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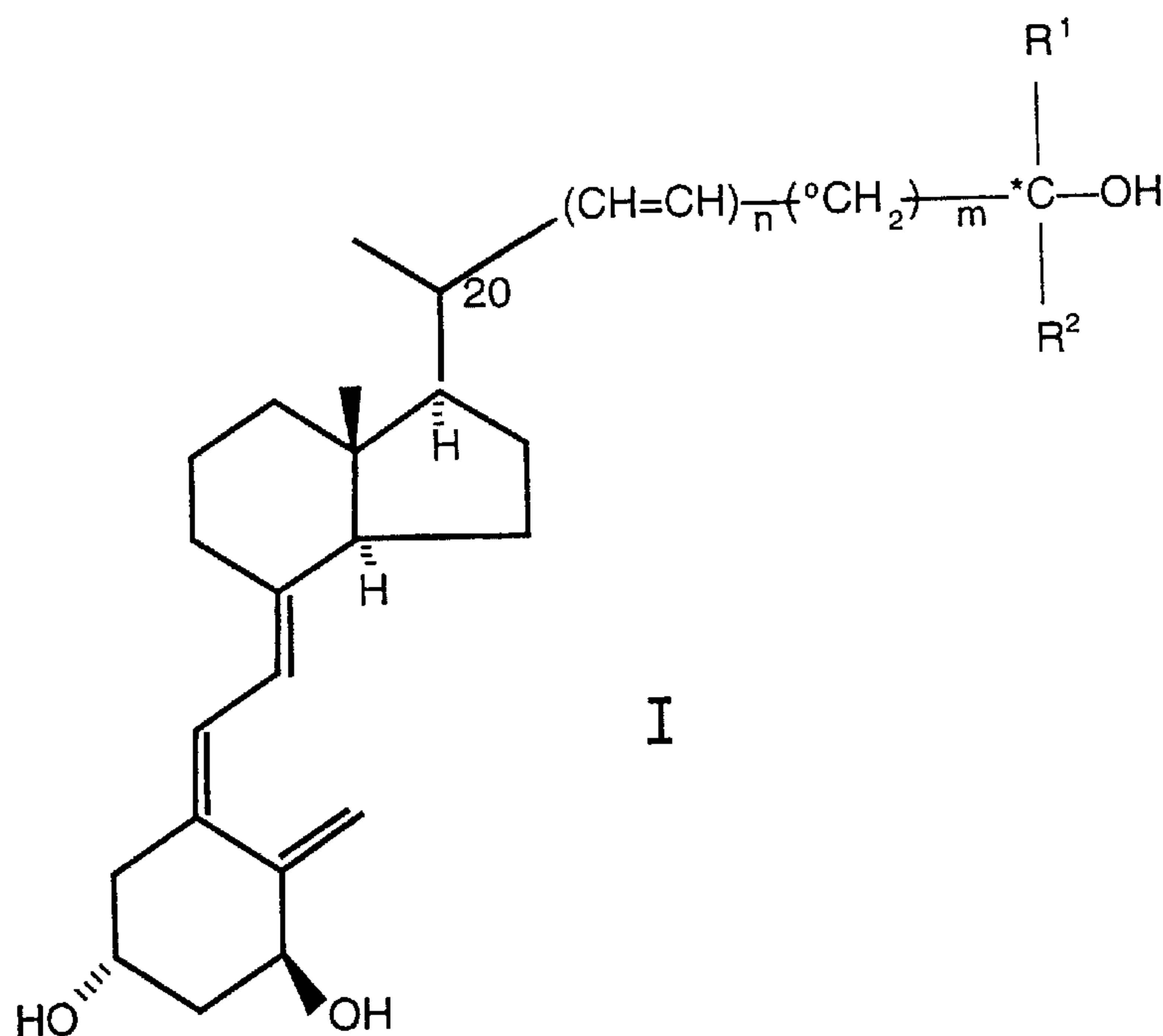
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(54) Title: VITAMIN D ANALOGUES



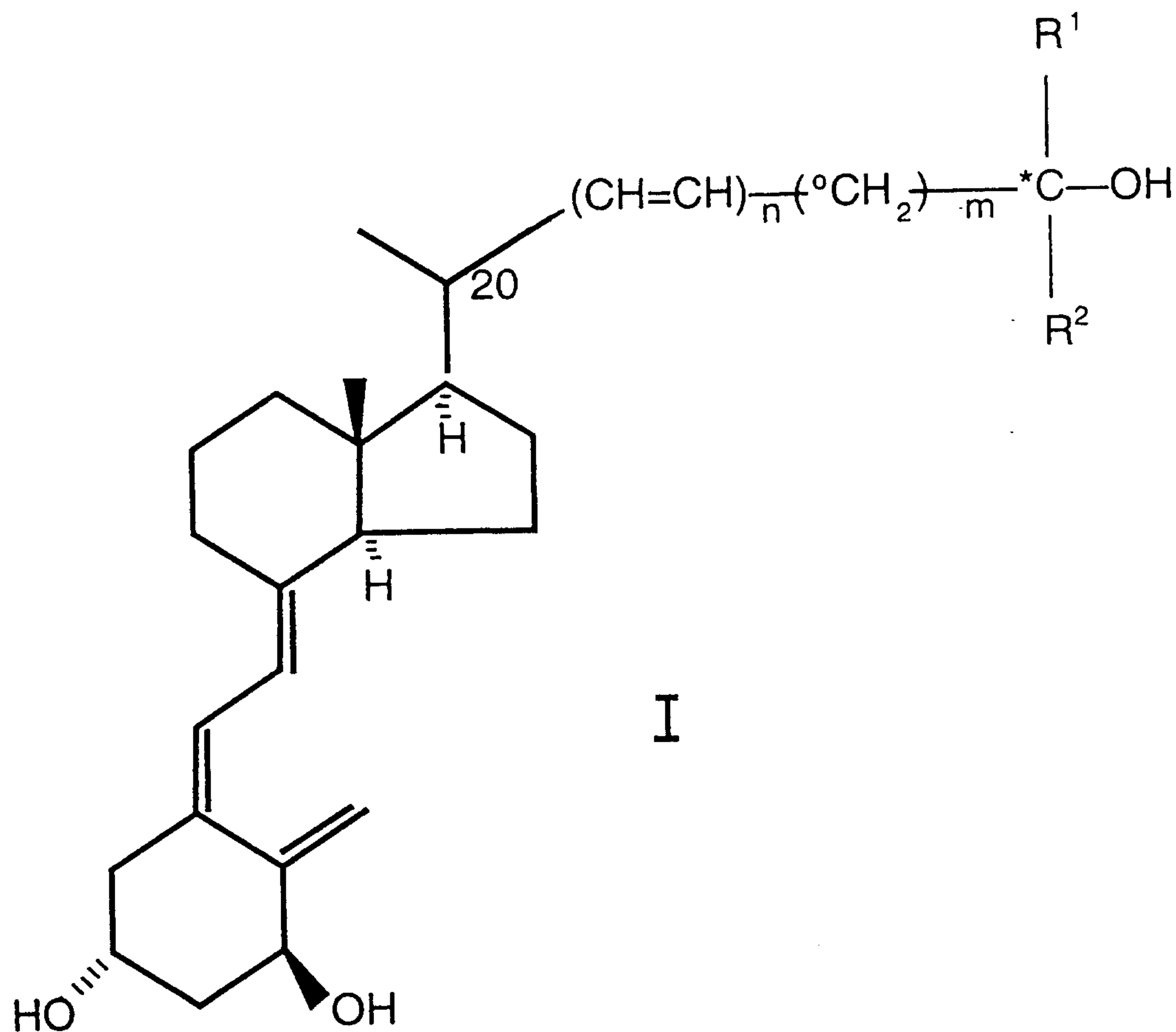
(57) **Abrégé/Abstract:**

The present invention provides compounds of the Formula I (see formula I) in which Formula I, n, m, R¹ and R² are as specifically defined in the specification. Derivatives of the compounds of Formula I are also provided in which at least one hydroxy has been transformed into a masked -O-acyl group, or a masked -O- glycosyl group or a masked phosphate ester group, the masked group being hydrolyzable in vivo. Other prodrugs thereof are also provided. Such compounds find use in both human and veterinary practice in the treatment or prophylaxis of autoimmune diseases, hypertension, acne, alopecia, skin ageing, imbalance in the immune system, inflammatory diseases, as well as diseases characterized by abnormal cell differentiation and/or cell proliferation.



ABSTRACT

The present invention provides compounds of the Formula I



in which Formula I, n , m , R^1 and R^2 are as specifically defined in the specification. Derivatives of the compounds of Formula I are also provided in which at least one hydroxy has been transformed into a masked -O-acyl group, or a masked -O-glycosyl group or a masked phosphate ester group, the masked group being hydrolyzable in vivo. Other prodrugs thereof are also provided. Such compounds find use in both human and veterinary practice in the treatment or prophylaxis of autoimmune diseases, hypertension, acne, alopecia, skin ageing, imbalance in the immune system, inflammatory diseases, as well as diseases characterized by abnormal cell differentiation and/or cell proliferation.

(a) **TITLE OF THE INVENTION**

Vitamin D Analogues

(b) **TECHNICAL FIELD TO WHICH THE INVENTION RELATES**

5 This invention relates to a hitherto unknown class of compounds which show 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.

15 (c) **BACKGROUND ART**

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.

25 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, e.g., 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 $1,25(\text{OH})_2\text{D}_3$ was 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). Finally, the fact that topical application of $1,25(\text{OH})_2\text{D}_3$ reduced the size of sebaceous glands in the ears of male Syrian hamsters suggested that this compound might be useful for the treatment of acne (Mally, V.L. et al., the Tricontinental Meeting for Investigative Dermatology, Washington, 1989).

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 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, and a 24-hydroxy group and in which carbon atoms 25,26 and 27 are incorporated in a three membered ring, has been found to be a potent inducer of cell differentiation and inhibitor of cell proliferation which showed only moderated activity on calcium metabolism in vivo [Binderup, L. and Bramm, E., Biochemical Pharmacology 37, 889-895 (1988)]. However, this selectivity was not paralleled by in vitro studies, which showed that MC 903 bound equally as well as $1,25(\text{OH})_2\text{D}_3$ to the intestinal vitamin D receptor. It may therefore be that the low in vivo activity on calcium metabolism of MC 903 was due to a rapid metabolism of the compound, thus limiting the potential of this compound for systemic use.

24-Homo-1,25-dihydroxyvitamin D_3 and 26-homo-1,25-dihydroxyvitamin D_3 (together with their 22,23-didehydroanalogues) [Ostrem, V.K.; Tanaka, Y.; Prahl, J.;

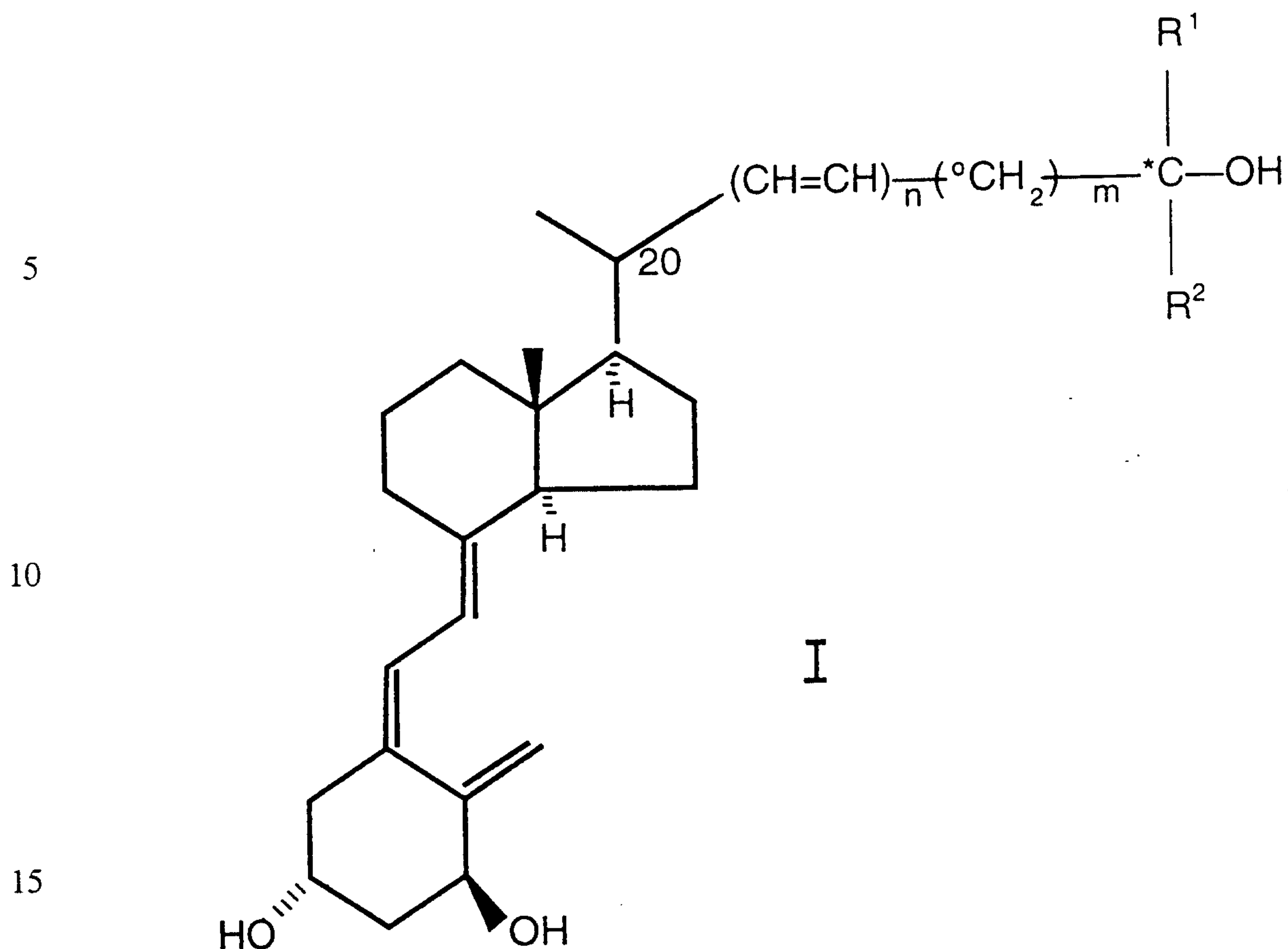
DeLuca, H.F.; and Ikekawa, N.; Proc. Natl. Acad. Sci. USA 84, 2610-14 (1987)] have been claimed to have the same binding affinity as $1,25(\text{OH})_2\text{D}_3$ to both the rat and chicken intestinal receptor and the receptor in a human myeloid leukemia cell line (HL-60), and yet to be 10-fold more potent than $1,25(\text{OH})_2\text{D}_3$ in inducing differentiation of HL-60 cells in vitro. In vivo, these compounds were respectively "significantly less potent" and "more potent" than $1,25(\text{OH})_2\text{D}_3$ in calcium metabolism assessments.

26,27-Dimethyl- $1\alpha,25$ -dihydroxyvitamin D_3 has been synthesized, but the published information regarding its biological activities was 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- $1\alpha,25$ -dihydroxyvitamin D_3 was also reported by these authors; in this case it was reported as having "almost no vitamin D activity" (i.e. calcium metabolism effects) while being 10-fold more potent than $1,25(\text{OH})_2\text{D}_3$ 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.

(d) DESCRIPTION OF THE INVENTION

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



in which Formula, n is 2 or 3, m is 0 or an integer from 1 - 4; R^1 and R^2 (which may be the same or different) stand for hydrogen or 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 cyclic unsaturated hydrocarbon, or taken together 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; in addition, at least one of R^1 , R^2 and one of the " m " carbons designated by the " $^\circ$ " being unsubstituted or being substituted with at least one chlorine or fluorine atom; and finally one of the carbons designated " $^\circ$ " being unsubstituted or being substituted by at least one C_1 - C_2 alkyl group; and derivatives of the compounds of Formula I in which at least one hydroxy has been transformed into a masked -O-acyl

group, or a masked -O-glycosyl group or a masked phosphate ester group, the masked group being hydrolyzable *in vivo*; and other prodrugs thereof.

By two variants of this aspect of the invention, such compound is in the form of a diastereoisomer, in pure form, or in the form of a mixture of diastereoisomers.

Specific species variants of the compounds of aspects of this invention include:

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

b) 1(S),3(R)-Dihydroxy-20-(5'-ethyl-5'-hydroxy-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E)-10(19)-triene;

c) 1(S),3(R)-Dihydroxy-20-(6'-hydroxy-hexa-1'(E),-3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene;

d) 1(S),3(R)-Dihydroxy-20-(5'-cyclopropyl-5'-hydroxy-penta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),-7(E),10(19)-triene (5'(R) and 5'(S) isomers); and

e) 1(S),3(R)-Dihydroxy-20-(6'-hydroxy-6'-methyl-hepta-1'(E),3'(E)-dien-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 R¹ and R², when taken separately, (apart from hydrogen) include, but are not limited to, methyl, trifluoromethyl, ethyl, vinyl, normal-, iso- and cyclopropyl, and 1-methylvinyl.

Examples of R¹ and R², when taken together, include di-, tri-, tetra- and penta-methylene.

As can be seen from Formula I, the compounds of aspects of the invention include diastereoisomeric forms (e.g., E or Z configuration of a side chain double bond; R or S configuration at C-20 and at the starred carbon atom depending on the meanings of R¹ and R²). The compounds of aspects of this invention in their various variants cover all these diastereoisomers in pure form and also mixtures of diastereoisomers. It should be noted, however, that the investigations of aspects of the

present invention indicate a notable difference in activity between the stereoisomeric forms. In addition, derivatives of the compounds 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 other aspects of the invention, (namely,
5 "bioreversible derivatives or pro-drugs of the compounds of Formula I").

The term "bioreversible derivatives or prodrugs of the compounds 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 masked by being transformed into a masked -O-acyl group, or a masked -O-glycosyl group or a masked phosphate ester group, such
10 masked groups being hydrolyzable *in vivo*.

Also within the scope of various aspects of this invention is another type of prodrug of the compounds 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
15 hydroxylation after administration to the patient.

The compounds of various aspects of the present invention are distinguished structurally from all vitamin D analogues which have been reported to have potent effects on cell differentiation/proliferation by the presence of a conjugated diene or triene moiety in the side chain.

