



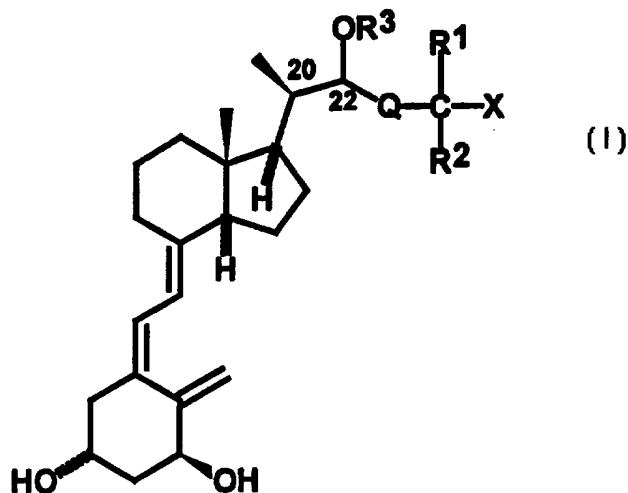
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07C 401/00, A61K 31/59	A1	(11) International Publication Number: WO 97/46522 (43) International Publication Date: 11 December 1997 (11.12.97)
(21) International Application Number: PCT/DK97/00225 (22) International Filing Date: 15 May 1997 (15.05.97) (30) Priority Data: 9611603.3 4 June 1996 (04.06.96) GB (71) Applicant (for all designated States except US): LEO PHARMACEUTICAL PRODUCTS LTD. A/S (LØVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB) [DK/DK]; Industriparken 55, DK-2750 Ballerup (DK). (72) Inventor; and (75) Inventor/Applicant (for US only): BRETTING, Claus, Aage, Svendsgaard [DK/DK]; Smallegade 42, 4. sal, tv., DK-2000 Frederiksberg (DK). (74) Agent: KRISTENSEN, Per, Rydahl; Leo Pharmaceutical Products LTD. A/S, Patent Dept., Industriparken 55, DK-2750 Ballerup (DK).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>

(54) Title: NOVEL VITAMIN D ANALOGUES

(57) Abstract

The present invention relates to compounds of formula (I), in which formula X is hydrogen or hydroxy; R¹ and R², which may be the same or different, stand for hydrogen or a C₁-C₃ alkyl radical; or R¹ and R², taken together with the carbon atom bearing the group X, can form a C₃-C₆ carbocyclic ring; R³ stands for a C₁-C₃ alkyl radical, an aryl or an aralkyl radical, or for YR⁴, in which Y stands for the radicals -CO-S-, -CS-O- or -CS-S-, and R⁴ stands for a C₁-C₃ alkyl radical or an aryl or an aralkyl radical; Q is (CH₂)_n, n being 1-4. R¹, R² and Q independently may optionally be substituted with one or more fluorine atoms. The compounds show strong activity in inducing differentiation and inhibiting undesirable proliferation of certain cells as well as immunomodulating and anti-inflammatory effects.



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NOVEL VITAMIN D ANALOGUES

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This invention relates to a hitherto unknown class of compounds which shows strong activity in inducing differentiation and inhibiting undesirable proliferation of certain cells, including skin cells and cancer cells, as well as immunomodulating and antiinflammatory effects, to pharmaceutical preparations containing these compounds, to dosage units of such preparations, and to their use in the treatment and/or prophylaxis of diseases characterized by abnormal cell differentiation and/or cell proliferation such as e.g. psoriasis and other disturbances of keratinization, HIV-associated dermatoses, wound healing, cancer, including skin cancer, and of diseases of, or imbalance in, the immune system, such as host versus graft and graft versus host reaction and transplant rejection, and autoimmune diseases, such as discoid and systemic lupus erythematosus, diabetes mellitus and chronic dermatoses of autoimmune type, e.g. scleroderma and pemphigus vulgaris, and inflammatory diseases, such as rheumatoid arthritis and asthma, as well as a number of other disease states including hyperparathyroidism, particularly secondary hyperparathyroidism associated with renal failure, cognitive impairment or senile dementia (Alzheimers disease) and other neurodegenerative diseases, hypertension, acne, alopecia, skin atrophy, e.g. steroid induced skin atrophy, skin ageing, including photo-ageing, and to their use for promoting osteogenesis and treating/preventing osteoporosis and osteomalacia.

