin aging, photoageing, inflammatory diseases, rheumatoid arthritis and asthma, as well as diseases which are characterized by abnormal cell differentiation and/or cell proliferation and/or imbalance in the immune system.

35. The use of at least one of the pharmaceutical compositions of any one of claims 29 to 32, for the treatment and/or prophylaxis of autoimmune diseases, diabetes mellitus, hypertension, acne, alopecia, skin aging, photoageing, inflammatory diseases, rheumatoid arthritis and asthma, as well as diseases which are characterized by abnormal cell differentiation and/or cell proliferation and/or imbalance in the immune system.

36. The use of at least one of the compounds of any one of claims 1 to 6 or of at least one of the pharmaceutical compositions of any one of claims 29 to 32, for the treatment or prophylaxis of cancer.

37. The use of at least one of the compounds of any one of claims 1 to 6 or of at least one of the pharmaceutical compositions of any one of claims 29 to 32, for the treatment or prophylaxis of psoriasis.