Corresponding compounds which have a saturated side chain or an isolated double bond (22,23-didehydro-derivatives) have been disclosed in published International Patent Application No. PCT/DK89/00079, international filing date 7th April, 1989, which corresponds to U.S. Patent No. 5,206,229, patented Apr. 27, 1993 and (for one pair of examples) in the Ostrem et al., reference discussed above, but
20 none of these disclosures suggest processes for the incorporation of a conjugated polyene system into the side chain. The studies of the present invention have now opened up general routes to such polyene systems, and it has been surprisingly found that this type of functionality has an advantageous biological significance. Thus a particular compound of Formula I of aspects of the present invention, when compared
25

to the corresponding compound in which all, or all but the 22,23-double bond, are saturated, is observed to show one or more of the following advantages:

- (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 potent effects on the production and action of interleukins; and
- (d) a greater selectivity in favour of the effects on interleukin production and action contra the effects on calcium metabolism.

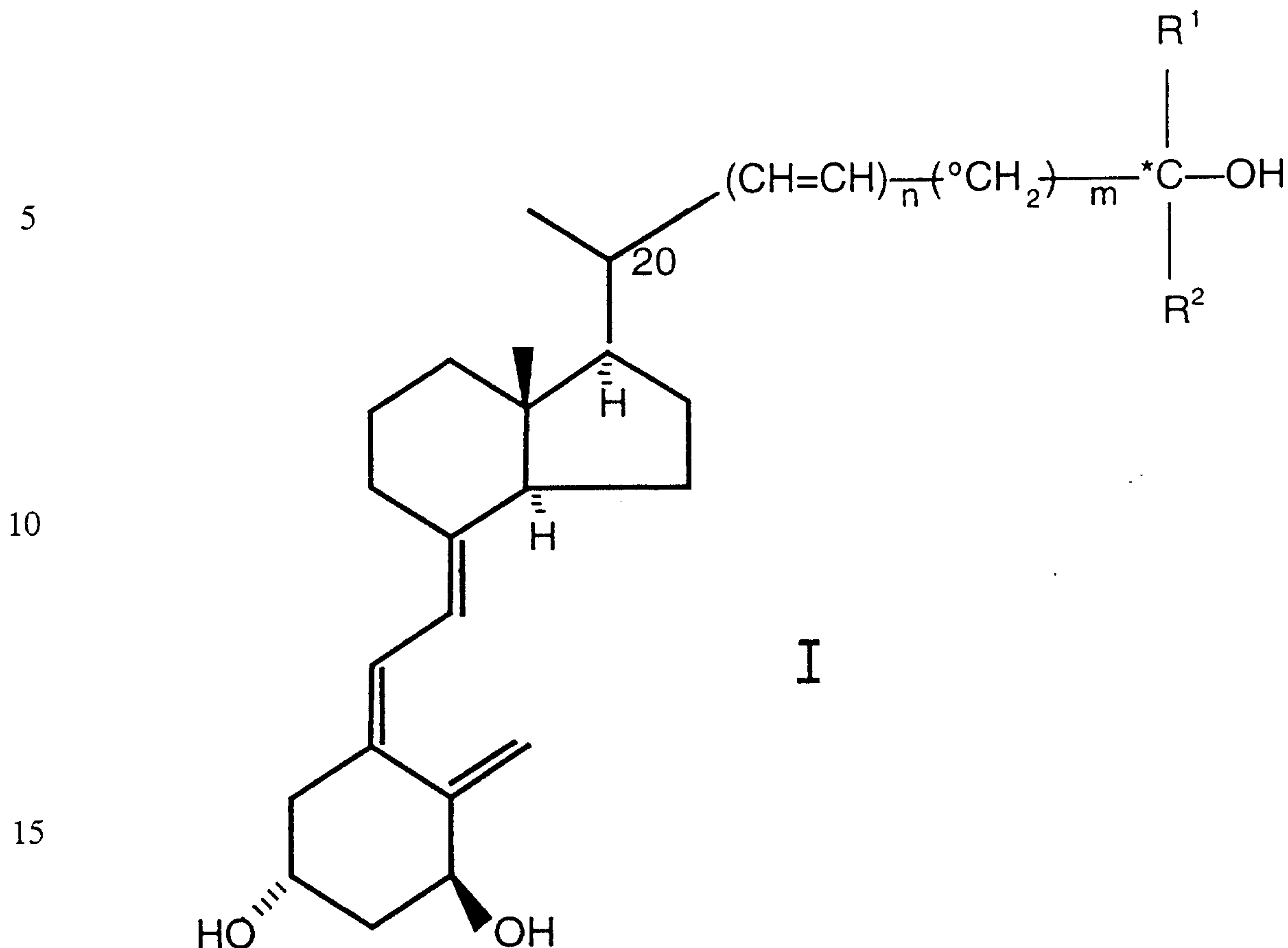
An additional advantage conferred on the compounds of the various aspects of the present invention of Formula I, by the presence of the polyene moiety results from the more restricted conformational freedom of the side chain: the compounds of Formula I of aspects of the present invention are more readily obtained in crystalline form than the corresponding side chain saturated or partially saturated analogues.

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

The compounds of aspects of the present 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.

By another aspect of this invention, a process is provided for producing a compound in Formula I

7 a



in which Formula, n is 2 or 3, m is 0 or an integer from 1 - 4; R^1 and R^2 (which may be the same or different) stand for hydrogen or 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 together 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; in addition, at least one of R^1 , R^2 and one of the "m" carbons designated by the "°" being unsubstituted or being substituted with at least one chlorine or fluorine atom; and finally one of the carbons designated "°" being unsubstituted or being substituted by at least one C_1 - C_2 alkyl group; and derivatives of

7 b

the compounds of Formula I in which at least one hydroxy has been transformed into a masked -O-acyl group, or a masked -O-glycosyl group or a masked phosphate ester group, the masked group being hydrolyzable in vivo; and other prodrugs thereof, or an analogue thereof, which process comprises: a) elaborating the side chain attached to C-20 in a compound of Formula I from the 20(R) or 20(S) isomers of 1(S),3(R)-bis-(tert-butyl dimethylsilyloxy)-20-formyl-9,10-secopregna-5(E),7(E),10(19)-triene, or 1(S),3(R)-bis-(tert-butyl dimethylsilyloxy)-20-(2'-formyl-1'(E)-ethen-1' yl)-9,10-secopregna-5(E),7(E),10(19)-triene, or their corresponding 5(Z) isomers, either (i) by reaction with a Wittig-type reagent followed by reaction of the resulting ester with an organometallic reagent or a reducing agent; or (ii) by reaction with a Wittig-type reagent followed by reaction of the resulting ketone with a reducing agent; or (iii) by reaction with the carbanion 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 base followed by reductive elimination of the product β -hydroxy-sulphone; and then disilylating the compound from step (a), e.g., with tetrabutylammonium fluoride.

By one variant, the Wittig-type reagent used in step a) (i) comprises $\text{Ph}_3\text{P}^+\text{-CH}^-\text{-CH=CH-COOCH}_3$.

By another variant thereof, the organometallic reagent used in step a)(i) is R^1L_1 .

By yet another variant, the reducing agent used in step a)(i) comprises $\text{I-Bu}_2\text{AlH}$.

By still another variant thereof, the Wittig-type reagent used in step a)(ii) comprises $\text{Ph}_3\text{P}^+\text{-CH}^-\text{-C(O)-R}^2$.

By a still further variant thereof, the reducing agent used in step a)(ii) comprises NaBH_4 .

By another variant thereof, the base used in step a) (iii) comprises two equivalents of lithium di-isopropylamide.

By yet another variant thereof, the reductive elimination in step a)(iii) is carried out by using sodium amalgam.

7 c

By a still further variant thereof, the second step in a)(iii) includes derivatisation of the β -hydroxy group, e.g., where the derivatisation of the β -hydroxy group is carried out with benzoyl chloride and a base.

5 By yet a further variant thereof, the process includes the step of separating a pure diastereoisomer compound from a mixture of diastereoisomers from step (a), e.g., by chromatography.

By a still further variant thereof, the process includes the step of subjecting the compound from step (a) to a triplet-sensitized photoisomerisation to the 5Z isomer.

10 By variants of any one of the above aspects or variants, the process provides a mixture of diastereoisomers of the compound; or provides a diastereoisomer of the compound in pure form by carrying out the further step of separation, e.g., by chromatography.

By specific variants thereof, the process provides for the preparation of:

15 1(S),3(R)-dihydroxy-20-(5'-hydroxy-5'-methyl-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E)-,10(19)-triene; or 1(S),3(R)-dihydroxy-20-(5'-ethyl-5'-hydroxy-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E)-,10(19)-triene; or 1(S),3(R)-dihydroxy-20-(6'-hydroxy-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene; or 1(S),3(R)-dihydroxy-20-(5'-cyclopropyl-5'-hydroxy-penta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5-(Z),7(E),10(19)-triene (5'(R) and 5'(S) isomers); or
20 1(S),3(R)-dihydroxy-20-(6'-hydroxy-6'-methyl-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7-(E),10(19)-triene.

By yet a further specific aspect of this invention, a process is provided for producing the 20(R) and 20(S) isomers of 1(S),3(R)-dihydroxy-20-(6'-hydroxy-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E)-10(19)-triene, the process
25 comprising treating the 20(R) and 20(S) isomers of 1(S),3(R)-dihydroxy-20-(3'-cyclopropyl-3'-hydroxyprop-1'(E)-en-1'-yl)-9,10-secopregna-5(Z),7(E)-10(19)-triene with a carboxylic anhydride, and then subjecting the product to basic hydrolysis.

7 d

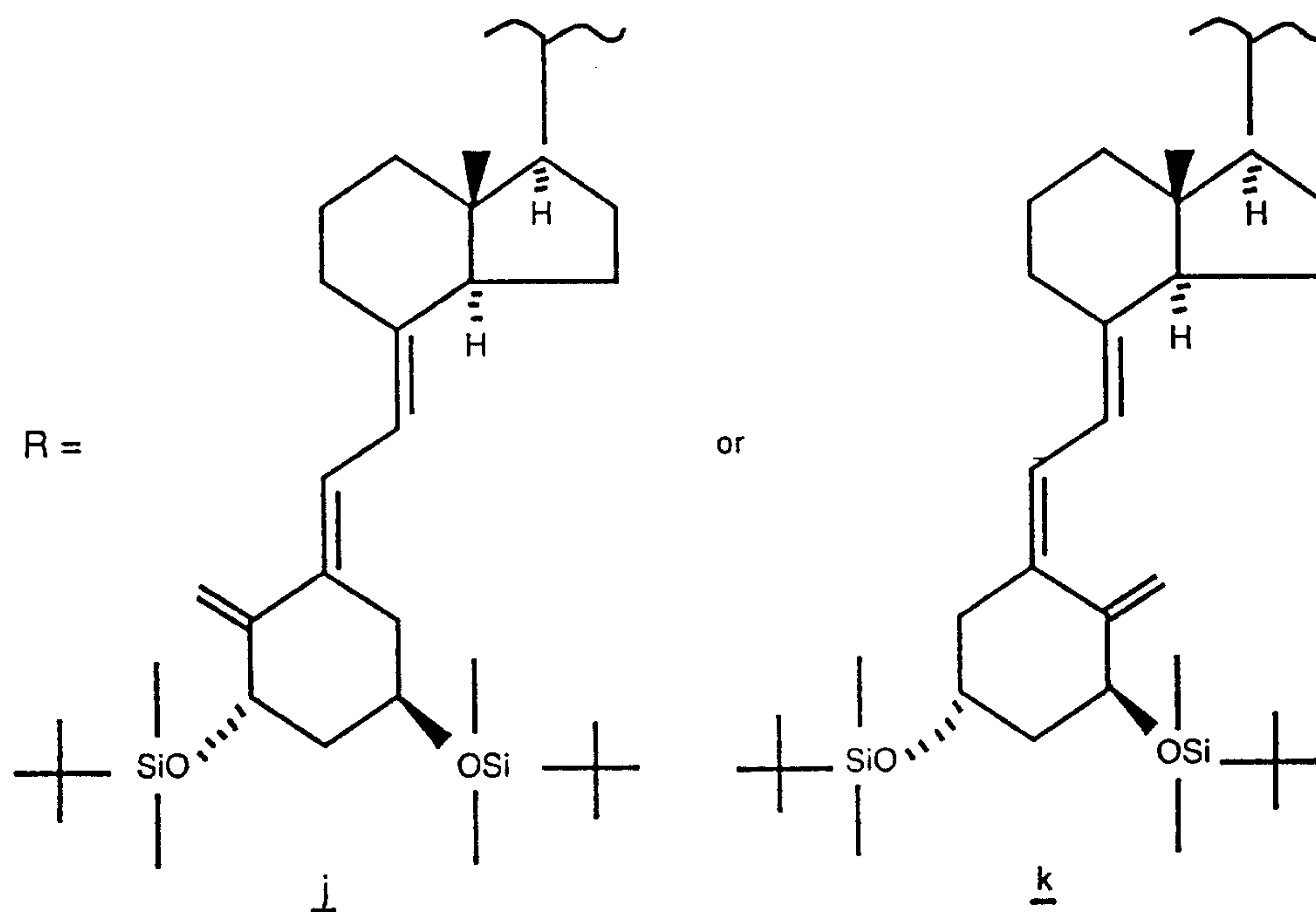
By one variant thereof, the carboxylic anhydride comprises trifluoroacetic anhydride.

By yet another variant thereof, the basic hydrolysis is carried out with alcoholic alkali hydroxide.

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

The exemplified key intermediates of types 2 and 3 are listed in Table 1.

In the Schemes, the following abbreviations are used:

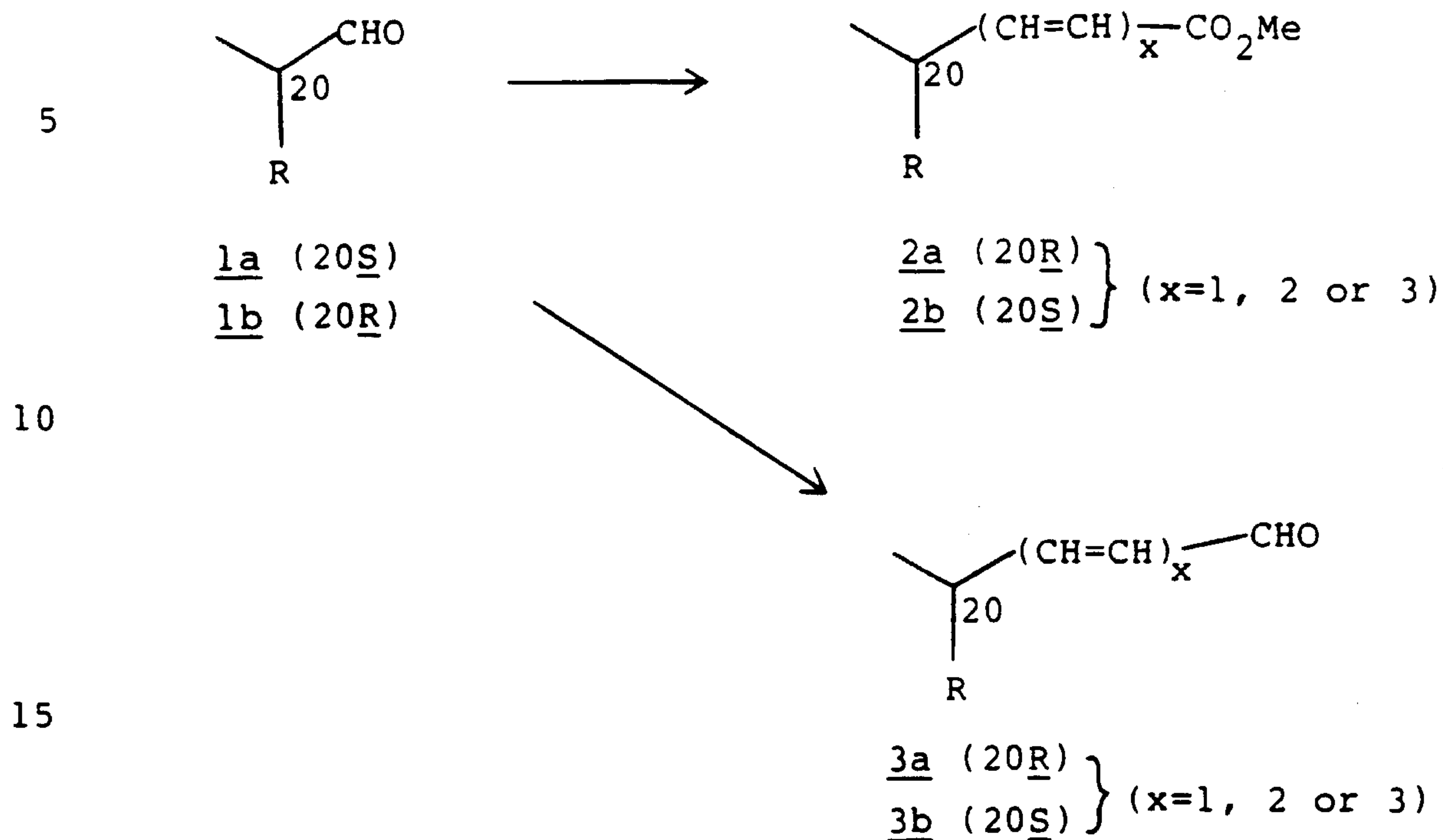


7 e

In the Notes to Schemes, appropriate aqueous work-up steps are implicit. The absolute configuration at C-20 can be either R or S. For an explanation of the expression "side chain fragment", see the following text.

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Scheme 1Notes to Scheme 1

20

1j $\rightarrow$ 1k:

h ν - anthracene (toluene or CH₂Cl₂ containing trace Et₃N).

1 $\rightarrow$ 2:

Ph₃⁺P⁻CH-(CH=CH)_{x-1}-CO₂Me (heat in solvent e.g. toluene or CHCl₃).

25 2 $\rightarrow$ 3:

(i) i-Bu₂AlH (THF); (ii) pyridinium dichromate (CH₂Cl₂).

3 (x=1) $\rightarrow$ 2 (x=3): Ph₃⁺P⁻CH-(CH=CH)-CO₂Me (heat in solvent e.g. CHCl₃).