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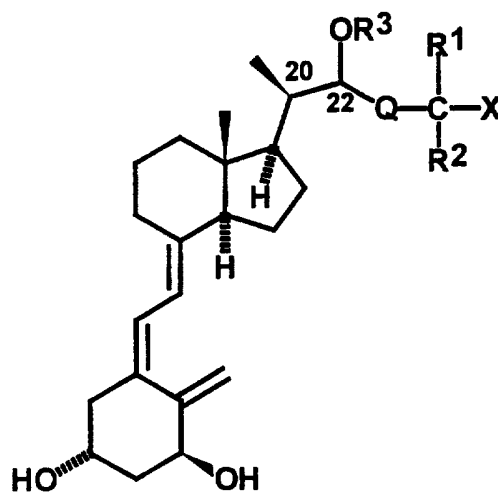
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The compounds of the invention constitute a novel class of vitamin D analogues and are represented by the general formula I

30



I

in which formula X is hydrogen or hydroxy; R^1 and R^2 , which may be the same or different, stand for hydrogen or a C_1 - C_3 alkyl radical; or R^1 and R^2 ,
 5 taken together with the carbon atom bearing the group X, can form a C_3 - C_6 carbocyclic ring; R^3 stands for a C_1 - C_3 alkyl radical, an aryl or an aralkyl radical, or for YR^4 , in which Y stands for the radicals -CO-S-, -CS-O- or -CS-S-, and R^4 stands for a C_1 - C_3 alkyl radical or an aryl or an aralkyl radical; Q is $(CH_2)_n$, n being 1 - 4. R^1 , R^2 and Q independently may optio-
 10 nally be substituted with one or more fluorine atoms.

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

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

Examples of R^3 and R^4 include, but are not limited to, methyl, ethyl, propyl, normal-, iso- and cyclopropyl, phenyl and benzyl.

Most preferred examples of Q include di- and trimethylene.

As can be seen from formula I, depending on the meanings of R^1 , R^2 , R^3 , Q and X the compounds of the invention can comprise several diastereoisomeric forms (e.g. $\underline{R}$ or $\underline{S}$ configuration at the carbon atom bearing the radicals R^1 , R^2 , and X). The invention covers all these diastereoisomers
5 in pure form as well as mixtures thereof.

In particular, both diastereoisomers having the two possible configurations (in the following designated "A" and "B") at the carbon atom marked "22" are included. A is the preferred one.

In addition, prodrugs of I in which one or more of the hydroxy
10 groups are masked as groups which can be reconverted to hydroxy groups in vivo can also be envisaged.

Compounds of formula I in which X is hydrogen also may act as prodrugs, as these compounds are relatively inactive in vitro, but are converted to active compounds of formula I by enzymatic hydroxylation
15 after administration to the patient.

It has been known for more than two decades that vitamin D (D_3/D_2) is a pro-hormone which is hydroxylated in vivo to the active hormone $1\alpha,25$ -dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$ or calcitriol). Vitamin D_2 is metabolized in the same way as D_3 and is bioequivalent with D_3 in
20 humans.

$1,25(OH)_2D_3$ is responsible for maintaining calcium (and phosphate) homeostasis by regulation of the intestinal calcium absorption, the renal calcium excretion and the bone mineralization/resorption. Other hormones such as parathyroid hormone (PTH) and calcitonin function as
25 positive and negative feedback calcium regulators respectively in concert with $1,25(OH)_2D_3$ [1],[2].

This knowledge has led to the use of $1,25(OH)_2D_3$ and its prodrug 1α -hydroxy- D_3 (alfacalcidol, INN) in the treatment of patients with kidney failure, where the important renal 1α -hydroxylation of 25-hydroxy vitamin D
30 is impaired, leading to hypocalcemia, secondary hyperparathyroidism and

bone demineralization (renal osteodystrophy) [1].

It has since been shown that the (nuclear) receptor for $1,25(\text{OH})_2\text{D}_3$ (VDR) is present, not only in the intestine, bone and kidney, but in a large number of other locations, such as e.g. parathyroid glands, islets of the pancreas, mammary gland cells, keratinocytes and fibroblasts of the skin, circulating monocytes and (activated) lymphocytes, and many other normal cell types and tissue; in addition the VDR is also present in several cancer cell lines [2],[3],[4].

In accordance with this widespread occurrence of the VDR, it has been experimentally demonstrated that $1,25(\text{OH})_2\text{D}_3$ has biological effects over and beyond the "classical" effects on calcium regulation.

It was shown that $1,25(\text{OH})_2\text{D}_3$ is able to stimulate the differentiation of cells and inhibit excessive cell proliferation [5], suggesting potential use in the treatment of e.g. psoriasis and cancer. It was also shown that $1,25(\text{OH})_2\text{D}_3$ influences the effects and/or production of interleukins [6], indicating the potential use of this compound in the treatment of immunological disorders, such as e.g. autoimmune diseases and rejection of transplants.

The use of $1,25(\text{OH})_2\text{D}_3$, or its pro-drug $1\alpha\text{-OH-D}_3$, for the treatment of several other disease states has also been suggested: hypertension [7], diabetes mellitus [8], alopecia [9], acne [10], osteoporosis [11] and neurodegenerative disorders [12].

The inhibition of angiogenesis by $1,25(\text{OH})_2\text{D}_3$ [13] indicates a possible inhibition of tumour growth via reduction of the growth of new blood vessels into the tumour.

However, the therapeutic possibilities of $1,25(\text{OH})_2\text{D}_3$ in several of these indications are severely limited by the potent effect of this hormone on calcium metabolism, because serious side effects due to hypercalcemia will result from the high doses necessary to obtain a therapeutic effect on e.g. psoriasis or cancer or immunological disorders.

In order to overcome this problem a large number of vitamin D analogues have been described, and some of these show selectivity in favour of the cell differentiation inducing/cell proliferation inhibiting activity as compared with the effect on calcium metabolism [3],[4],[14].

5 This work has resulted in therapeutically useful, or potentially useful, vitamin D analogues. Thus, the vitamin D₃ analogue, MC 903 (calcipotriol, calcipotriene, INN, cf. table 1), is a potent inducer of cell differentiation and inhibitor of cell proliferation which shows only moderate activity on calcium metabolism in vivo [15].

10 Calcipotriol is on the market as a safe and effective drug for the treatment of the hyperproliferative disease of the skin, psoriasis. Calcipotriol renders improvement, without hypercalcemia, in 70 - 80% of the patients [16],[17]. However, this selectivity is not paralleled by in vitro studies, which show that calcipotriol binds equally well as 1,25(OH)₂D₃ to the
15 intestinal vitamin D receptor. The low in vivo activity on calcium metabolism of calcipotriol is due to a rapid metabolism of the compound, thus limiting the potential of this compound for systemic use [16].

 The efficacy of several vitamin D analogues in inducing differentiation and inhibiting proliferation of cancer cells has been
20 demonstrated, both in vitro and in vivo, see e.g. [3], [4], [11], [14], [18], [19], [20], [21], [22], [23].

 One such interesting analogue is EB 1089 [22], [24] which inhibits the growth of breast cancer cells in vitro and in vivo [4], [25]. There is a definite selectivity between the anti-cancer and the calcemic effects in vivo,
25 but the molecular basis for this selectivity is not really understood [4]. EB 1089 is presently in clinical study [26].

 A promising series of vitamin D analogues having differentiation inducing and antiproliferative activity are the 20-epi-analogues [18], [27], [28] in which the stereo-chemistry at carbon-20 in the side chain is altered
30 to the "unnatural", so-called 20-epi, configuration. The two most studied of these 20-epi-analogues are KH 1060 (20-epi-22-oxa-25,26,27-trihomo-1,25-(OH)₂D₃; lexacalcitol, INN) [18], [29] and MC 1288 (20-epi-1,25(OH)₂D₃;

cf. table 1) [18], [30].

It was found that the change from 20-"normal" to 20-"epi" configuration has a profound and advantageous biological significance. Generally speaking, the most active of these analogues are characterized by their high, or very high, potencies as regulators of cell growth and/or immune responses; their calcemic activity being equivalent to that of $1,25(\text{OH})_2\text{D}_3$, or a few times stronger [18].

Separation of immunoregulating activity from calcemic activity has also been demonstrated for some vitamin D analogues [18], [27]. Some important findings concerning the immunological effects of $1,25(\text{OH})_2\text{D}_3$ itself will be illustrative of the present state of the art; references to original papers can be found in recent articles, e.g. [27], [31] and [32] (dermatology in particular).