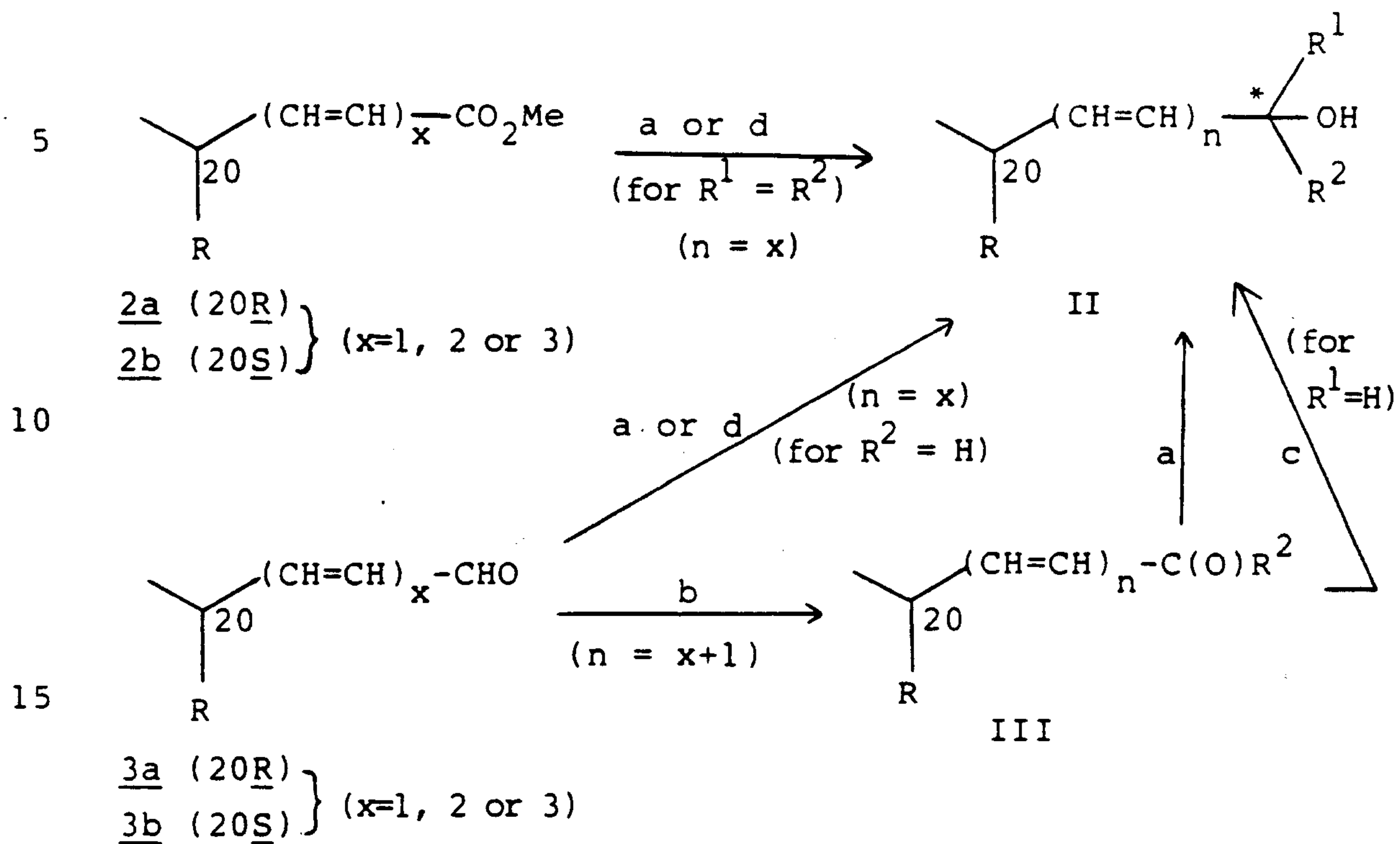
1 $\rightarrow$ 3 (x=2)

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3(x=1) $\rightarrow$ 3(x=3)

$$\begin{array}{c} \text{O} \\ || \\ \text{P} \end{array} \text{---} \text{CH}=\text{CH}-\text{CH}=\text{N}-\text{C}_6\text{H}_{11}$$
 (i) (EtO)₂P(=O)CH=CH-CH=N-C₆H₁₁, LiN(Prⁱ)₂;
 (ii) hydrolysis during flash chromatography

35

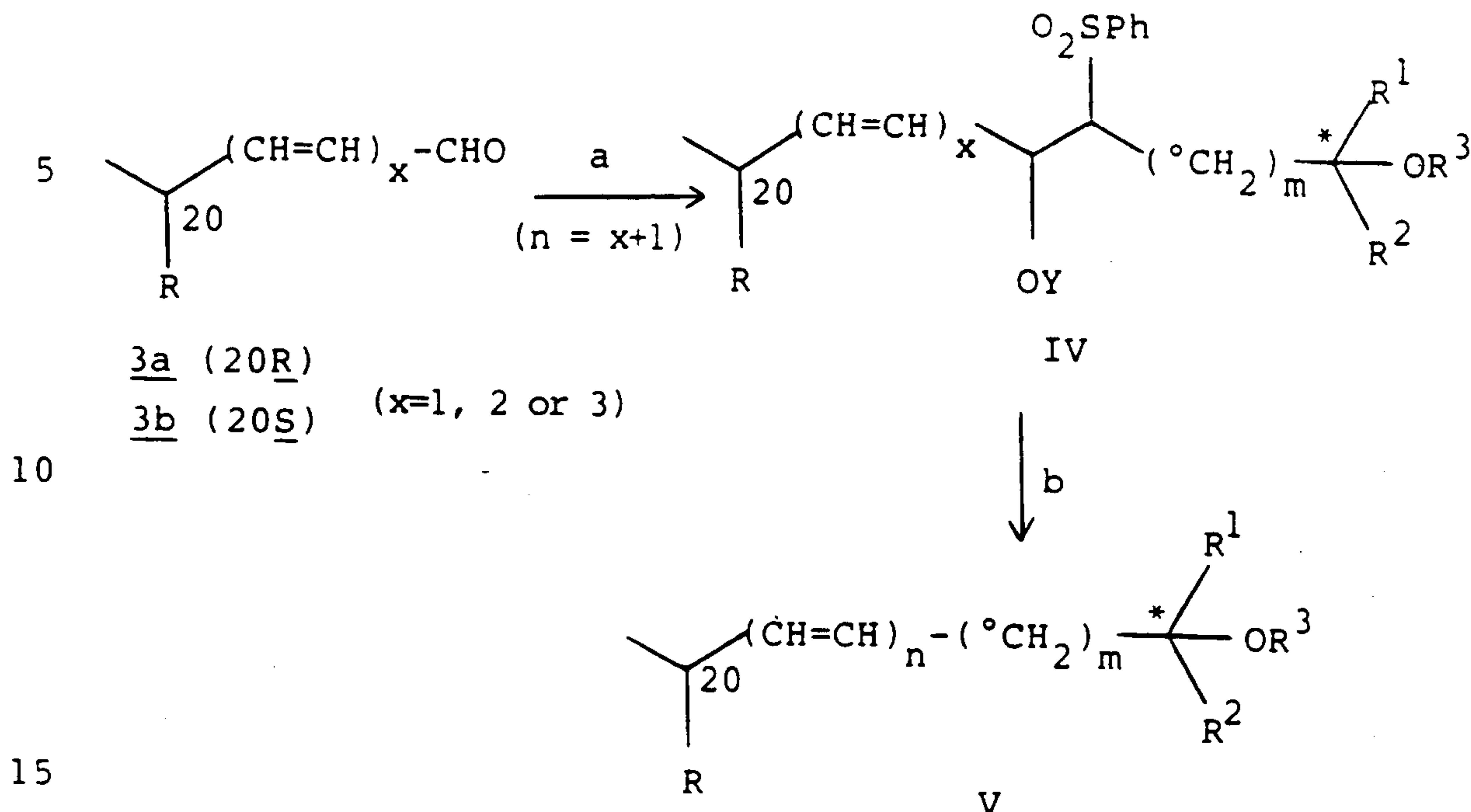
Scheme 2Notes to Scheme 2

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a. R^1MgBr (R^1MgI) or R^1Li (THF);b. Metallated derivative or ylide (A') from side chain fragment A (anhydrous solvent or phase transfer conditions);25 c. $\text{NaBH}_4\text{-CeCl}_3$ (THF-MeOH).d. for $\text{R}^1 = \text{R}^2 = \text{H}$: $i\text{-Bu}_2\text{AlH}$ (THF).

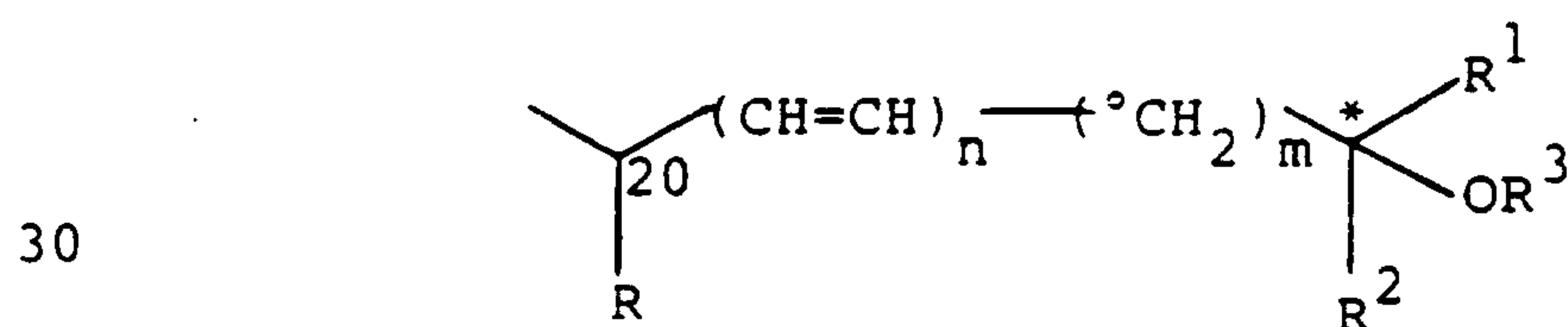
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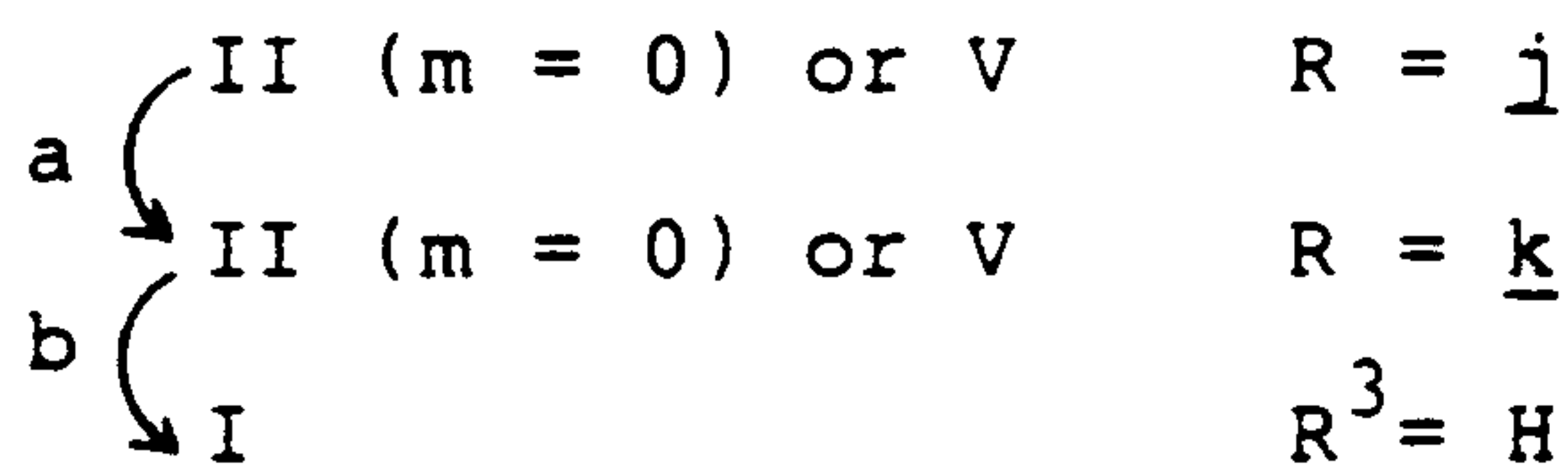
Scheme 3Notes to Scheme 3

- 20 a. (i) Metallated derivative (B') of side chain fragment B (THF); (ii) Optional derivatisation of the intermediate alkoxide (Y=M) or the isolated Y=H compound;
- b. Reductive elimination mediated by e.g. Na-Hg [for Y=H, MeC(O)-, PhC(O)- or MeS(O₂)-]

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Scheme 4

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Notes to Scheme 4

R^3 = H or alcohol protective group

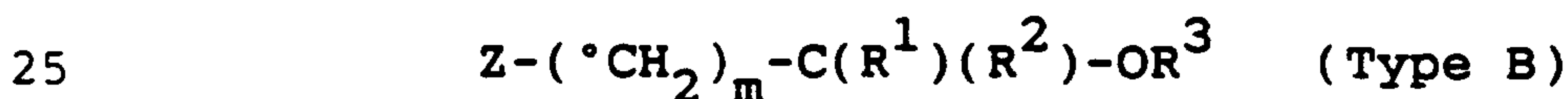
- a. anthracene - $h\nu$ (toluene or CH_2Cl_2 containing trace
 5 Et_3N);
 b. (i) $n-Bu_4N^+F^-$ (THF) or HF ($MeCN-H_2O$);
 (ii) any necessary reaction (sequence) for deprotecting
 $OR^3 \rightarrow OH$.

10

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

All these types of reactions are well known in the art of carbon-carbon bond formation in synthetic organic chemistry.

20 In general, the side chain fragments have the structure:



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

For type A, $Z = Ph_3P^+-CH_2-$ or $Z = Q_2P(O)-CH_2-$, where Q = methoxy, ethoxy or phenyl, and the corresponding A' has
 $Z = Ph_3P^+-CH^-$ or $Q_2P(O)-CHM-$ (M = metal e.g. Li).

35 For type B, $Z = PhS(O_2)-CH_2-$, and the corresponding B' has $Z = PhS(O_2)-CHM-$, where M = metal, e.g. Li.

R^3 is optionally hydrogen or an alcohol protective group such as tri(loweralkyl)silyl or THP. In the case

where $R^3 = H$ in B, then $R^5 = M$ ($M = \text{metal, e.g., XMg or Li}$) in the derived B'.

Fragments of type A, A' or B are known compounds or are readily available, as described, for example, in international patent application No. PCT/DK89/00079, international filing date 7th April, 1989, which corresponds to U.S. Patent No. 5,206,229 patented Apr. 27, 1993. Some Examples are listed in Tables 2 and 3.

Some of these side chain fragments are converted (see Preparations and Examples) to the appropriate compounds of Formula I via the intermediates indicated in the Schemes. The intermediates are specified in Table 4 and the exemplified compounds of Formula I in Table 5.

Specific compounds of Formula I may also be produced by special reactions. For example, compound 112 (Table 5) is obtained by isomerisation of MC 903 by treatment with trifluoroacetic anhydride, followed by saponification.

Table 1: Exemplified Key intermediates prepared from Compounds 1a or 1b

(Scheme 1)

	Compound Number	Formula	
		x	Configuration of side chain polyene *
5	2aj	1	<u>E</u>
	2ak	1	<u>E</u>
	2aj	2	<u>E,E</u>
	2aj; isomer A	3	<u>E,E,E</u>
	2aj; isomer B	3	<u>E,Z,E</u>
10	3aj	1	<u>E</u>
	2bj	2	<u>E,E</u>
	2ak	3	<u>E,E,E</u>

* Reading from left to right.

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

Compound Number ⁺	R ²	Z
5 4	-CHMe ₂	Ph ₃ [⊕] PCH [⊖]
5 5 y=1	$\overline{\text{CH}(\text{CH}_2)_y\text{CH}_2}$	Ph ₃ [⊕] PCH [⊖]
5 5 y=2		
5 5 y=3		
5 5 y=4		
10 6	$\overline{\text{CCl}-\text{CH}_2-\text{CH}_2}$	Ph ₃ [⊕] PCH [⊖]
7	$\overline{\text{CF}-\text{CH}_2-\text{CH}_2}$	(EtO) ₂ P(O)CH ₂
8	-CMe ₃	Ph ₃ [⊕] PCH [⊖]
9	-CHEt ₂	Ph ₃ [⊕] PCH [⊖]
10	-CH(n-Pr) ₂	Ph ₃ [⊕] PCH [⊖]

15 ⁺ As referred to in the Preparations

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Table 3: Some Specific Side Chain Fragments (Type B)
[PhS(O₂)CH₂-(°CH₂)_m-C(R¹)(R²)OR³]

Compound Number	+	† m	Formula		
			R ¹	R ²	R ³
5		1	Me	Me	H
		1	Et	Et	H
		1	-(CH ₂) ₂ -		THP
		2	Et	Et	H
		3	Me	Me	H
10		4	Me	Me	H
	++	1 (CH(Me))	Me	Me	H
	**	1 (CH(Me))	Me	Me	H

+ As referred to in the Preparations
++ S-Form
** R-Form
† Unsubstituted CH₂ unless otherwise indicated by specifying an alternative meaning of "(°CH₂)".

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Table 4: Compounds of Schemes 2-4 which are Intermediates in the Preparation of Compounds I of Scheme 4

5	Com- pound Number (R=j or k)	Type	Scheme	n	m ⁺	R ¹	R ²	R ³	Config- uration of the side chain poly- ene *	Con- fig- ura- tion at C-20
10	101j	III	2	2	-	-	$\overline{\text{CHCH}_2\text{CH}_2}$	-	<u>E, E</u>	<u>R</u>
	102j	II	2	} 2	-	H	$\overline{\text{CHCH}_2\text{CH}_2}$	-	<u>E, E</u>	<u>R</u>
	103j	II	2		-	H	$\overline{\text{CHCH}_2\text{CH}_2}$	-	<u>E, E</u>	<u>R</u>
	102k	II	4	} 2	-	H	$\overline{\text{CHCH}_2\text{CH}_2}$	-	<u>E, E</u>	<u>R</u>
	103k	II	4		-	H	$\overline{\text{CHCH}_2\text{CH}_2}$	-	<u>E, E</u>	<u>R</u>
15	104j	II	2	2	-	Me	Me	-	<u>E, E</u>	<u>R</u>
	104k	II	4	2	-	Me	Me	H	<u>E, E</u>	<u>R</u>
	105j	II	2	2	-	Et	Et	-	<u>E, E</u>	<u>R</u>
	105k	II	4	2	-	Et	Et	H	<u>E, E</u>	<u>R</u>
	106j	II	2	3	-	Me	Me	-	<u>E, E, E</u>	<u>R</u>
20	107j	V	3	2	1	Me	Me	H	<u>E, E</u>	<u>R</u>
	107k	II	4	2	1	Me	Me	H	<u>E, E</u>	<u>R</u>
	113j	II	2	2	-	Me	Me	-	<u>E, E</u>	<u>S</u>
	113k	II	4	2	-	Me	Me	H	<u>E, E</u>	<u>S</u>
	114j	II	2	2	-	Et	Et	-	<u>E, E</u>	<u>S</u>
25	114k	II	4	2	-	Et	Et	H	<u>E, E</u>	<u>S</u>
	117j	II	2	2	-	H	H	-	<u>E, E</u>	<u>S</u>
	117k	II	4	2	-	H	H	H	<u>E, E</u>	<u>S</u>
	119j	II	2	2	-	Pr	Pr	-	<u>E, E</u>	<u>R</u>
	119k	II	4	2	-	Pr	Pr	H	<u>E, E</u>	<u>R</u>

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Table 4 (continued):

5	Com- pound Number (R=j or k)	Type	Scheme	n	m [†]	R ¹	R ²	R ³	Config- uration of the side chain poly- ene *	Con- fig- ura- tion at C-20
10	121j	II	2	2	-	H	H	-	<u>E</u> , <u>E</u>	<u>R</u>
	121k	II	4	2	-	H	H	H	<u>E</u> , <u>E</u>	<u>R</u>
	123k	II	2	1	-	H	H	-	<u>E</u>	<u>R</u>
	124k	II	2	3	-	Me	Me	-	<u>E</u> , <u>E</u> , <u>E</u>	<u>R</u>
	126k	II	2	3	-	Et	Et	-	<u>E</u> , <u>E</u> , <u>E</u>	<u>R</u>
15	128k	II	2	3	-	H	H	-	<u>E</u> , <u>E</u> , <u>E</u>	<u>R</u>

† Note as for Table 3

* Reading from left to right

NB 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.