$1,25(\text{OH})_2\text{D}_3$ stimulates the differentiation of monocytes towards macrophages and enhances their antibacterial activity, and $1,25(\text{OH})_2\text{D}_3$ restores normal immune functions in vitamin D deficiency states in vivo. On the other hand $1,25(\text{OH})_2\text{D}_3$ has an immunosuppressive effect on the antigen-mediated part of the immune system. The proliferation of activated T-lymphocytes is inhibited with down-regulation of cytokines IL-2 and INF- γ . In vitro, this down-regulation leads to an indirect inhibition of the formation of antibodies (IgM and IgG) from B-lymphocytes. Cytotoxic T-cells are also inhibited and regulatory/suppressor T-lymphocytes are stimulated. Some studies also report downregulation by $1,25(\text{OH})_2\text{D}_3$ of the production/-release of cytokines such as IL-1 and TNF- α from antigen-stimulated monocytes/macrophages.

These findings suggest clinical applications of $1,25(\text{OH})_2\text{D}_3$ in the fields of organ or cell transplantations and in autoimmune diseases, but its calcemic effects severely limit its usefulness in clinical practice.

The new vitamin D analogues [18], [27] however, show some promise in this direction, as the following examples will indicate.

The 20-epi-analogue MC 1288 was effective as an immunosuppressant in a rat model of heart and small bowel transplantations, preventing graft rejection [30]; the serum calcium level was moderately increased.

5 The 20-epi- and the 20-normal analogues KH 1060 and CB 966 prolonged skin allograft survival in mice [33]. KH 1060 was the most potent immunosuppressor, but induced hypercalcemia in the highest, and most effective, dose. Combination treatment with Cyclosporin A (CyA) was more effective than either agent alone, with moderate rise of serum calcium. MC
10 1288 and two other 20-epi-analogues were also very effective in this assay [34e] and were less hypercalcemic than KH 1060.

 KH 1060 was an effective immunoregulator in the autoimmune disease, type I diabetes, which was studied in the non-obese diabetic (NOD) mouse [35]. The effect on calcium and bone was only slight, in contrast to
15 $1,25(\text{OH})_2\text{D}_3$ (which otherwise was an effective immunomodulator, too).

 In a related study [36] where the effect of autoimmune memory was studied by the transplantation of completely MHC¹-matched, or syngeneic, β -cells of the islets of the pancreas to NOD mice, both KH 1060 and CyA were very effective in delaying autoimmune disease recurrence, but both
20 were toxic in the most effective high doses. KH 1060 and CyA combined, in lower, nontoxic, doses were as effective as each compound in high dose, and the effect on calcium metabolism was reduced.

 There is recent evidence [37] which indicates that the powerful activity of the 20-epi-analogues KH 1060 and MC 1288 may be connected with
25 enhanced transcriptional activity, compared to $1,25(\text{OH})_2\text{D}_3$, but in vivo there is a long range of other factors, such as e.g. absorption, transport to target cells (binding proteins) and metabolic and cellular uptake properties, that may determine the non-classic versus calcitropic activities of vitamin D analogues [11], [14](p.301), [20], so that the selection of potential
30 candidates for clinical application cannot solely be based on in vitro

¹ major histocompatibility complex

screening.

As will be seen from the above description of the present state of the art, the newer vitamin D analogues are quite effective agents for treating psoriasis and they are promising as immunosuppressive and anticancer agents. However, there is still a need for an improved efficacy and a higher safety ratio in respect to the calcitropic side effects.

The compounds of the present invention have new and unexpected advantageous properties, which mean that they are promising agents, possessing increased efficacy or reduced side effects, for treating such pathological states for which $1,25(\text{OH})_2\text{D}_3$ or its analogues would be indicated, but for their calcemic (side) effect.

The topic of the relationship between the chemical structure of vitamin D analogues and their biological activity (in vitro or in vivo) has been discussed; for recent reviews see e.g. [3], [21]. For newer analogues from LEO, see [34a-d] and [38a-d]; in these studies systematic structural modifications has been correlated with inhibition of proliferation and induction of differentiation of U 937 leukaemia cells, with calcemic activity in the rat, and with vitamin D receptor binding. The structural modifications include: side chain length and branching [34a-d], [38a-d], do.-unsaturation [34a,b,c], [38c,d], C-20-stereochemistry [34a,b,c], [38b,c], heteroatoms or aromatic rings in the side chain [34b], [38b] and hydroxy or alkoxy substitution at C-20 [34d], C-22 [34c] and C-24 [38c]. It appears that there is frequently very big variation in the activity, even for small structural changes [34a,d], [38b,c]. In most cases there is little relationship between in vitro anti-cancer activity and in vivo calcemic activity, or receptor binding affinity. Some receptor binding is evidently necessary for cell regulating activity [27], but e.g. in the case of 20- and 22-hydroxy/alkoxy substituted analogues, potent anti-cancer activity is compatible with very low receptor binding [34c,d]. Correlations between structure and immunological activity has also been discussed [18], [27]; it is found that some of the 20-epi analogues are potent immunosuppressive agents.