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Table 5: Exemplified Compounds I

5	Compound Number	m^+	n	R^1	R^2	Config-uration of side chain polyene*	Con-fig-uration at C-20
10	108 } 109 }	0	2	H	$\overline{-CHCH_2}CH_2$	<u>E</u> , <u>E</u>	<u>R</u>
	110	0	2	Me	Me	<u>E</u> , <u>E</u>	<u>R</u>
	111	0	2	Et	Et	<u>E</u> , <u>E</u>	<u>R</u>
	112	1	2	H	H	<u>E</u> , <u>E</u>	<u>R</u>
	115	0	2	Me	Me	<u>E</u> , <u>E</u>	<u>S</u>
	116	0	2	Et	Et	<u>E</u> , <u>E</u>	<u>S</u>
	118	0	2	H	H	<u>E</u> , <u>E</u>	<u>S</u>
	120	0	2	Pr	Pr	<u>E</u> , <u>E</u>	<u>R</u>
	122	0	2	H	H	<u>E</u> , <u>E</u>	<u>R</u>
	125	0	3	Me	Me	<u>E</u> , <u>E</u> , <u>E</u>	<u>R</u>
20	127	0	3	Et	Et	<u>E</u> , <u>E</u> , <u>E</u>	<u>R</u>
	129	0	3	H	H	<u>E</u> , <u>E</u> , <u>E</u>	<u>R</u>
	130	1	2	H	H	<u>E</u> , <u>E</u>	<u>S</u>
	131 } 132 }	0	2	H	$\overline{-CHCH_2}CH_2$	<u>E</u> , <u>E</u>	<u>S</u>
	133	1	2	Me	Me	<u>E</u> , <u>E</u>	<u>R</u>
25	134	1	2	Me	Me	<u>E</u> , <u>E</u>	<u>S</u>
	135	1	2	Et	Et	<u>E</u> , <u>E</u>	<u>S</u>
	136	1	2	Et	Et	<u>E</u> , <u>E</u>	<u>R</u>
	137-38	1(CH(Me))	2	Me	Me	<u>E</u> , <u>E</u>	<u>R</u>
	139-40	1(CH(Me))	2	Me	Me	<u>E</u> , <u>E</u>	<u>S</u>

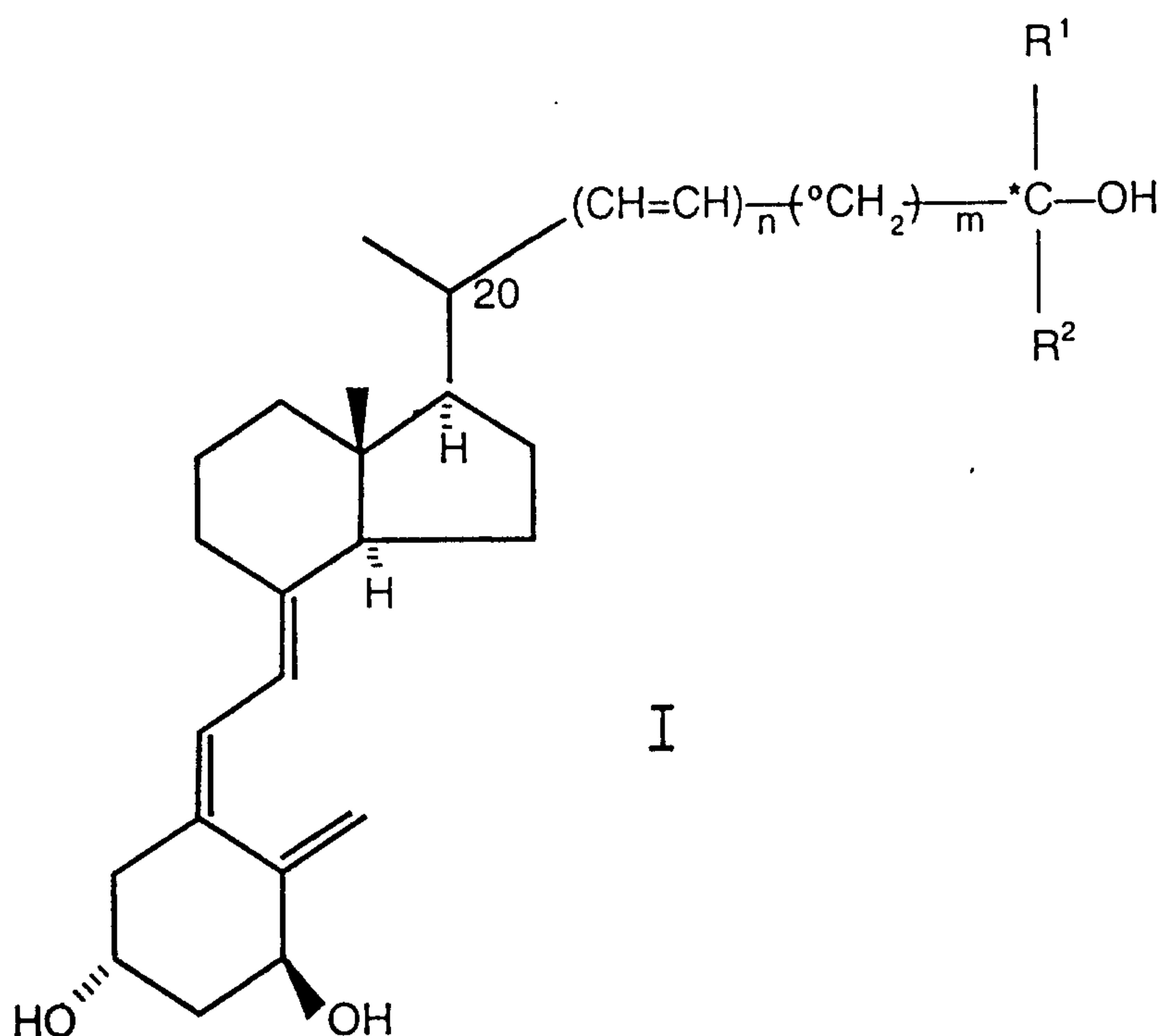
Parallel reactions can be used to convert other side chain fragments to the corresponding compounds of Formula I.

In cases where $R^1 \neq R^2$ in compounds of Formula II or of Formula V, the isomers can be separated 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 route of Scheme 3, using the appropriate side chain fragment of structure $Z-(^{\circ}\text{CH}_2)_m-\text{CH}(R^1)(R^2)$.

The compounds of aspects of the present invention find use in both human and veterinary practice in the treatment and prophylaxis of autoimmune diseases, hypertension, acne, alopecia, skin ageing, imbalance in the immune system, inflammatory diseases, as well as diseases characterized by abnormal cell differentiation and/or cell proliferation. The compounds of aspects of the present invention are intended for use in pharmaceutical compositions which are useful in the treatment of human and veterinary disorders as described above.

The present invention, in another aspect, therefore provides a pharmaceutical composition containing at least one of the active compounds of the Formula I



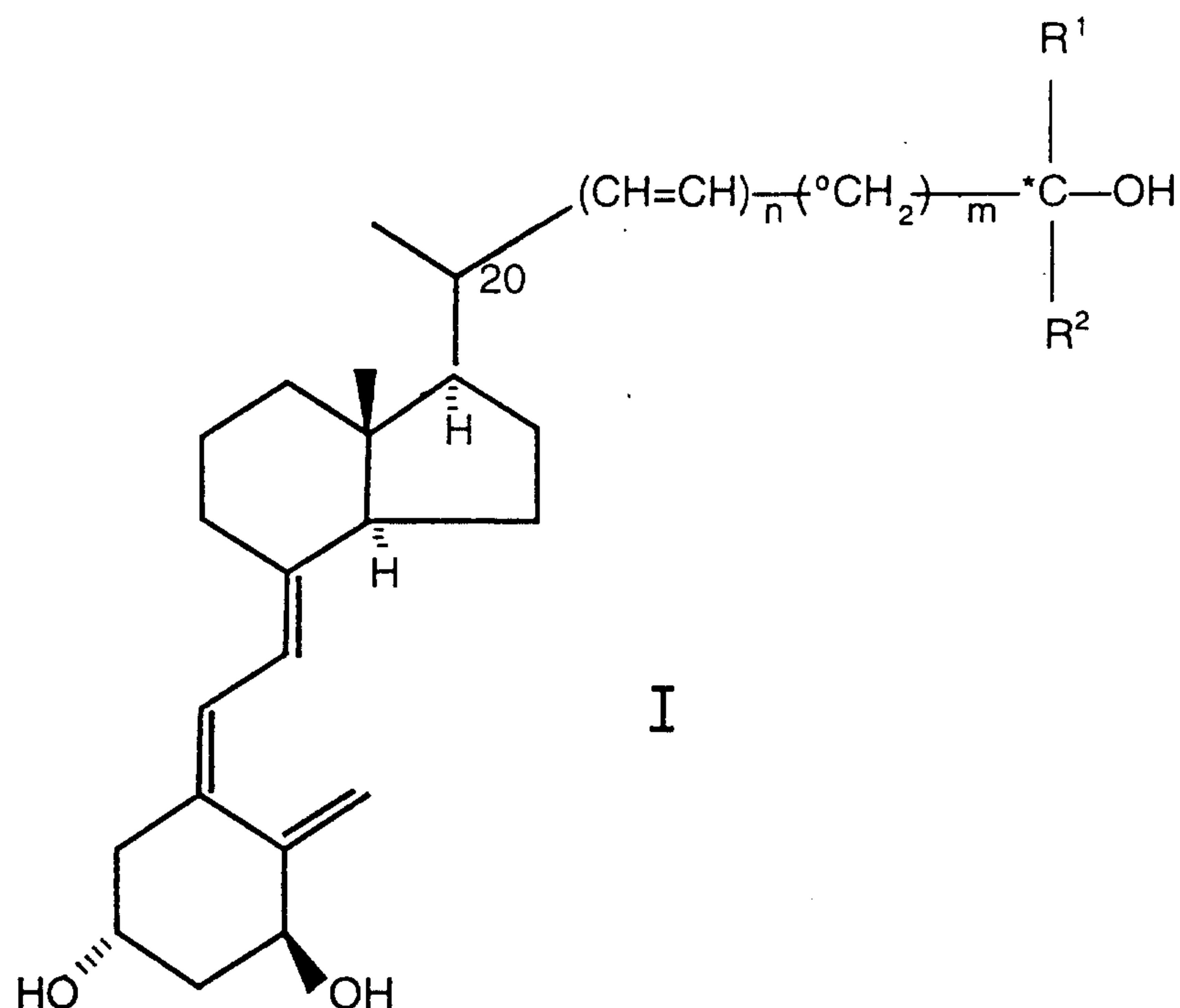
in which Formula, n is 2 or 3, m is 0 or an integer from 1 - 4; R¹ and R² (which may be the same or different) stand for hydrogen or C₁-C₈-hydrocarbyl, hydrocarbyl indicating the residue after removal of a hydrogen atom from a straight saturated hydrocarbon, a straight unsaturated hydrocarbon, a branched saturated hydrocarbon, a branched unsaturated hydrocarbon, a cyclic saturated hydrocarbon or a cyclic unsaturated hydrocarbon, or, taken together 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; in addition, at least one of R¹, R² and one of the "m" carbons designated by the "o" being unsubstituted or being substituted with at least one chlorine or fluorine atom; and finally one of the carbons designated "o" being unsubstituted or being substituted by at least one C₁-C₂ alkyl group; and derivatives of the compounds of Formula I in which at least one hydroxy has been transformed into a masked -O-acyl group, or masked -O-glycosyl group or a masked phosphate ester group, the masked group being hydrolyzable *in vivo*; and other prodrugs thereof, either a mixture of diastereoisomers of a compound of Formula I or a diastereoisomer of a compound of Formula I, in pure form, together with at least one of a pharmaceutically-acceptable, non-toxic carrier and an auxiliary agent.

Variants of such pharmaceutical compositions include those in which the active compound comprises: 1(S),3(R)-dihydroxy-20-(5'-hydroxy-5'-methyl-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene; or 1(S),3(R)-dihydroxy-20-(5'-ethyl-5'-hydroxy-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene; or comprises 1(S),3(R)-dihydroxy-20-(6'-hydroxy-hexa-1'(E),-3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene; or 1(S),3(R)-dihydroxy-20-(5'-cyclopropyl-5'-hydroxy-penta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),-7(E),10(19)-triene (5'(R) and 5'(S) isomers); or 1(S),3(R)-dihydroxy-20-(6'-hydroxy-6'-methyl-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.

By variations of such aspect and variants, such pharmaceutical composition is for topical use and contains from 0.1 - 100 µg of such compound; or is for oral and parenteral use and contains from 0.01 - 100 µg of such compound.

By another variation thereof, the pharmaceutical composition is in dosage unit form.

The present invention, in yet another aspect, provides a method for producing a pharmaceutical composition which comprises admixing an effective amount of at least one of the active compounds of the Formula I



in which Formula n is 2 or 3, m is 0 or an integer from 1 - 4; R¹ and R² (which may be the same or different) stand for hydrogen or 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 together 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; in addition, at least one of R¹, R² and one of the "m" carbons designated by the "°" being unsubstituted or being substituted with at least one chlorine or fluorine atom; and finally one of the carbons designated "°" being

unsubstituted or being substituted by at least one C₁-C₂ alkyl group; and derivatives of the compounds of Formula I in which at least one hydroxy has been transformed into a masked -O-acyl group, or a masked -O-glycosyl group or a masked phosphate ester group, the masked group being hydrolyzable *in vivo*; and other prodrugs thereof, together with at least one of a pharmaceutically acceptable, non-toxic carrier and an auxiliary agent.

Variants of such method are those in which the active compound of Formula I is 1(S),3(R)-dihydroxy-20-(5'-hydroxy-5'-methyl-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene; or 1(S),3(R)-dihydroxy-20-(5'-ethyl-5'-hydroxy-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene; or 1(S),3(R)-dihydroxy-20-(6'-hydroxy-hexa-1'(E),-3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene; or 1(S),3(R)-dihydroxy-20-(5'-cyclopropyl-5'-hydroxy-penta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),-7(E),10(19)-triene (5'(R) and 5'(S) isomers); or 1(S),3(R)-dihydroxy-20-(6'-hydroxy-6'-methyl-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.

By another aspect of this invention, in its various aspects, variants and variations, a method is provided for producing a pharmaceutical composition, as defined hereinabove, for topical use, containing from 0.1 - 100 µg/g of the active compound.

By yet another aspect of this invention, in its various aspects, variants and variations, a method is provided for producing a pharmaceutical composition as defined hereinabove, for oral or parenteral use, containing from 0.01 - 100 µg/g of a compound of Formula I.

By still a further aspect of this invention, in its various aspects, variants and variations, the use is provided for preparing a pharmaceutical composition for the treatment or prophylaxis of auto-immune diseases (including diabetes mellitus), hypertension, acne, alopecia, skin ageing (including photoageing), inflammatory diseases, rheumatoid arthritis, asthma, and diseases characterized by abnormal cell differentiation and/or cell proliferation, and/or imbalance in the immune system.

21 a

By variants of that aspect, the use is provided of such compound for the treatment or prophylaxis of cancer, or psoriasis, or skin aging.

By other aspects of these two aspects or variants of the invention, such use is one where the compound is: 1(S),3(R)-dihydroxy-20-(5'-hydroxy-5'-methyl-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene; or 1(S),3(R)-dihydroxy-20-(5'-ethyl-5'-hydroxy-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene; or 1(S),3(R)-dihydroxy-20-(5'-hydroxy-hexa-1-1'(E),3'(E)-cyclopropyl-5'-hydroxy-penta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene (5'(R) and 5'(S) isomers); 1(S),3(R)-dihydroxy-20-(6'-hydroxy-6'-methyl-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.

By variants of that aspect, the use is provided for preparing a pharmaceutical composition for the treatment or prophylaxis of cancer; or for preparing a pharmaceutical composition for the treatment or prophylaxis of psoriasis; or for preparing a pharmaceutical composition for the treatment or prophylaxis of skin ageing.

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 the aspects of the present 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 does comprising either the active material as such, or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

21 b

The formulations of aspects of the present invention, both for veterinary and for human medical use, comprise an active ingredient in association with a pharmaceutically-acceptable carrier therefore, and optionally another therapeutic ingredient or other therapeutic ingredients. The carrier or carriers 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 of aspects of the present invention include, e.g., those in a form suitable for oral, rectal, parenteral (including transdermal, subcutaneous, intramuscular and intravenous), intra-articular and topical administration.

The formulations of aspects of the present invention may conveniently be provided in dosage unit form and may be prepared by any of the procedures well known in the art of pharmacy. All procedures 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 aspects of the present invention which are suitable for oral administration may be in the form of discrete units, e.g., capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; or in the form of a powder or granules; or 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.

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, e.g., a powder or granules, optionally mixed by a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding,

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in a suitable machine, a mixture of the powdered active ingredient and suitable carrier, which has been moistened with an inert liquid diluent.

Formulations of aspects of the present invention which are suitable for rectal administration may be in the form of a suppository incorporating the active ingredient and a carrier, e.g., cocoa butter, or in the form of an enema.

Formulations which are 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 of aspects of the present invention which are 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 provide the active ingredient for both intra-articular and ophthalmic administration.

Formulations of aspects of the present invention which are suitable for topical administration 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 solutions or suspensions, e.g., drops; or as sprays.

For asthma treatment, inhalation of powder, self-propelling or spray formulations, which are 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 .

Such formulations of aspects of the present invention are most preferably in the form of a finely comminuted powder for pulmonary administration from a powder inhalation device or from a self-propelling powder-dispensing formulations. In the case of self-propelling solutions or 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

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ingredient as a suspended powder in controlled particle size. These self-propelling formulations may be either powder-dispensing formulations or formulations dispensing the active ingredient as droplets of a solution or suspension.

5 Self-propelling powder-dispensing formulations of aspects of the present invention preferably comprise dispersed particles of solid active ingredients, and a liquid propellant having a boiling point below 18°C 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
10 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 while the active ingredient constitutes 1 ppm to 0.1% w/w of the formulation.

15 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.

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

25 In the use of the compounds of aspects of this invention or the formulations of aspects of this invention for the treatment of systemic disorders, daily doses of from 0.01 - 100 µg, preferably from 0.025 - 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 0.5 - 10 µg/g, of a compound of Formula I are administered. The oral compositions are formulated, preferably as tablets, capsules, or drops, containing from 0.01 - 100 µg, preferably from 0.025 - 50 µg, of a compound of Formula I, per dosage unit.

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(f) AT LEAST ONE MODE FOR CARRYING OUT THE INVENTION

The invention in its various aspects will now be further described in the

following non-limiting Preparations and Examples:

Preparations and Examples

General

5 The compounds referred to in the Preparations and Examples are to be identified by number or letter with the corresponding formulae in the Schemes and/or Tables. Ultra-violet spectra (λ) were measured for solutions in 96% ethanol. For nuclear magnetic resonance spectra chemical
10 shift values (δ) are quoted in p.p.m. for deuterio-chloroform 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
15 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
20 refers to the pentane fraction. Brine is saturated sodium chloride solution. Organic solutions were dried over dried magnesium sulphate and concentrated on a rotary evaporator at water aspirator pressure.

25 Preparation 1 Compound 1ak

A mixture of anthracene (0.10 g), triethylamine (20 mg), and the compound 1aj (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
30 radiation from a high pressure Hg lamp (type: HANAU_{TM} TQ 71822) 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, using 5% ether in petroleum ether as eluant) to give 1ak; δ (300 MHz) 0.05
35 (12H; bs), 0.56 (3H, s), 0.86 (18H, s), 1.12 (3H, d, J 7), 1.15-2.05 (13H, m), 2.20 (1H, dd), 2.35 (1H, m), 2.43 (1H, m), 2.81 (1H, bd), 4.18 (1H, m), 4.36 (1H, m), 4.84 (1H, m), 5.16 (1H, m), 6.01 (1H, d, J 11), 6.21 (1H, d, J 11)

and 9.57 (1H, d, $\underline{J}$ 3).

Preparation 2: Compound 2aj (x = 1)

A stirred solution of 1aj (3.9 g), and methoxy-
5 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
10 recrystallization from ether-methanol gave 2aj (x=1), as
needles, m.p. 129-130°C, δ (300 MHz) 0.05 (12H, bs), 0.56
(3H, s), 0.86 (9H, s), 0.89 (9H, s), 1.09 (3H, d, $\underline{J}$ 6.6),
1.1-2.1 (13H, m), 2.28 (2H, m), 2.54 (1H, dd), 2.87 (1H,
dd), 3.71 (13H, s), 4.21 (1H, m), 4.52 (1H, m), 4.94 (1H,
15 bs), 4.98 (1H, bs), 5.75 (1H, d, $\underline{J}$ 15.5), 5.81 (1H, d, $\underline{J}$
11.5), 6.43 (1H, d, $\underline{J}$ 11.5), 6.84 (1H, dd, $\underline{J}$ 15.5 and
9.0).

Preparation 3: Compound 2ak (x = 1)

20 The compound was prepared using the procedure of
Preparation 2, but using 1ak as starting material instead
of 1aj. The product was not obtained crystalline after this
chromatographic purification, δ (300 MHz) in agreement with
assigned structure.

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Procedure 1 Reduction of Compound 2 or 3 to
the Corresponding Compound II
(Scheme 2)

To a stirred solution of 2 or 3 (5 mmol) in dry THF
30 (25 ml) at -70°C under N₂ 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
35 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 II, which was option-
ally purified by chromatography and/or recrystallisation.

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Preparation 4: 1(S),3(R)-bis-tert-butyl-dimethyl-silyloxy-20(R)-(3'-hydroxyprop-1'(E)-enyl)-9,10-secopregna-5(E),7(E),10(19)-triene

5 The compound was prepared using Procedure 1 in which the starting material was compound 2aj (x=1). The crude product was of sufficient purity for use as starting material in Preparation 5. An analytical sample was obtained by recrystallisation from ether-MeOH; m.p. 118-120°C; δ (300
10 MHz) 0.05 (12H, bs), 0.55 (3H, s), 0.86 (9H, s), 0.89 (9H, s), 1.04 (3H, d, J 6), 1.10-2.20 (15H, m), 2.29 (1H, d), 2.54 (1H, dd), 2.87 (1H, m), 4.06 (2H, m), 4.21 (1H, m), 4.52 (1H, m), 4.93 (1H, bs), 4.98 (1H, bs), 5.56 (2H, m), 5.82 (1H, d, J 11.5), 6.44 (1H, d, J 11.5).

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Preparation 5: Compound 3aj (x = 1)

Pyridinium dichromate (0.5 g) was added at room temperature to a stirred solution of the compound from Preparation 4 (0.53 g) in dichloromethane (10 ml). After
20 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 3aj (x=1) which crystallized on treatment with methanol. M.p.: 101-103°C; δ (300 MHz) 0.06 (12H, m),
25 0.59 (3H, s), 0.86 (9H, s), 0.89 (9H, s), 1.15 (3H, d, J 6.6), 1.20-2.10 (13H, m), 2.30 (1H, bd), 2.42 (1H, m), 2.55 (1H, dd), 2.89 (1H, m), 4.21 (1H, m), 4.53 (1H, m), 4.94 (1H, m), 4.98 (1H, m), 5.82 (1H, d, J 11.4), 6.06 (1H, dd, J 15.6 and 7.8), 6.44 (1H, d, J 11.4), 6.71 (1H, dd, J 15.6
30 and 8.8), 9.48 (1H, d, J 7.8).

Preparation 6: Compound 2aj (x = 2)

A mixture of 1aj (4.56 g), 3-(methoxycarbonyl)-2-propenyl-1-idene-triphenylphosphorane (3.03 g) and
35 alcohol-free chloroform (12 ml) was heated at 62°C with stirring under N_2 while part of the chloroform was evaporated in vacuo. The mixture was kept at 62°C overnight, cooled and partitioned between ether and water.

The organic layer was dried and evaporated in vacuo. The resulting oil was purified by chromatography (silica gel, hexane-ether 97:3 as eluant) to give an oil which crystallized from ether/methanol. M.p.: 99-101°C; $\lambda_{\text{max}} =$
5 268 nm ($\epsilon = 52372$); δ (300 MHz) 0.05 (12H, m), 0.56 (3H, s), 0.85 (9H, s), 0.89 (9H, s), 1.07 (3H, d, J 6.69), 1.17-2.10 (13H, m), 2.25 (2H, m), 2.55 (1H, dd), 2.87 (1H, m), 3.73 (3H, s), 4.21 (1H, m), 4.52 (1H, m), 4.94 (1H, m), 4.98 (1H, m), 5.78 (1H, d, J 15.3), 5.81 (1H, d, J 11.4),
10 6.05 (2H, m), 6.44 (1H, d, J 11.4), 7.24 (1H, dd).

Preparation 7: Compound 2aj (x = 3) Isomers A and B

A mixture of 3aj (x=1) (1 g), 3-(methoxycarbonyl)-2-propenyl-1-idene-triphenylphosphorane (1.26 g) and
15 alcohol-free chloroform (3 ml) was heated with stirring at 62°C while part of the chloroform was evaporated in vacuo. After 2 hours at 62°C the mixture was cooled and partitioned between ether and water. The organic layer was dried, concentrated and purified by chromatography (silica
20 gel, hexane-ether 9:1 as eluant). The first eluted title compound was isomer B; δ (300 MHz) 0.06 (12H, m), 0.58 (3H, s), 0.86 (9H, s), 0.89 (9H, s), 1.08 (3H, d, J 6,6) 1.17-2.35 (15H, m), 2.58 (1H, dd), 2.88 (1H, m), 3.75 (3H, s), 4.21 (1H, m), 4.53 (1H, m), 4.94 (1H, m), 4.98 (1H, m),
25 5.82 (3H, m), 5.98 (1H, t, J 11.2), 6.26 (1H, t, J 11.2), 6.45 (1H, d, J 11.3), 6.57 (1H, dd), 7.75 (1H, m).

The second eluted title compound was isomer A; δ (300 MHz) 0.05 (12H, m), 0.56 (3H, s), 0.86 (9H, s), 0.89 (9H, s), 1.07 (3H, d, J 6,6), 1.15-2.35 (15H, m), 2.55 (1H, dd),
30 2.87 (1H, m), 3.73 (3H, s), 4.21 (1H, m), 4.52 (1H, m), 4.93 (1H, m), 4.98 (1H, m), 5.81 (3H, m), 6.07 (1H, dd), 6.20 (1H, dd), 6.48 (2H, m), 7.29 (1H, dd).

Procedure 2

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Reaction of Compound 3 with side chain fragment A' ($Z = \text{Ph}_3\text{P}^+-\text{CH}^-$) to give Compound III (Scheme 2)

A stirred mixture of 3 and a molar excess of A' in toluene (5-10 ml per gram 1) was heated under reflux under

an N₂ atmosphere until a reasonable or complete conversion of 3 was obtained (4 to 16 hours). After cooling, the mixture was filtered, and the filtrate concentrated and purified by chromatography (5 - 20% ether in hexane or petroleum ether for the examples of Table 2) to give III.

Preparation 8: Compound 101j

Using the method of Procedure 2, a mixture of 3aj (x=1) (0.6 g) and cyclopropylcarbonylmethylenetriphenylphosphorane (5a) (0.86 g) and toluene (4 ml) was stirred at 110°C for 4 hours. After cooling to room temperature and filtration, the filtrate was concentrated in vacuo and purified by chromatography (silica gel, hexane-ether 85:5 as eluant) to give 101j as an oil which crystallized from methanol. M.p.: 106-108°C; λ_{max} 279.2 nm (ϵ = 50220); δ (300 MHz) 0.05 (12H, m), 0.56 (3H, s), 0.86 (9H, s), 0.89 (9H, s), 0.80-0.95 (2H, m), 1.00-1.15 (2H, m), 1.08 (3H, d, J 6.5), 1.17-2.35 (16H, m), 2.55 (1H, dd), 2.88 (1H, m), 4.21 (1H, m), 4.53 (1H, m), 4.93 (1H, m), 4.98 (1H, m), 5.81 (1H, d, J 11.4), 6.12 (3H, m), 6.44 (1H, d, J 11.4), 7.18 (1H, dd).

Procedure 3

Reduction of Compound III
to Compound II ($R^1 = H$) (Scheme 2)

Sodium borohydride (0.29 g) was added to an ice-cooled, stirred solution of III (2.5 g) in tetrahydrofuran (8 ml) and 0.4 M CeCl₃·7H₂O in ethanol (11.5 ml). Methanol (6 ml) was added over 10 minutes, and after stirring for a further 20 minutes the mixture was partitioned between ethyl acetate and water. The organic layer was washed with water, dried and concentrated in vacuo. The residue was purified by chromatography to give the compound II.

Preparation 9: Compounds 102j and 103j

Using the method of Procedure 3 (101j as starting material), two isomers were isolated by chromatography (3% acetone in toluene as eluant). First eluted isomer was

102j; δ (300 MHz) 0.05 (12H, m), 0.20-0.40 (2H, m), 0.56 (3H, s), 0.45-0.60 (2H, m), 0.86 (9H, s), 0.89 (9H, s), 1.05 (3H, d, J 6.6), 0.70-2.35 (17H, m), 2.56 (1H, dd), 2.87 (1H, m), 3.48 (1H, t), 4.21 (1H, m), 4.53 (1H, m), 4.93 (1H, m), 4.98 (1H, m), 5.56 (1H, dd, J 15 and 8.6), 5.65 (1H, dd, J 15 and 6.6), 5.81 (1H, d, J 11.4), 5.97 (1H, dd, J 15 and 10.4), 6.17 (1H, dd, J 15 and 10.4), 6.45 (1H, d, J 11.4).

Second eluted isomer was 103j; δ (300 MHz) 0.05 (12H, m), 0.20-0.40 (2H, m), 0.56 (3H, s), 0.44-0.65 (2H, m), 0.86 (9H, s), 0.89 (9H, s), 1.05 (3H, d, J 6.6), 0.70-2.35 (17H, m), 2.56 (1H, dd), 2.87 (1H, m), 3.49 (1H, t), 4.21 (1H, m), 4.53 (1H, m), 4.94 (1H, m), 4.98 (1H, m), 5.57 (1H, dd, J 15 and 8.6), 5.66 (1H, dd, J 15 and 6.4), 5.81 (1H, d, J 11.4), 5.97 (1H, dd, J 15 and 10.4), 6.19 (1H, dd, J 15 and 10.4), 6.45 (1H, d, J 11.4).

Procedure 4

Reaction of Compound 2 or 3 with R^1Li to give Compound II (Scheme 2)

Alkyl-lithium (in ether, 3 molar equivalents for compound 2; 1.5 molar equivalent for compound 3) was added dropwise at $-45^\circ C$ to a stirred solution of compound 2 or 3 (0.16 g) in dry THF (5 ml). After a further 50 minutes at $-45^\circ C$ the mixture was partitioned between ether and water. The organic layer was washed with brine, dried, and concentrated. The residue was purified by chromatography (silica gel) to give II.

Preparation 10 Compound 104j

The compound was prepared using procedure 4 in which the alkyl-lithium was methyl-lithium (1.5 M) and the starting material was 2aj ($x=2$). (Eluant: hexane-ether; 85:15). 104j δ (300 MHz) 0.06 (12H, m), 0.56 (3H, s), 0.87 (9H, s), 0.90 (9H, s), 1.05 (3H, d, J 6.6), 1.33 (6H, s), 1.15-2.35 (16H, m), 2.56 (1H, dd), 2.87 (1H, m), 4.21 (1H, m), 4.53 (1H, m), 4.94 (1H, m), 4.98 (1H, m), 5.56 (1H, dd, J 15 and 8.6), 5.70 (1H, d, J 15.3), 5.81 (1H, d, J 11.4), 5.95 (1H, dd, J 15 and 10.3), 6.15 (1H, dd, J 15 and 10.3),

6.45 (1H, d, $\underline{J}$ 11.4).

Preparation 11 Compound 105j

The compound was prepared using procedure 4 in which
5 the alkyl-lithium was ethyl-lithium (1.5 M) and the
starting material was 2aj (x=2). (Eluant: hexane-ether;
85:15). The compound crystallized from MeOH; m.p.: 84-85°C,
 λ_{max} 232 nm (ϵ = 37350) and 269.5 nm (ϵ = 26900); 105j δ
(300 MHz) 0.06 (12H, m), 0.56 (3H, s), 0.86 (9H, s), 0.89
10 (9H, s), 0.86 (6H, t), 1.05 (3H, d, $\underline{J}$ 6.6), 1.20-2.20 (19H,
m), 2.30 (1H, bd), 2.56 (1H, dd), 2.87 (1H, m), 4.21 (1H,
m), 4.53 (1H, m), 4.94 (1H, m), 4.98 (1H, m), 5.52 (1H, dd,
 $\underline{J}$ 15.3), 5.54 (1H, dd, $\underline{J}$ 15 and 8.6), 5.82 (1H, d, $\underline{J}$ 11.4),
5.97 (1H, dd, $\underline{J}$ 15 and 10.3), 6.15 (1H, dd, $\underline{J}$ 15 and 10.3),
15 6.45 (1H, d, $\underline{J}$ 11.4).

Preparation 12 Compound 106j

The compound was prepared using procedure 4 in which
the alkyl-lithium was methyl-lithium (1.5 M) and the
20 starting material was 2aj (x=3) isomer A. (Eluant:
hexane-ether; 85:15). 106j δ (300 MHz) in agreement with
structure.

Procedure 5

Preparation of Compounds V from
Aldehyde (3) and Side Chain
Fragment B (Scheme 3)

25 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
30 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 (3) (2 mmol) 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
35 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 IV ($Y = \text{PhC(O)}$) as a mixture of diastereoisomers. This was dissolved in ethyl acetate (5 ml) and diluted with methanol (50 ml, saturated with and
5 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)
10 (decanting from the mercury), and the organic layer was washed with brine, dried and concentrated in vacuo. Purification of the residue by chromatography gave V.

Preparation 13 Compound 107j

15 This compound was prepared using Procedure 5 [aldehyde 3aj ($x=1$) as starting material] in which the side chain fragment B was compound 11 (0.55 g) and 12 ml of the lithium di-iso-propylamide solution was used. The intermediate IV has $R^3 = \text{OH}$. The chromatography was performed on
20 150 g silica gel using 10% ethyl acetate in petroleum ether as eluant. 107j; δ 0.05 (6H, bs), 0.56 (3H, s), 0.86 (9H, s), 0.89 (9H, s), 1.04 (3H, d, J 6), 1.1-2.70 (31H, m), 2.86 (1H, bd), 4.21 (1H, bs), 4.52 (1H, m), 4.94 (1H, bs), 4.98 (1H, bs), 5.45-5.65 (2H, m), 5.82 (1H, d, J 11),
25 5.9-6.20 (2H, m), 6.44 (1H, d, J 11).

Procedure 6

Preparation of Compound II or V ($R=k$) from the Corresponding Compound ($R=j$) (Scheme 4)

30 A mixture of anthracene (0.10 g), triethylamine (20 mg), and the compound II or V ($R=j$) (0.20 g) in dichloromethane (15 ml), stirred under an atmosphere of nitrogen in a Pyrex flask immersed in a water bath at 20°C, was illuminated with radiation from a high pressure Hg lamp
35 (type: Hanau TQ 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 II or V ($R=k$).