Summarizing this evidence: while it may be possible, within a

confined series of very closely related compounds, to some extent to correlate a structural change with the result from a well-known biological assay, it is impossible to make predictions of the activity in a new assay from the chemical structure alone.

5 Surprisingly, compounds 101 and 102 of the present invention have new and unexpected biological activity in the assays presented in table 1, in which table also the corresponding activities of some closely related reference compounds are included. The calcemic activities of the reference compounds have been described [15], [18], [34c], and also MLR-data for MC
10 1288 [18], but it is apparent that the potent effects of the compounds of the invention on skin cell proliferation and mixed lymphocyte reaction combined with only moderate calcemic activity could not be predicted from these prior art data.

European patent application 0 296 800, filing date 21st June, 1988,
15 discloses compounds which are vitamin D analogues containing a saturated, all carbon, side chain, substituted at position 22 with a hydroxy or a lower alkyloxy group and these compounds are claimed to be useful in the treatment of disease states characterized by metabolic calcium deficiencies or having tumour cell differentiation-inducing activity. Similar compounds
20 are also described in the non-patent literature [39], [40]. They were tested for vitamin D activity, which they did not have, i.e. no significant hypercalcemic effect in rats [39], and for their ability to induce differentiation of HL-60 cancer cells. The most active compound was 22S-methoxy-1,25(OH)₂D₃ which was 0.25 times as potent as 1,25(OH)₂D₃ in this assay.
25 The receptor binding affinity of 22S-methoxy-1,25(OH)₂D₃ was 0.03 times that of 1,25(OH)₂D₃, [40].

The compounds I of the present invention differ from these prior art compounds by having the above mentioned "unnatural" 20-epi-configuration. This configuration is also present in several other newer
30 vitamin D analogues, among them the compounds disclosed in our previous international patent application number PCT/DK90/00156, filing date 19th June, 1990, publication number WO 91/00271, and international patent

application number PCT/DK93/00105, filing date 23rd March, 1993, publication number WO 93/19044, and in Japanese patent application, publication number 7-304733, filing date 10th May 1994. These 20-epi-analogues are stated to have cell differentiation inducing activity etc.

5 The present compounds I are distinguished from the compounds of PCT/DK90/00156 and Japanese patent application 7-304733 in having an alkyloxy or alkyl(aryl)oxy carbonyloxy (or thio-/dithio-alkyl(aryl)oxy carbonyloxy) substituent in position 22 of the side chain, instead of
10 hydrogen atoms or a hydroxy group or a protected hydroxy group in this position, and are distinguished from the compounds of PCT/DK93/00105 which carry a carbon-carbon triple bond in position 23,24 of the side chain, in having only carbon-carbon single bonds in the side chain. The structural differences of the present compounds I from the related 20-epi vitamin D
15 analogues of the above mentioned patent applications made it possible to achieve new and unexpected advantages, as demonstrated in the biological assays mentioned in the following.

 In order to demonstrate the effectiveness of the compounds of formula I of the invention, the information of Table 1 is referred to: in particular columns "HaCaT, rel.", "HaCaT, max.%", "MLR, rel.", and "Calc.,
20 rel."; the meaning of which is explained in the following.

 A useful assay for the rating of test compounds for antiproliferative activity in skin cells, e. g. antipsoriatic effect, is the in vitro assay using HaCaT, a spontaneously immortalized, non-tumorigenic human skin keratinocyte cell line, [41], measuring ^3H -thymidine uptake.

25 An *in vitro* assay for the rating of test compounds for immunosuppressive potency is the mixed lymphocyte reaction assay, "MLR", measuring the allogeneic stimulation of mouse spleen lymphocytes: lymphocytes, obtained from the spleens of BALB/c and CB6F1 mice, are stimulated by co-cultivating $5 \times 10^6/\text{ml}$ cells from BALB/c mice (responders)
30 with $7.5 \times 10^6/\text{ml}$ cells from CB6F1 mice (inducers). The mixed cultures of lymphocytes are incubated with the test compounds for 72 hours. Cellular DNA-synthesis is assessed by the incorporation of ^3H -thymidine in the DNA.

Generally, the classical effects of 1,25(OH)₂ vitamin D₃ on the calcium balance in the organism, including calcemic and calciuric activities, are unwanted in the vitamin D analogues of the present invention, in which selectivity for e.g. inhibition of the proliferation of certain cells and/or
5 immunosuppressive activity is normally desired.

The calcemic activity of the compounds was determined in rats *in vivo*, as previously described [15]. In table 1, column "Calc., rel.", the calcemic activities of selected compounds (relative to 1,25(OH)₂D₃) are listed; as mentioned, low values for the compounds of the present invention
10 are ordinarily preferred.

It appears from table 1 that the two selected exemplified compounds, Comp. 101 and Comp. 102 are considerably more potent than 1,25(OH)₂D₃ in the HaCaT-assay (psoriasis model), while retaining the same, or higher, maximal inhibition at 10⁻⁷ M as 1,25(OH)₂D₃. In addition
15 the calcemic activity is only about half as large as that of 1,25(OH)₂D₃.

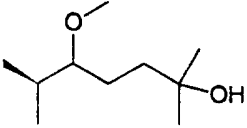
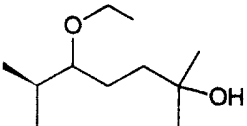
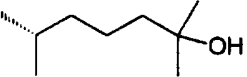
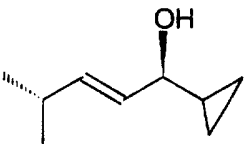
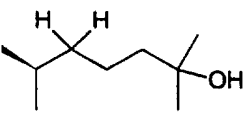
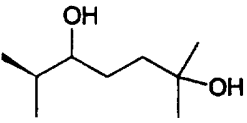
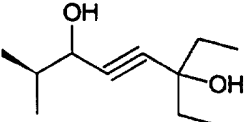
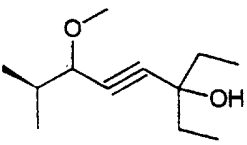
Concerning the other important property of the compounds I of the invention, their immunosuppressive activity, it is apparent from Table 1, column "MLR, rel.", that the selected Compounds 101 and 102 have potent effects, also in comparison with the prior art reference compounds. Of these,
20 the compound MC1288 is particularly interesting, as it has been demonstrated to have a valuable immunosuppressive activity in animal transplantation experiments [30]. In addition the compounds of the present invention exhibit a favourable ratio between the relative MLR-potency and the relative calcemic activity.

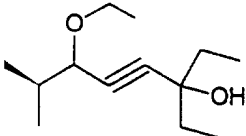
25 Thus, also when the immunosuppressive properties are considered, less danger of calcemic side effects is to be expected from the present compounds I, than from those of prior art mentioned in table 1.

Table 1

Biological Tests of Compounds I and Reference Compounds

5

Side chain at C-17 O	Comp. No.	Code No.	HaCaT rel. □, ¶	HaCaT max.% •	MLR rel. □, ¶	Calc. rel. □
	101		28	92	175	0.45
	102		137	85	161	0.50
Reference compounds						
		1,25*	1	85	1	1
		MC903#	1.8	78	0.6	0.005
		MC1288	43	76	150	2.5
		CB1297	45	75	12	n.d.
		GS1535	313	82	13	8.2
		GS1725	4.4	96	150	12

Side chain at C-17 ○	Comp. No.	Code No.	HaCaT rel. α, ¶	HaCaT max. % •	MLR rel. α, ¶	Calc. rel. α
		GS1720	3.9	70	36	1.2