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Preparation 14 Compound 102k

The compound was prepared using Procedure 6 in which starting material II was compound 102j. (Eluant: toluene-acetone, 97:3) 102k; δ (300 MHz) 0.05 (12H, s), 0.18-0.40 (2H, m), 0.54 (3H, s), 0.45-0.65 (2H, m), 0.87 (18H, s), 1.04 (3H, d, $\underline{J}$ 7), 0.80-2.35 (16H, m), 2.44 (1H, dd), 2.80 (1H, bd), 2.58 (1H, m), 2.81 (1H, m), 3.49 (1H, t), 4.18 (1H, m), 4.36 (1H, m), 4.85 (1H, d, $\underline{J}$ 2), 5.17 (1H, m), 5.61 (2H, m), 5.97 (2H, m), 6.18 (2H, m).

10

Preparation 15 Compound 103k

The compound was prepared using Procedure 6 in which starting material II was compound 103j. (Eluant: toluene-acetone, 97:3) 103k; δ (300 MHz) 0.05 (12H, s), 0.18-0.40 (2H, m), 0.54 (3H, s), 0.45-0.65 (2H, m), 0.87 (18H, s), 1.04 (3H, d, $\underline{J}$ 7), 0.80-2.35 (16H, m), 2.44 (1H, dd), 2.80 (1H, bd), 2.81 (1H, m), 3.48 (1H, t), 4.16 (1H, m), 4.36 (1H, m), 4.85 (1H, m), 5.17 (1H, m), 5.61 (2H, m), 5.97 (2H, m), 6.18 (2H, m).

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Preparation 16 Compound 104k

The compound was prepared using Procedure 6 in which starting material II was compound 104j. (Eluant: 25% ether in petroleum ether) 104k; δ (300 MHz) 0.05 (12H, bs), 0.54 (3H, s), 0.88 (18H, s), 1.04 (3H, d, $\underline{J}$ 7), 1.32 (6H, s), 1.15-2.35 (16H, m, including 1.19 (6H, s)), 2.20 (1H, dd, $\underline{J}$ 13 and 7), 2.43 (1H, dd), 2.81 (1H, m), 4.18 (1H, m), 4.36 (1H, m), 4.86 (1H, bd), 5.17 (1H, dd), 5.55 (1H, dd), 5.69 (1H, d, $\underline{J}$ 15), 5.96 (2H, m), 6.22 (1H, d, $\underline{J}$ 11),

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Preparation 17 Compound 105k

The compound was prepared using Procedure 6 in which starting material II was compound 105j. (Eluant: 25% ether in petroleum ether) 105k; δ (300 MHz) 0.05 (12H, m), 0.54 (3H, s), 0.85 (6H, t), 0.87 (18H, s), 1.04 (3H, d), 1.15-2.15 (19H, m), 2.20 (1H, dd), 2.43 (1H, dd), 2.82 (1H, bd), 4.18 (1H, m), 4.36 (1H, m), 4.85 (1H, m), 5.16 (1H, m), 5.51 (1H, d, $\underline{J}$ 15.3), 5.53 (1H, dd, $\underline{J}$ 15.0 and 8.7),

5.96 (1H, dd, J 15.0 and 13.0), 6.00 (1H, d), 6.14 (1H, dd, J 15.3 and 10.3), 6.22 (1H, d).

Preparation 18 Compound 2bj (x=2)

Using the method of Preparation 6 and by starting from lbj (see Canadian Patent Application No. 2,051,418) instead of laj, compound 2bj was obtained as an oil which crystallized from ether/methanol. M.p.: 108-110°C; $\lambda_{\max}$ = 268 nm (ϵ = 50887); δ (300 MHz) 0.05 (12H, bs), 0.48 (3H, s), 0.86 (9H, s), 0.88 (9H, s), 0.97 (3H, d), 1.05-2.05 (13H, m), 2.20 (1H, m), 2.30 (1H, bd), 2.53 (1H, dd), 2.84 (1H, bd), 3.72 (3H, s), 4.21 (1H, m), 4.51 (1H, m), 4.92 (1H, bs), 4.97 (1H, bs), 5.77 (1H, dd), 5.79 (1H, d), 5.95-6.15 (2H, m), 6.43 (1H, d), 7.25 1H, dd).

Preparation 19 Compound 113j

The compound was prepared using Procedure 4 in which the alkyl-lithium was methyl-lithium, and the starting material was 2bj (x = 2). 113j crystallized from MeOH; $\lambda_{\max}$ = 232 nm (ϵ = 35228) and 269 nm (ϵ = 25416); δ (300 MHz) 0.05 (12H, m), 0.49 (3H, s), 0.85 (9H, s), 0.89 (9H, s), 0.94 (3H, d, J 6.6), 1.34 (6H, s), 1.00-2.15 (15H, m), 2.30 (1H, bd), 2.55 (1H, dd), 2.85 (1H, bd), 4.21 (1H, m), 4.52 (1H, m), 4.93 (1H, m), 4.98 (1H, m), 5.55 (1H, dd), 5.68 (1H, d), 5.81 (1H, d, J 11.4), 5.91 (1H, dd), 6.15 (1H, dd), 6.45 (1H, d, J 11.4).

Preparation 20 Compound 113k

The compound was prepared using Procedure 6 in which starting material II was compound 113j. (Eluant: hexane-ether 80:20) 113k; δ (300 MHz) 0.05 (12H, m), 0.48 (3H, s), 0.85 (9H, s), 0.86 (9H, s), 0.93 (3H, d, J 6.6), 1.33 (6H, s), 1.00-2.15 (15H, m), 2.20 (1H, dd), 2.43 (1H, dd), 2.80 (1H, bd), 4.18 (1H, m), 4.35 (1H, m), 4.85 (1H, m), 5.17 (1H, m), 5.54 (1H, dd), 5.68 (1H, d), 5.91 (1H, dd), 5.99 (1H, d, J 11.3), 6.15 (1H, dd), 6.22 (1H, d, J 11.3).

Preparation 21 Compound 114j

The compound was prepared by following the procedure described in Preparation 19 and by using ethyl-lithium instead of methyl-lithium. (Eluant: hexane-ether 80:20)
5 114j; δ (300 MHz) 0.05 (12H, m), 0.50 (3H, s), 0.85 (6H, t), 0.85 (9H, s), 0.89 (9H, s), 0.94 (3H, d, J 6.6), 1.05-2.15 (19H, m), 2.30 (1H, bd), 2.55 (1H, dd), 2.85 (1H, bd), 4.21 (1H, m), 4.52 (1H, m), 4.93 (1H, m), 4.97 (1H, m), 5.50 (1H, d), 5.53 (1H, dd), 5.80 (1H, d, J 11.5), 5.94
10 (1H, dd), 6.15 (1H, dd), 6.44 (1H, d, J 11.5).

Preparation 22 Compound 114k

The compound was prepared using Procedure 6 in which starting material II was compound 114j. (Eluant:
15 hexane-ether 90:10) 114k; δ (300 MHz) 0.05 (12H, m), 0.48 (3H, s), 0.86 (6H, t), 0.87 (9H, s), 0.88 (9H, s), 0.94 (3H, d, J 6.6), 1.00-2.15 (19H, m), 2.20 (1H, dd), 2.43 (1H, dd), 2.79 (1H, bd), 4.18 (1H, m), 4.36 (1H, m), 4.85 (1H, m), 5.17 (1H, m), 5.50 (1H, d), 5.53 (1H, dd), 5.93 (1H, dd),
20 6.00 (1H, d), 6.14 (1H, dd), 6.22 (1H, d).

Preparation 23 Compound 117j

The compound was prepared using Procedure 1 in which the starting material was compound 2bj ($x=2$). (Eluant:
25 hexane-ether 70:30) 117j; δ (300 MHz) 0.05 (12H, m), 0.49 (3H, s), 0.85 (9H, s), 0.89 (9H, s), 0.94 (3H, d, J 6.6), 1.05-2.17 (15H, m), 2.30 (1H, bd), 2.55 (1H, dd), 2.84 (1H, bd), 4.16 (2H, m), 4.21 (1H, m), 4.52 (1H, m), 4.93 (1H, m), 4.97 (1H, m), 5.58 (1H, dd), 5.71 (1H, m), 5.81 (1H, d, J 11.4),
30 J 11.4), 5.96 (1H, dd), 6.20 (1H, dd), 6.44 (1H, d, J 11.4).

Preparation 24 Compound 117k

The compound was prepared using Procedure 6 in which
35 starting material II was compound 117j. (Eluant: hexane-ether 70:30) 117k; δ (300 MHz) 0.05 (12H, m), 0.48 (3H, s), 0.86 (9H, s), 0.87 (9H, s), 0.93 (3H, d), 1.02-2.15 (15H, m), 2.21 (1H, dd), 2.43 (1H, dd), 2.80 (1H, bd), 4.16 (2H,

bd), 4.19 (1H, m), 4.36 (1H, m), 4.85 (1H, m), 5.17 (1H, m), 5.57 (1H, dd), 5.70 (1H, m), 5.95 (1H, dd), 6.00 (1H, d), 6.20 (2H, m).

5 Preparation 25 Compound 119j

The compound was prepared using Procedure 4 in which the alkyl-lithium was n-propyl-lithium and the starting material was 2aj (x=2). 119j; δ (300 MHz) 0.05 (12H, m), 0.55 (3H, s), 0.86 (9H, s), 0.89 (9H, s), 0.89 (6H, t),
10 1.05 (3H, d, $\underline{J}$ 6.6), 1.15-2.20 (23H, m), 2.30 (1H, bd), 2.55 (1H, dd), 2.87 (1H, bd), 4.21 (1H, m), 4.52 (1H, m), 4.93 (1H, m), 4.98 (1H, m), 5.50 (1H, dd), 5.54 (1H, d), 5.81 (1H, d, $\underline{J}$ 11.4), 5.95 (1H, dd), 6.13 (1H, dd), 6.45 (1H, d, $\underline{J}$ 11.4).

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Preparation 26 Compound 119k

The compound was prepared using Procedure 6 in which starting material II was compound 119j. (Eluant: hexane-ether 85:15) 119k; δ (300 MHz) 0.05 (12H, m), 0.54 (3H, s), 0.86 (18H, s), 0.89 (6H, t), 1.04 (3H, d, $\underline{J}$ 6.6),
20 1.15-2.15 (23H, m), 2.20 (1H, dd), 2.43 (1H, dd), 2.81 (1H, bd), 4.18 (1H, m), 4.35 (1H, m), 4.85 (1H, m), 5.16 (1H, m), 5.52 (1H, dd), 5.53 (1H, dd), 5.94 (1H, dd), 6.00 (1H, d), 6.12 (1H, dd), 6.22 (1H, d).

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Preparation 27 Compound 121k

Compound 121j was prepared by using Procedure 1 in which the starting material was compound 2aj (x=2). The crude 121j was of sufficient purity for use as starting
30 material in Procedure 6 by which method it was transformed into compound 121k. (Eluant: hexane-ether 70:30). 121k; δ (300 MHz) 0.05 (12H, m), 0.54 (3H, s), 0.86 (18H, s), 1.04 (3H, d, $\underline{J}$ 6.6), 1.12-2.30 (16H, m), 2.44 (1H, dd), 2.82 (1H, bd), 4.15 (2H, m), 4.17 (1H, m), 4.36 (1H, m), 4.85
35 (1H, m), 5.16 (1H, m), 5.57 (1H, dd), 5.70 (1H, m), 5.97 (1H, dd), 6.00 (1H, d), 6.18 (1H, dd), 6.22 (1H, d).

Preparation 28 Compound 2ak (x=1)

Using the method of Preparation 2 and by starting from 1ak instead of 1aj compound 2ak (x=1) was obtained as an oil. δ (300 MHz) 0.05 (12H, bs), 0.55 (3H, s), 0.87 (18H, s), 1.08 (3H, d), 1.15-2.10 (12H, m), 2.10-2.35 (3H, m), 2.44 (1H, dd), 2.82 (1H, bd), 3.70 (3H, s), 4.18 (1H, m), 4.36 (1H, m), 4.83 (1H, bd), 5.16 (1H, bd), 5.74 (1H, d), 6.00 (1H, d), 6.22 (1H, d), 6.87 (1H, dd).

Preparation 29 Compound 123k

The compound was prepared using Procedure 1 in which the starting material was compound 2ak (x=1). (Eluant: hexane-ether 7:3). 123k; δ (300 MHz) 0.05 (12H, m), 0.54 (3H, s), 0.87 (18H, s), 1.03 (3H, d, $\underline{J}$ 6.6), 1.12-2.30 (16H, m), 2.44 (1H, dd), 2.82 (1H, bd), 4.06 (2H, m), 4.18 (1H, m), 4.36 (1H, m), 4.85 (1H, m), 5.17 (1H, m), 5.54 (2H, m), 6.00 (1H, d, $\underline{J}$ 11.2), 6.22 (1H, d, $\underline{J}$ 11.2).

Preparation 30 Compound 3ak (x=1)

Using the method of Preparation 5 (compound 123k as starting material), compound 3ak (x=1) was prepared and purified by chromatography (Eluant: hexane-ether 4:1). δ (300 MHz) 0.05 (12H, m), 0.57 (3H, s), 0.86 (18H, s), 1.14 (3H, d, $\underline{J}$ 6.6), 1.10-1.90 (12H, m), 1.98 (1H, bd), 2.21 (1H, dd), 2.43 (2H, m), 2.83 (1H, bd), 4.18 (1H, m), 4.36 (1H, m), 4.85 (1H, m), 5.17 (1H, m), 6.04 (2H, m), 6.22 (1H, d, $\underline{J}$ 11.3), 6.70 (1H, dd), 9.47 (1H, d, $\underline{J}$ 7.8).

Preparation 31 Compound 2ak (x=3)

This compound was prepared by using the method of Preparation 6 and by starting from 3ak (x=1) instead of 1aj. The reaction mixture was only kept at 62°C for 2 hours. Compound 2ak (x=3) was isolated by chromatography. (Eluant: hexane-ether 4:1). δ (300 MHz) 0.05 (12H, m), 0.55 (3H, s), 0.87 (18H, s), 1.06 (3H, d, $\underline{J}$ 6.6), 1.15-2.30 (15H, m), 2.43 (1H, dd), 2.82 (1H, bd), 3.73 (3H, s), 4.18 (1H, m), 4.35 (1H, m), 4.84 (1H, m), 5.16 (1H, m), 5.79 (1H, dd), 5.82 (1H, d), 5.95-6.25 (4H, m), 6.50 (1H, dd),

7.29 (1H, dd).

Preparation 32 Compound 124k

The compound was prepared by following Procedure 4
5 and by using methyl-lithium and 2ak (x=3) as starting
material. (Eluant: hexane-ether 4:1). δ (300 MHz) 0.05
(12H, m), 0.54 (3H, s), 0.86 (18H, s), 1.04 (3H, d, $\underline{J}$ 6.6),
1.33 (6H, s), 1.15-2.30 (16H, m), 2.44 (1H, dd), 2.82 (1H,
bd), 4.18 (1H, m), 4.36 (1H, m), 4.85 (1H, m), 5.16 (1H,
10 m), 5.56 (1H, dd), 5.78 (1H, d), 5.92-6.30 (6H, m).

Preparation 33 Compound 126k

The compound was prepared by following Procedure 4
and by using ethyl-lithium and 2ak (x=3) as starting
15 material. (Eluant: hexane-ether 4:1). δ (300 MHz) 0.05
(12H, m), 0.54 (3H, s), 0.84 (6H, t), 0.87 (18H, s), 1.04
(3H, d, $\underline{J}$ 6.5), 1.00-2.30 (20H, m), 2.44 (1H, dd), 2.81
(1H, bd), 4.18 (1H, m), 4.36 (1H, m), 4.85 (1H, m), 5.17
(1H, m), 5.56 (1H, dd), 5.59 (1H, d), 6.00 (2H, m), 6.16
20 (4H, m).

Preparation 34 Compound 128k

This compound was prepared using Procedure 1 in which
the starting material was compound 2ak (x=3). δ (300 MHz)
25 0.05 (12H, m), 0.54 (3H, s), 0.87 (18H, s), 1.04 (3H, d, $\underline{J}$
6.6), 1.12-2.25 (16H, m), 2.43 (1H, dd), 2.82 (1H, bd),
4.18 (3H, m), 4.36 (1H, m), 4.85 (1H, m), 5.16 (1H, m),
5.59 (1H, dd), 5.79 (1H, m), 5.90-6.30 (6H, m).

30 Preparation 35 Compound 107k

This compound was prepared using Procedure 6 in which
starting material II was compound 107j. δ (300 MHz) 0.05
(12H, m), 0.54 (3H, s), 0.87 (18H, s), 1.04 (3H, d),
1.15-2.15 (22H, m), 2.21 (2H, d), 2.40 (1H, m), 2.82 (1H,
35 bd), 4.18 (1H, m), 4.36 (1H, m), 4.85 (1H, m), 5.17 (1H,
m), 5.51 (1H, dd), 5.60 (1H, m), 6.00 (3H, m), 6.24 (1H,
d).

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Procedure 7Preparation of Compound I from the
Corresponding Compound II or V (R=k)
(Scheme 4)

A solution of the compound II or V (0.2 g) and tetra-
5 n-butylammonium fluoride trihydrate (0.4 g) in THF (10 ml)
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
10 washed with water and brine, dried and concentrated. The
residue was purified by chromatography (30 g silica gel,
ethyl acetate as eluant) to give I.

The compounds of Examples 1-4 and 6-14 were prepared
15 using procedure 7. The respective starting materials II or
V are given in the Examples.

Example 1

20(R)-(5'-Cyclopropyl-5'-hydroxy-
penta-1'(E),3'(E)-dien-1'-yl)-1(S),
20 3(R)-dihydroxy-9,10-secopregna-5(Z),
7(E),10(19)-triene (Isomer A)
(Compound 108)

Starting material 102k; δ (300 MHz) 0.20-0.40 (2H,
m), 0.53 (3H, s), 0.46-0.65 (2H, m), 1.05 (3H, d, J 6.6),
25 0.90-2.20 (18H, m), 2.31 (1H, dd), 2.60 (1H, m), 2.83 (1H,
m), 3.49 (1H, t), 4.23 (1H, m), 4.43 (1H, m), 5.00 (1H, m),
5.33 (1H, m), 5.57 (1H, dd, J 15 and 8.7), 5.66 (1H, dd, J
15 and 6.5), 5.97 (1H, dd, J 15 and 10.3), 6.01 (1H, d, J
11.2) 6.17 (1H, dd, J 15 and 10.3), 6.38 (1H, d, J 11.2).