Notes to Table 1

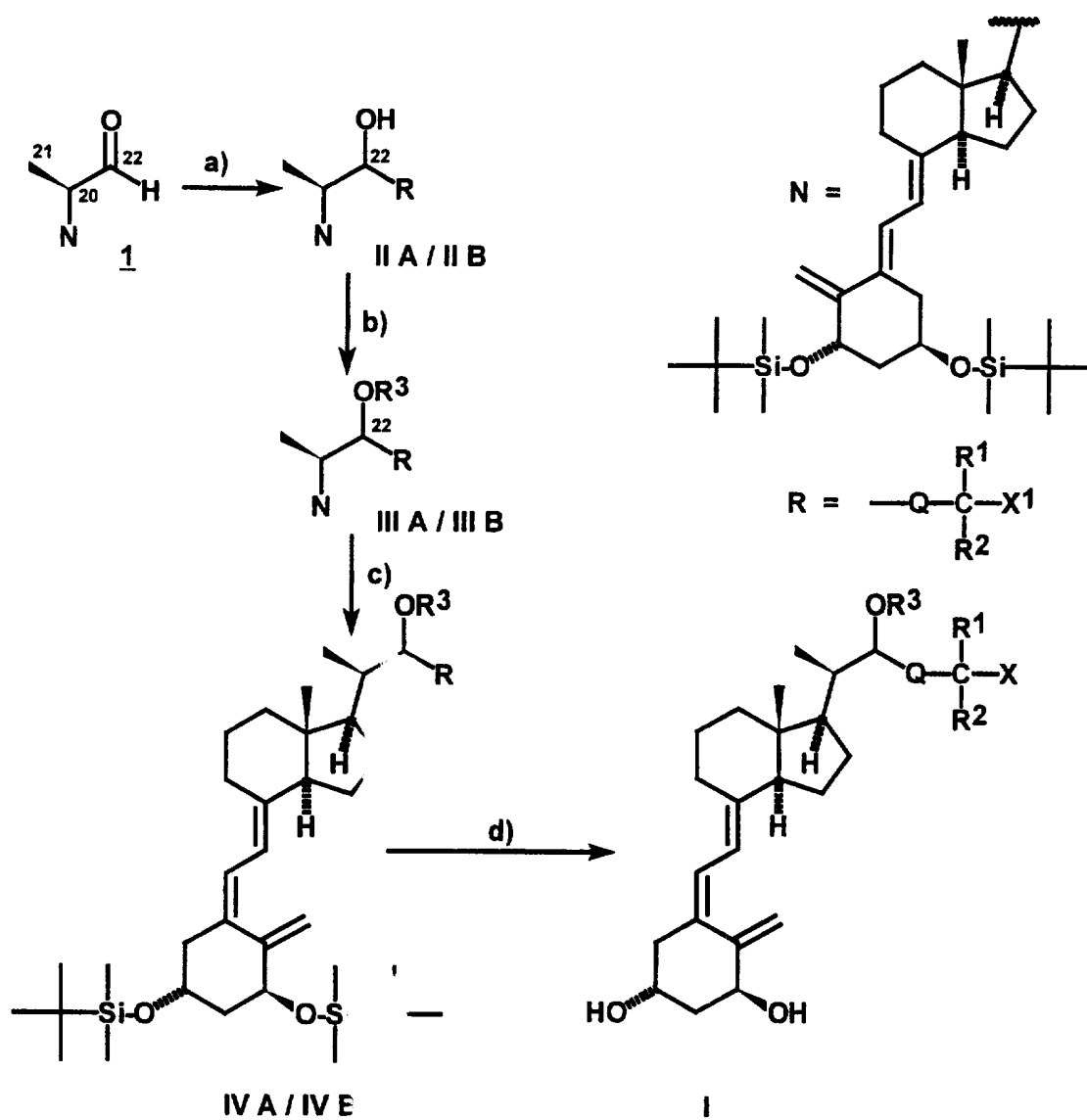
- The rest of the molecule is the same as in formula I. The 22-OH/OMe/OEt compounds are all 22A-isomers.
- 5 α The values are relative to 1,25(OH)₂D₃; a value greater than 1 indicates a compound which is more active than 1,25(OH)₂D₃ in the assay.
- ¶ Calculated as the ratio between the IC₅₀ value of 1,25(OH)₂D₃ and the IC₅₀ value of the compound; IC₅₀ being the concentration
- 10 which results in 50 % inhibition of the ³H-thymidine incorporation compared to controls.
- "HaCaT, max %" indicates the maximal inhibition of the cell proliferation (maximal efficacy) which is obtainable at the higher concentration of 10⁻⁷ M of a compound.
- 15 * 1,25 = 1,25(OH)₂D₃ = 1,25(OH)₂-vitamin-D₃ .
- # MC903 = Calcipotriol, (see text above).
- n.d. = not determined.

Compounds I can be prepared from the vitamin D-derived aldehyde compound 1 (Scheme 1); a synthesis of which has been reported [42] , for example by the routes outlined in Scheme 1.

The following standard abbreviations are used throughout this disclosure: Me = methyl; Et = ethyl; Pr = n-propyl; Bn = benzyl; Ph = phenyl; THP = tetrahydro-4H-pyran-2-yl; TMS = trimethylsilyl; DMAP = 4-dimethylaminopyridine; PPTS = pyridinium p-toluenesulfonate; pet.ether =

petroleum ether; THF = tetrahydrofuran; TBAF = tetra-(n-butyl)-ammonium fluoride; b.p. = boiling point; PLC = Preparative thin-Layer Chromatography; HPLC = High Performance Liquid Chromatography.