30

Example 2

20(R)-(5'-Cyclopropyl-5'-hydroxy-
penta-1'(E),3'(E)-dien-1'-yl)-1(S),
35 3(R)-dihydroxy-9,10-secopregna-5(Z),
7(E),10(19)-triene (Isomer B)
(Compound 109)

35

Starting material: 103k; δ (300 MHz) 0.22-0.40 (2H,
m), 0.56 (3H, s), 0.46-0.65 (2H, m), 1.05 (3H, d, J 6.6),
0.90-2.20 (18H, m), 2.31 (1H, dd), 2.60 (1H, m), 2.84 (1H,

m), 3.50 (1H, t), 4.23 (1H, m), 4.43 (1H, m), 5.00 (1H, m), 5.33 (1H, m), 5.58 (1H, dd, $\underline{J}$ 15.1 and 8.6), 5.67 (1H, dd, $\underline{J}$ 15.2 and 6.3), 5.97 (1H, dd, $\underline{J}$ 15.1 and 10.3), 6.01 (1H, d, $\underline{J}$ 11.3) 6.19 (1H, dd, $\underline{J}$ 15.1 and 10.3), 6.38 (1H, d, $\underline{J}$ 11.3).

Example 3

1(S),3(R)-Dihydroxy-20(R)-(5'-
-hydroxy-5'-methyl-hexa-1'(E),3'(E)-
-dien-1'-yl)-9,10-secopregna-5(Z),
7(E)-10(19)-triene (Compound 110)

Starting material: 104k. Crystallisation from ethyl acetate-hexane gave needles, m.p. 156-157°C; $\lambda_{\max}$ 231 nm (ϵ = 42530) and 264 nm (ϵ = 18040); δ (300 MHz) 0.56 (3H, s), 1.05 (3H, d, $\underline{J}$ 6,6), 1.34 (6H, s), 1.15-2.20 (17H, m), 2.31 (1H, dd), 2.60 (1H, dd), 2.84 (1H, m), 4.23 (1H, m), 4.43 (1H, m), 5.00 (1H, m), 5.33 (1H, m), 5.56 (1H, dd), 5.71 (1H, dd, $\underline{J}$ 15.4), 5.96 (2H, m), 6.16 (1H, dd), 6.38 (1H, d, $\underline{J}$ 11.2).

Example 4

1(S),3(R)-Dihydroxy-20(R)-(5'-ethyl-
-5'-hydroxy-hepta-1'(E),3'(E)-dien-
-1'-yl)-9,10-secopregna-5(Z),7(E),
10(19)-triene (Compound 111)

Starting material: 105k. Crystallisation from methyl formate-hexane gave needles, m.p. 123-125°C; $\lambda_{\max}$ 232 nm (ϵ = 43745) and 264 nm (ϵ = 18060); δ (300 MHz) 0.55 (3H, s), 0.85 (6H, t), 1.04 (3H, d, $\underline{J}$ 6.6), 1.12-2.20 (21H, m), 2.30 (1H, dd), 2.58 (1H, dd), 2.82 (1H, dd), 4.21 (1H, m), 4.41 (1H, m), 4.99 (1H, m), 5.31 (1H, m), 5.53 (2H, m), 5.95 (1H, dd, $\underline{J}$ 15 and 10.3), 6.00 (1H, d, $\underline{J}$ 11.3), 6.14 (1H, dd, $\underline{J}$ 15 and 10.3), 6.37 (1H, d, $\underline{J}$ 11.3).

Example 5

1(S),3(R)-Dihydroxy-20(R)-(6'-
hydroxy-hexa-1'(E),3'(E)-dien-1'-yl)-
9,10-secopregna-5(Z),7(E),10(19)-
-triene (Compound 112)

A solution of MC 903 [M.J. Calverley, Tetrahedron 43, 4609 (1987)] (0.45 g) in a mixture of alcohol-free

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chloroform (20 ml) and trifluoroacetic anhydride (9 ml) was kept at room temperature for 50 minutes. The reaction mixture was then slowly added to an ice-cold stirred solution of potassium hydroxide (19.8 g) in methanol (150 ml). After stirring for 10 minutes and concentration in vacuo, the residue was partitioned between methylene chloride and water. The organic layer was dried and concentrated. Purification by chromatography (silica gel, hexane-ethyl acetate 1:3 as eluant) gave the title compound which crystallized from ethyl acetate, m.p.: 132-35°C; $\lambda_{\max}$ = 232 nm (ϵ = 40980) and 264 nm (ϵ = 17494); δ (300 MHz) 0.56 (3H, s), 1.04 (3H, d, J 6.6), 1.15-2.25 (17H, m), 2.32 (3H, m), 2.60 (1H, dd), 2.82 (1H, dd), 3.66 (2H, m), 4.22 (1H, m), 4.43 (1H, m), 4.99 (1H, s), 5.32 (1H, s), 5.50 (2H, m), 6.00 (3H, m), 6.37 (1H, d, J 11.2).

Example 6

1(S),3(R)-Dihydroxy-20(R)-(6'-hydroxy-6'-methyl-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E)-10(19)-triene (Compound 133)

Starting material: 107k; Crystallization from methyl formate-hexane, m.p. 147-148°C; $\lambda_{\max}$ 233 nm (ϵ = 43322) and 264 nm (ϵ = 17916); δ (300 MHz) 0.56 (3H, s), 1.05 (3H, d), 1.22 (6H, s), 1.20-2.20 (17H, m), 2.23 (2H, d), 2.31 (1H, dd), 2.60 (1H, dd), 2.83 (1H, bd), 4.23 (1H, m), 4.43 (1H, m), 5.00 (1H, m), 5.32 (1H, m), 5.50 (1H, dd), 5.60 (1H, m), 6.01 (3H, m), 6.38 (1H, d).

Example 7

1(S),3(R)-Dihydroxy-20(R)-(7'-hydroxy-hepta-1'(E),3'(E),5'(E)-trien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene (Compound 129)

Starting material: 128k; δ (300 MHz) 0.59 (3H, s), 1.06 (3H, d, J 6.6), 1.89 (2H, t), 1.15-2.21 (15H, m), 2.25 (1H, dd), 2.52 (1H, dd), 2.87 (1H, bd), 4.09 (2H, bd), 4.12 (1H, m), 4.35 (1H, m), 4.89 (1H, m), 5.28 (1H, m), 5.56 (1H, dd), 5.75 (1H, m), 5.95-6.36 (6H, m).

Example 8

1(S),3(R)-Dihydroxy-20(S)-(5'-
-hydroxy-5'-methyl-hexa-1'(E),3'(E)-
-dien-1'-yl)-9,10-secopregna-5(Z),
7(E),10(19)-triene (Compound 115)

5 Starting material: 113k. The compound crystallized from ethyl acetate-hexane, m.p. 98-102°C; $\lambda_{\max}$ 232 nm (ϵ = 38238) and 265 nm (ϵ = 17418); δ (300 MHz) 0.50 (3H, s), 0.94 (3H, d, J 6.6), 1.35 (6H, s), 1.05-2.15 (17H, m), 2.31 (1H, dd), 2.57 (1H, bd), 2.82 (1H, bd), 4.22 (1H, m), 4.43
10 (1H, m), 5.00 (1H, m), 5.33 (1H, m), 5.56 (1H, dd), 5.69 (1H, d), 5.92 (1H, dd), 6.01 (1H, d, J 11.3), 6.16 (1H, dd), 6.37 (1H, d, J 11.3).

Example 9

15 1(S),3(R)-Dihydroxy-20(S)-(5'-ethyl-
-5'-hydroxy-hepta-1'(E),3'(E)-dien-
-1'-yl)-9,10-secopregna-5(Z),7(E),
10(19)-triene (Compound 116)

Starting material: 114k; $\lambda_{\max}$ 233 and 264 nm; δ (300 MHz) 0.51 (3H, s), 0.87 (6H, t), 0.95 (3H, d, J 6.7),
20 1.02-2.15 (21H, m), 2.31 (1H, dd), 2.60 (1H, bd), 2.81 (1H, bd), 4.23 (1H, m), 4.43 (1H, m), 5.00 (1H, m), 5.33 (1H, m), 5.51 (1H, d), 5.53 (1H, dd), 5.95 (1H, dd), 6.01 (1H, d), 6.16 (1H, dd), 6.38 (1H, d, J 11.2).

Example 10

25 1(S),3(R)-Dihydroxy-20(S)-(5'-
-hydroxy-penta-1'(E),3'(E)-dien-1'-
-yl-9,10-secopregna-5(Z),7(E),
10(19)-triene (Compound 118)

Starting material: 117k; δ (300 MHz) 0.50 (3H, s),
30 0.94 (3H, d, J 6.6), 1.02-2.20 (17H, m), 2.31 (1H, dd), 2.59 (1H, dd), 2.81 (1H, bd), 4.17 (2H, bd), 4.23 (1H, m), 4.42 (1H, m), 5.00 (1H, m), 5.33 (1H, m), 5.58 (1H, dd), 5.72 (1H, m), 5.96 (1H, dd), 6.01 (1H, d, J 11.3), 6.21 (1H, dd), 6.37 (1H, d, J 11.3).

Example 11 1(S),3(R)-Dihydroxy-20(R)-(5'-hydr-
-oxy-5'-n-propyl-octa-1'(E),3'(E)-
-dien-1'-yl)-9,10-secopregna-5(Z),
7(E),10(19)-triene (Compound 120)

5 Starting material: 119k; δ (300 MHz) 0.55 (3H, s),
0.89 (6H, t), 1.04 (3H, d, $\underline{J}$ 6.6), 1.15-2.18 (25H, m), 2.30
(1H, dd), 2.59 (1H, dd), 2.82 (1H, bd), 4.21 (1H, m), 4.41
(1H, m), 4.98 (1H, m), 5.31 (1H, m), 5.52 (1H, dd), 5.54
(1H, d), 5.93 (1H, dd), 6.00 (1H, d), 6.12 (1H, dd), 6.36
10 (1H, d, $\underline{J}$ 11.2).

Example 12 1(S),3(R)-Dihydroxy-20(R)-(5'-
-hydroxy-penta-1'(E),3'(E)-dien-1'-
-yl-9,10-secopregna-5(Z),7(E),
15 10(19)-triene (Compound 122)

Starting material: 121k. Crystals from methyl
formate; m.p.: 154-155°C; $\lambda_{\max}$ 231 nm (ϵ = 41228) and 264
nm (ϵ = 17876); δ (300 MHz) 0.58 (3H, s), 1.05 (3H, d, $\underline{J}$
6.6), 1.15-1.80 (12H, m), 1.89 (2H, t), 2.01 (2H, m), 2.14
20 (1H, m), 2.26 (1H, dd), 2.52 (1H, dd), 2.87 (1H, bd), 4.06
(2H, m), 4.12 (1H, m), 4.35 (1H, t), 4.89 (1H, m), 5.28
(1H, m), 5.53 (1H, dd), 5.67 (1H, d), 5.98 (1H, dd), 6.08
(1H, d, $\underline{J}$ 11.2), 6.16 (1H, dd), 6.32 (1H, d, $\underline{J}$ 11.2).

25 Example 13 1(S),3(R)-Dihydroxy-20(R)-(7'-hydr-
-oxy-7'-methyl-octa-1'(E),3'(E)-
5'(E)-trien-1'-yl)-9,10-secopregna-
-5(Z),7(E),10(19)-triene (Compound
125

30 Starting material: 124k. Compound 125 was
crystallized from methyl formate; $\lambda_{\max}$ 259 nm (ϵ = 53692),
268 nm (ϵ = 67103), and 279 nm (ϵ = 53256); δ (300 MHz)
0.56 (3H, s), 1.05 (3H, d, $\underline{J}$ 6.6), 1.34 (6H, s), 1.15-2.20
(17H, m), 2.31 (1H, dd), 2.60 (1H, bd), 2.83 (1H, bd), 4.22
35 (1H, m), 4.42 (1H, m), 4.99 (1H, m), 5.32 (1H, m), 5.57
(1H, dd), 5.79 (1H, d), 5.90-6.30 (5H, m), 6.38 (1H, d, $\underline{J}$
11.2).

Example 14

1(S),3(R)-Dihydroxy-20(R)-(7'-hydr-
-oxy-7'-ethyl-nona-1'(E),3'(E)-
5'(E)-trien-1'-yl)-9,10-secopregna-
-5(Z),7(E),10(19)-triene (Compound
127

5

Starting material 126k. Crystals from methyl
 formate-hexane; m.p.: 115-118°C. λ_{max} 260 nm ($\epsilon = 58040$),
 270 nm ($\epsilon = 72111$), and 281 nm ($\epsilon = 56714$); δ (300 MHz)
 0.56 (3H, s), 0.85 (6H, t), 1.05 (3H, d, J 6.6), 1.15-2.20
 10 (21H, m), 2.31 (1H, dd), 2.60 (1H, dd), 2.83 (1H, bd), 4.22
 (1H, m), 4.42 (1H, m), 5.00 (1H, m), 5.32 (1H, m), 5.59
 (1H, dd), 5.61 (1H, d), 6.00 (2H, m), 6.10-6.30 (3H, m),
 6.37 (1H, d, J 11.3).

15

Example 15

20(S)-(5'-Cyclopropyl-5'-hydroxy-
-penta-1'(E),3'(E)-dien-1'-yl)-1(S),
3(R)-dihydroxy-9,10-secopregna-5(Z),
7(E),10(19)-triene (Compounds 131 and
132)

20

These two isomeric compounds are prepared by using
 the procedures described in Preparations 8, 9, 14, 15 and
 Examples 1 and 2 and by substituting 3b (x=1) (described in
 Canadian Patent Application No. 2,051,418) for 3aj (x=1) in
 Preparation 8.

25

Example 16

1(S),3(R)-Dihydroxy-20(S)-(6'-hydr-
-oxy-hexa-1'(E),3'(E)-dien-1'-yl)-
-9,10-secopregna-5(Z),7(E),10(19)-
-triene (Compound 130)

30

This compound was prepared by following the procedure
 described in Example 5 and by using 20(S)-(3'-cyclopropyl-
 -3'-hydroxyprop-1'(E)-enyl)-1(S),3(R)-dihydroxy-9,10-seco-
 preгна-5(Z), 7(E), 10(19)-triene - isomer A or isomer B or
 mixtures thereof - (described in Canadian Patent Application No.
 2,051,418) as starting material instead of MC 903.

35

δ (300 MHz) 0.50 (3H, s), 0.93 (3H, d), 1.05-2.10
 (17H, m), 2.30 (1H, m), 2.34 (2H, q), 2.58 (1H, dd), 2.81
 (1H, bd), 3.67 (2H, t), 4.22 (1H, m), 4.42 (1H, m), 4.99

(1H, bs), 5.32 (1H, bs), 5.45-5.60 (2H, m), 5.85-6.15 (3H, m), 6.37 (1H, d).

Example 17

5

1(S),3(R)-Dihydroxy-20(S)-(6'-hydr-
-oxy-6'-methyl-hepta-1'(E),3'(E)-
-dien-1'-yl)-9,10-secopregna-5(Z),
7(E),10(19)-triene (Compound 134)

This compound is prepared by using the procedure described in Preparations 13 and 35 and Procedure 7 and by substituting 3bj (x=1) (described in Canadian Patent Application No. 2,051,418) for 3aj (x=1) in Preparation 13.

Example 18

15

1(S),3(R)-Dihydroxy-20(S)-(6'-ethyl-
-6'-hydroxy-octa-1'(E),3'(E)-
-dien-1'-yl)-9,10-secopregna-5(Z),
7(E),10(19)-triene (Compound 135)

This compound is prepared by using the procedure described in Example 17 but substituting compound 12 for compound 11 in Preparation 13.

Example 19

25

1(S),3(R)-Dihydroxy-20(R)-(6'-ethyl-
-6'-hydroxy-octa-1'(E),3'(E)-
-dien-1'-yl)-9,10-secopregna-5(Z),
7(E),10(19)-triene (Compound 136)

This compound is prepared by using the procedure described in Preparations 13 and 35 and Procedure 7 but substituting compound 12 for compound 11 in Preparation 13; δ (300 MHz) 0.56 (3H, s), 0.88 (6H, t), 1.04 (3H, d), 1.48 (4H, q), 1.15-2.17 (17H, m), 2.20 (2H, d), 2.32 (1H, dd), 2.60 (1H, dd), 2.83 (1H, dd), 4.23 (1H, m), 4.43 (1H, m), 5.00 (1H, m), 5.32 (1H, m), 5.52 (2H, m), 6.00 (3H, m), 6.38 (1H, d).

35

Example 20

1(S),3(R)-Dihydroxy-20-(5',6'-di-
-methyl-6'-hydroxy-hepta-1'(E),3'(E)-
-dien-1'-yl)-9,10-secopregna-5(Z),
7(E),10(19)-triene
(Compounds 137-140)

5

The four diastereoisomers of the title compound are prepared separately using the methods of Procedures 5, 6 and 7 and the appropriate starting materials 3aj (x=1) or 3bj (x=1) and 17 or 18.

10

Example 21Dermatological Cream Containing
Compound 111

In 1 g almond oil was dissolved 0.1 mg 111. To this solution was added 40 g of mineral oil and 20 g of
15 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 1 µg of 111 per gram of cream.

20

Example 22Capsules containing Compound 111

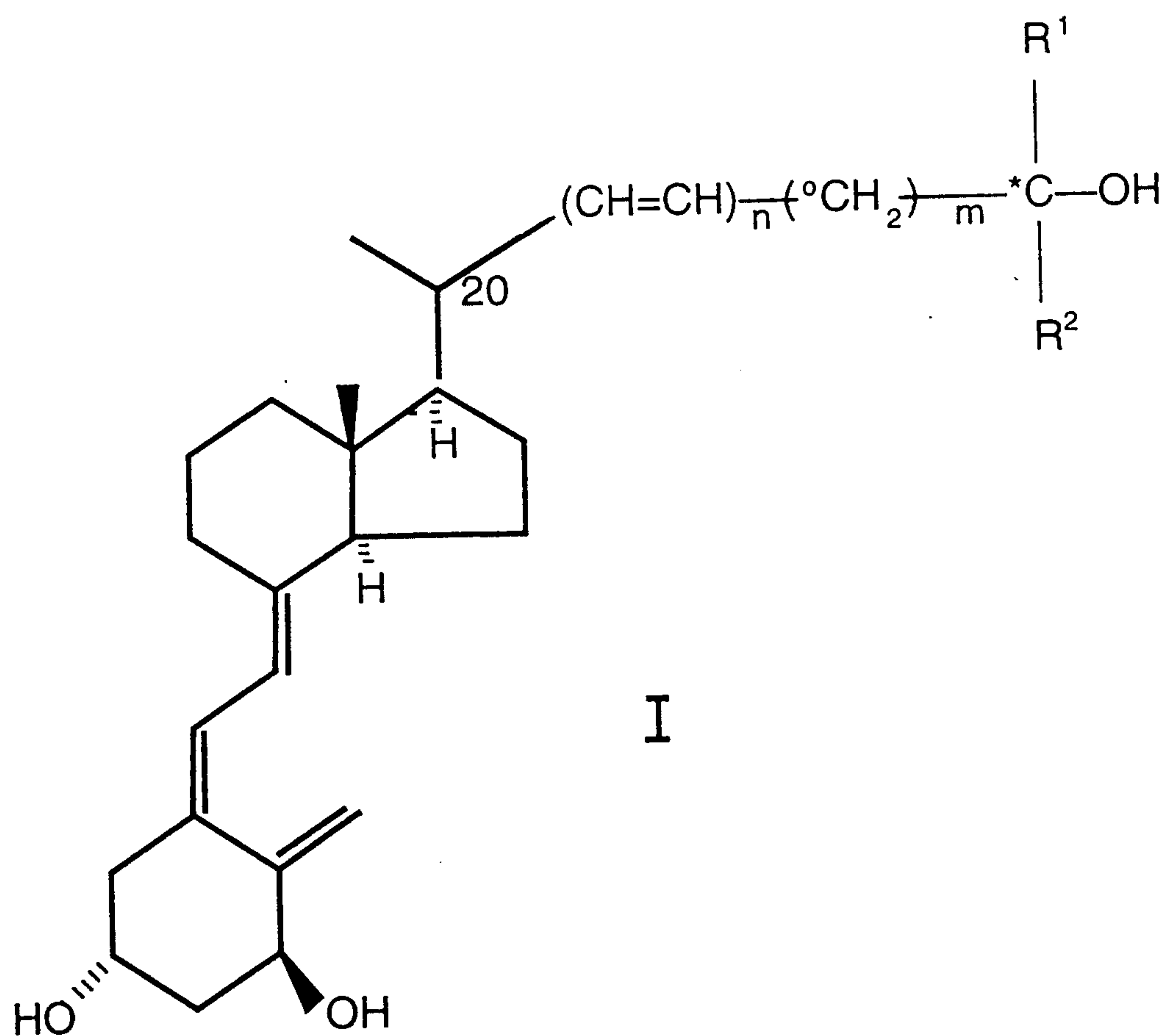
111 was suspended in arachis oil to a final concentration of 5 µg 111/ml oil. 10 Parts by weight of gelatine, 5 parts by weight glycerine, 0.08 parts by weight potassium sorbate, and 14 parts by weight distilled water
25 were mixed together with heating and formed into soft gelatine capsules. These were then filled each with 100 µl of the 111 in oil suspension, such that each capsule contained 0.5 µg 111.

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CLAIMS:

1. A compound of the Formula I

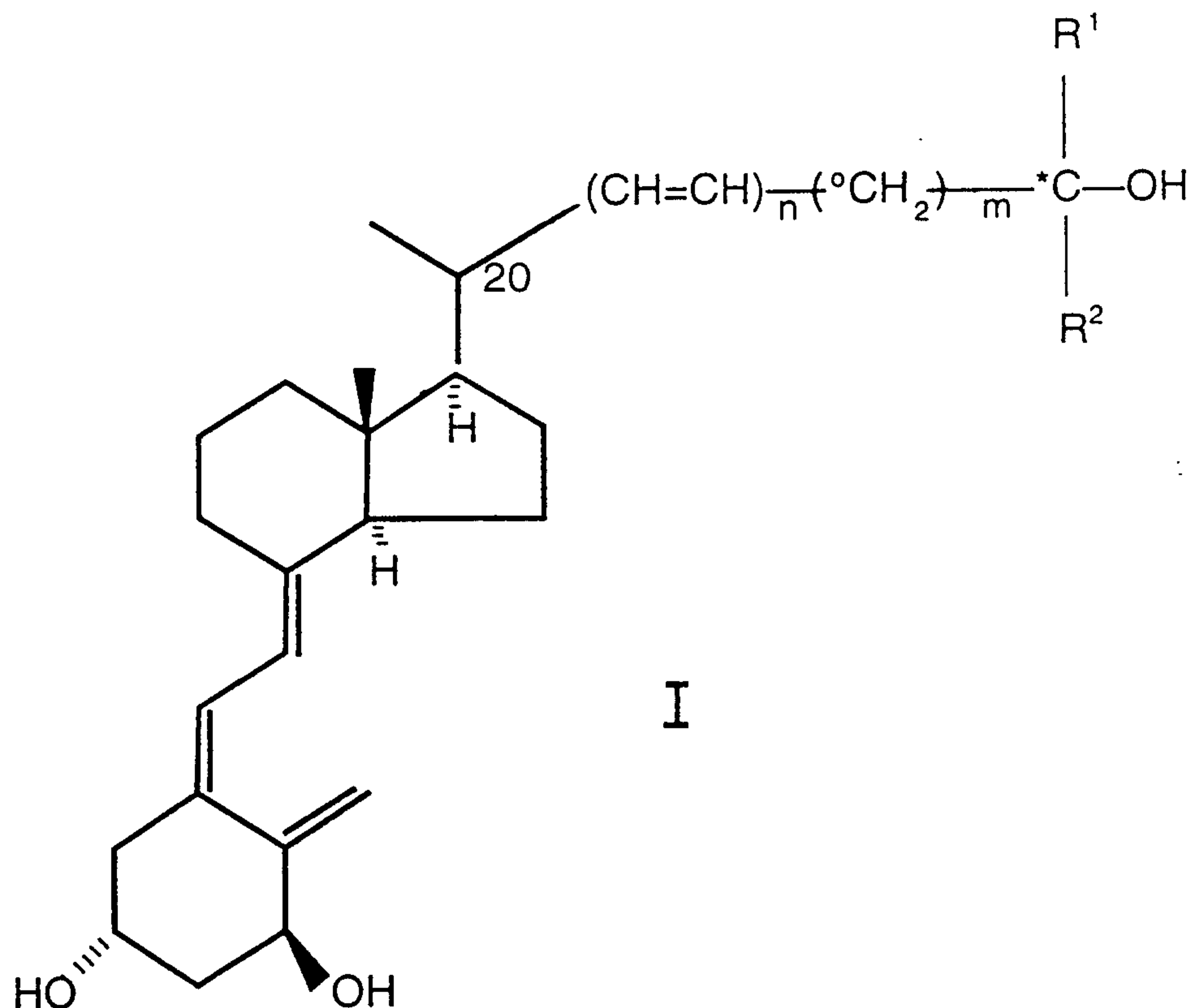


in which Formula, n is 2 or 3, m is 0 or an integer from 1 - 4; R^1 and R^2 (which may be the same or different) stand for hydrogen or C_1 - C_8 -hydrocarbyl, hydrocarbyl indicating the residue after removal of a hydrogen atom from a straight saturated hydrocarbon, a straight unsaturated hydrocarbon, a branched saturated hydrocarbon, a branched unsaturated hydrocarbon, a cyclic saturated hydrocarbon or a cyclic unsaturated hydrocarbon, or, taken together 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; in addition, at least one of R¹, R² and one of the m carbons designated by the "o" being unsubstituted or being substituted with at least one chlorine or fluorine atom; and finally one of the carbons designated "o" being unsubstituted or being substituted by at least one C₁-C₂ alkyl group; and derivatives of the compounds of Formula I in which at least one hydroxy has been transformed into a masked -O-acyl group, or a masked -O-glycosyl group or a masked phosphate ester group, said masked group being hydrolyzable *in vivo*; and other prodrugs thereof.

2. A mixture of diastereoisomers of a compound according to claim 1.
3. A diastereoisomer of a compound according to claim 1, in pure form.
4. 1(S),3(R)-Dihydroxy-20-(5'-hydroxy-5'-methyl-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.
5. 1(S),3(R)-Dihydroxy-20-(5'-ethyl-5'-hydroxy-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.
6. 1(S),3(R)-Dihydroxy-20-(6'-hydroxy-hexa-1'(E),-3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.
7. 1(S),3(R)-Dihydroxy-20-(5'-cyclopropyl-5'-hydroxy-penta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),-7(E),10(19)-triene (5'(R) and 5'(S) isomers).
8. 1(S),3(R)-Dihydroxy-20-(6'-hydroxy-6'-methyl-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.

9. A process for producing a compound of Formula I



in which Formula, n is 2 or 3, m is 0 or an integer from 1 - 4; R^1 and R^2 (which may be the same or different) stand for hydrogen or 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 together 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; in addition, at least one of R^1 , R^2 and one of the " m " carbons designated by the " ^{0} " being unsubstituted or being substituted with at least one chlorine or fluorine atom; and finally one of the carbons designated " ^{0} " being unsubstituted or being substituted by at least one C_1 - C_2 alkyl group; and derivatives of

the compounds of Formula I in which at least one hydroxy has been transformed into a masked -O-acyl group, or a masked -O-glycosyl group or a masked phosphate ester group, said masked group being hydrolyzable in vivo; and other prodrugs thereof, or an analogue thereof, which process comprises:

a) elaborating the side chain attached to C-20 in said compound of Formula I from the 20(R) or 20(S) isomers of 1(S),3(R)-bis-(tert-butyldimethylsilyloxy)-20-formyl-9,10-secopregna-5(E),7(E),10(19)-triene, or 1(S),3(R)-bis-(tert-butyldimethylsilyloxy)-20-(2'-formyl-1'(E)-ethen-1'yl)-9,10-secopregna-5(E),7(E),10(19)-triene or their corresponding 5(Z) isomers, either:

- (i) by reaction with a Wittig-type reagent followed by reaction of the resulting ester with an organometallic reagent or a reducing agent; or
- (ii) by reaction with a Wittig-type reagent followed by reaction of the resulting ketone with a reducing agent; or
- (iii) by reaction with the carbanion 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 base, followed by reductive elimination of the product β -hydroxy-sulphone; and

b) desilylating the product from step (a).

10. The process of claim 9 wherein said desilylation is carried out with tetrabutylammonium fluoride.

11. The process of claim 9 or claim 10, wherein said Wittig-type reagent used in step a)(i) comprises $\text{Ph}_3\text{P}^+\text{-CH}^-\text{-CH=CH-COOCH}_3$.

12. The process of claim 9, claim 10 or claim 11, wherein said organometallic reagent used in step a)(i) is R^1Li .

13. The process of claim 9, claim 10 or claim 11, wherein said reducing agent used in step a)(i) comprises $\text{I-Bu}_2\text{ AlH}$.

14. The process of claim 9 or claim 10, wherein said Wittig-type reagent used in step a)(ii) comprises $\text{Ph}_3\text{P}^+-\text{CH}^--\text{C}(\text{O})-\text{R}^2$.

15. The process of claim 9, claim 10 or claim 13, wherein the reducing agent used in step a)(ii) comprises NaBH_4 .

16. The process of claim 9 or claim 10, wherein said base used in step a) (iii) comprises two equivalents of lithium di-isopropylamide.

17. The process of claim 9 or claim 10, wherein said reductive elimination in step a)(iii) is carried out by using sodium amalgam.

18. The process of claim 9, claim 10 or claim 15, further including in step a)(iii), a step of derivitisation of said β -hydroxy group.

19. The process of claim 18 wherein said derivitisation of said β -hydroxy group is carried out with benzoyl chloride and a base.

20. The process of any one of claims 9 to 19, further including the step of separating a pure diastereoisomer in said compound from step (a) from a mixture of diastereoisomers.

21. The process of claim 20 wherein said separation is carried out by chromatography.

22. The process of any one of claims 9 to 21, further including the step of subjecting said compound from step (a) to a triplet-sensitized photoisomerisation to the 5Z isomer.

23. The process according to any one of claims 9 to 19, for preparing a mixture of diastereoisomers of a compound as defined in claim 1.

24. The process according to claim 23, further including the step of separating the mixture of diastereoisomers so formed, thereby preparing a diastereoisomer of a compound of Formula I as defined in claim 1, in pure form.

25. A process according to any one of claims 9 to 22, for preparing 1(S),3(R)-dihydroxy-20-(5'-hydroxy-5'-methyl-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E)-,10(19)-triene.

26. A process according to any one of claims 9 to 22, for preparing 1(S),3(R)-dihydroxy-20-(5'-ethyl-5'-hydroxy-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E)-,10(19)-triene.

27. A process according to any one of claims 9 to 22, for preparing 1(S),3(R)-dihydroxy-20-(6'-hydroxy-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene.

28. A process according to any one of claims 9 to 22, for preparing 1(S),3(R)-dihydroxy-20-(5'-cyclopropyl-5'-hydroxy-penta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5-(Z),7(E),10(19)-triene (5'(R) and 5'(S) isomers).

29. A process according to any one of claims 9 to 22, inclusive, for preparing 1(S),3(R)-dihydroxy-20-(6'-hydroxy-6'-methyl-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7-(E),10(19)-triene.

30. A process for producing the 20(R) and 20(S) isomers of 1(S),3(R)-dihydroxy-20-(6'-hydroxy-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E)-10(19)-triene, which process comprises: treating the 20(R) and 20(S) isomers of 1(S),3(R)-dihydroxy-20-(3'-cyclopropyl-3'-hydroxyprop-1'(E)-en-1'-yl)-9,10-secopregna-5(Z),7(E)-10(19)-triene with a carboxylic anhydride; and subjecting said product to basic hydrolysis.

31. The process of claim 30, wherein said carboxylic anhydride comprises trifluoroacetic anhydride.

32. The process of claim 30 or claim 31, wherein said basic hydrolysis is carried out with alcoholic alkali hydroxide.

33. A pharmaceutical composition containing at least one of the compounds of Formula I of claim 1, claim 2 or claim 3, together with at least one of a pharmaceutically-acceptable, non-toxic carrier and an auxiliary agent.

34. The pharmaceutical composition of claim 33, wherein said compound of claim 1 comprises 1(S),3(R)-dihydroxy-20-(5'-hydroxy-5'-methyl-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.

35. The pharmaceutical composition of claim 33, wherein said compound of claim 1 comprises 1(S),3(R)-dihydroxy-20-(5'-ethyl-5'-hydroxy-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.

36. The pharmaceutical composition of claim 33, wherein said compound of claim 1 comprises 1(S),3(R)-dihydroxy-20-(6'-hydroxy-hexa-1'(E),-3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.

37. The pharmaceutical composition of claim 33, wherein said compound of claim 1 comprises 1(S),3(R)-dihydroxy-20-(5'-cyclopropyl-5'-hydroxy-penta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),-7(E),10(19)-triene (5'(R) and 5'(S) isomers).

38. The pharmaceutical composition of claim 33 wherein said compound of claim 1 comprises 1(S),3(R)-dihydroxy-20-(6'-hydroxy-6'-methyl-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.

39. A pharmaceutical composition according to any one of claims 33 to 38, for topical use, containing from 0.1 - 100 $\mu\text{g/g}$ of a compound of Formula I.
40. A pharmaceutical composition according to any one of claims 33 to 38, for oral and parenteral use, containing from 0.01 - 100 μg of a compound of Formula I.
41. A pharmaceutical composition according to claim 39 or claim 40 in dosage unit form.
42. A method for producing a pharmaceutical composition which comprises admixing at least one of the compounds of Formula I of claim 1, together with at least one of a pharmaceutically acceptable, non-toxic carrier and an auxiliary agent.
43. The method of claim 42, wherein said compound of Formula I is 1(S),3(R)-dihydroxy-20-(5'-hydroxy-5'-methyl-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.
44. The method of claim 42, wherein said compound of Formula I is 1(S),3(R)-dihydroxy-20-(5'-ethyl-5'-hydroxy-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.
45. The method of claim 42, wherein said compound of Formula I is 1(S),3(R)-dihydroxy-20-(6'-hydroxy-hexa-1'(E),-3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.
46. The method of claim 42, wherein said compound of Formula I is 1(S),3(R)-dihydroxy-20-(5'-cyclopropyl-5'-hydroxy-penta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),-7(E),10(19)-triene (5'(R) and 5'(S) isomers).

47. The method of claim 42, wherein said compound of Formula I is 1(S),3(R)-dihydroxy-20-(6'-hydroxy-6'-methyl-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.

48. A method for producing a pharmaceutical composition as defined in any one of claims 42 to 47, for topical use, containing from 0.1 - 100 $\mu\text{g/g}$ of a compound of Formula I.

49. A method for producing a pharmaceutical composition as defined in any one of claims 42 to 47, for oral or parenteral use, containing a daily dose of from 0.01 - 100 μg of a compound of Formula I.

50. Use of a compound as defined in claim 1 for preparing a pharmaceutical composition for the treatment or prophylaxis of auto-immune diseases, diabetes mellitus, hypertension, acne, alopecia, skin ageing, photoageing, inflammatory diseases, rheumatoid arthritis, asthma, and diseases characterized by at least one of abnormal cell differentiation, cell proliferation and imbalance in the immune system.

51. Use of a compound as defined in claim 50, for preparing a pharmaceutical composition for the treatment or prophylaxis of cancer.

52. Use of a compound as defined in claim 50, for preparing a pharmaceutical composition for the treatment or prophylaxis of psoriasis.

53. Use of a compound as defined in claim 50, for preparing a pharmaceutical composition for the treatment or prophylaxis of skin ageing.

54. Use of a compound as defined in claim 1 for the treatment or prophylaxis of auto-immune diseases, diabetes mellitus, hypertension, acne, alopecia, skin ageing, photoageing, inflammatory diseases, rheumatoid arthritis, asthma, and diseases

characterized by at least one of abnormal cell differentiation, cell proliferation and imbalance in the immune system.

55. Use of a compound as claimed in claim 54 for the treatment or prophylaxis of cancer.

56. Use of a compound as claimed in claim 54 for the treatment or prophylaxis of psoriasis.

57. Use of a compound as claimed in claim 54 for the treatment or prophylaxis of skin aging.

58. The use as claimed in any one of claims 50 to 57, wherein said compound is 1(S),3(R)-dihydroxy-20-(5'-hydroxy-5'-methyl-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.

59. The use as claimed in any one of claims 50 to 57, wherein said compound is 1(S),3(R)-dihydroxy-20-(5'-ethyl-5'-hydroxy-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.

60. The use as claimed in any one of claims 50 to 57, wherein said compound is 1(S),3(R)-dihydroxy-20-(6'-hydroxy-hexa-1'(E),-3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.

61. The use as claimed in any one of claims 51 to 57, wherein said compound is 1(S),3(R)-dihydroxy-20-(5'-cyclopropyl-5'-hydroxy-penta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),-7(E),10(19)-triene (5'(R) and 5'(S) isomers).

62. The use as claimed in any one of claims 50 to 57, wherein said compound is 1(S),3(R)-dihydroxy-20-(6'-hydroxy-6'-methyl-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),-10(19)-triene.