Scheme 1
Synthesis of Compounds I



$X^1 = H, OH, OR^5$

$R^5 =$ alcohol protective group, e.g. tri(loweralkyl)-silyl or THP

R^1, R^2, R^3, Q and X have the above meanings.

Notes to Scheme 1

- 5 a) (i) Compound 1 is reacted with an organometallic reagent R-Met-Hal or R-Met, such as e.g. RMgHal, where Hal is Cl, Br or I, or RLi, which may be prepared from the side chain building block of general formula V, RHal, (see below) by reaction with a suitable metal, such as magnesium or lithium.
- (ii) The resulting mixture of the two C-22-epimers, IIA and IIB, is separated.
- 10 b) Alkylation of the C-22-hydroxy compounds of type II to the corresponding compound III, where $R^3 = C_1-C_{10}$ hydrocarbyl, or, optionally, acylation of the compounds of type II to the corresponding compound III, where $R^3 = YR^4$; Y and R^4 having the above meanings.
- 15 c) Isomerization of Compounds III to the corresponding compound IV, by means of UV-light in the presence of a triplet sensitizer, e.g. anthracene.
- d) Deprotection of Compounds IV to the corresponding compound I, e.g. by TBAF, by HF, or by TBAF followed by PPTS, or vice versa.
- 20 The compounds of type II or III may be subjected to optional functional group modification in the side chain, if considered desirable or necessary during a particular synthesis.

The order of the synthetic steps, which in Scheme 1 is: a), b), c), d), may, if for any reason desirable, be rearranged to the order: a), c), b), d), or
 25 the order: a), b), d), c).

The side chain building blocks of general formula V, RHal, are known compounds, or they can be prepared by standard methods known to the specialist.



- 30 in which Hal, Q, R^1 , R^2 and X^1 have the above meanings. In particular, this applies to the side chain building blocks of general formula V necessary

for the preparation of the exemplified compounds (101-108, 110-112, 114-116 and 121); these RHal are described in table 2. Other similar RHal may be prepared by methods analogous to those used for synthesizing the compounds V of table 2. For $X^1 = O\text{-THP}$, see e.g. WO 93/19044.

5

Table 2

Some Side Chain Building Blocks, R-Hal of General Formula V

Compound	Formula	References
10		
501	$\text{Br}(\text{CH}_2)_2\text{C}(\text{CH}_3)_2\text{OSi}(\text{CH}_3)_3$	WO 91/00271
502	$\text{Br}(\text{CH}_2)_2\text{C}(\text{C}_2\text{H}_5)_2\text{OSi}(\text{CH}_3)_3$	WO 94/14766
503	$\text{Br}(\text{CH}_2)_3\text{C}(\text{CH}_3)_3\text{OSi}(\text{CH}_3)_3$	WO 91/15475
504	$\text{Br}(\text{CH}_2)_3\text{C}(\text{C}_2\text{H}_5)_2\text{OSi}(\text{CH}_3)_3$	WO 89/10351
15	505 $\text{Br}(\text{CH}_2)_4\text{C}(\text{C}_2\text{H}_5)_2\text{OSi}(\text{CH}_3)_3$	WO 89/10351

The reaction of the aldehyde 1 with the organometallic reagents derived from the side chain building blocks, e.g. RMgHal or RLi , can be performed by standard methods of nucleophilic addition of Grignard or lithium reagents to carbonyl compounds; i.e. by reacting the RHal with magnesium or lithium in a suitable anhydrous solvent, such as ether and/or THF, to generate the organometallic reagent, then adding 1, to give II after usual aqueous work-up (which is normally implied in all the reactions of Scheme 1. In general the reaction product II is a mixture of the two possible C-22-epimers, here designated IIA and IIB. It is usually preferable to separate the IIA and IIB epimers which can conveniently be done by chromatography.

Nonlimiting illustrations of such compounds of formula II are given in Table 3. In this table these compounds are described as separate 22-epimers IIA or IIB (preparations 1-5). The compounds IIA are formed in much higher yields than the corresponding IIB epimers, typically in the ratio of

30

about 95 to 5.

The alkylation or acylation of the C-22-hydroxy compounds of general formula II to yield the corresponding compound III where R^3 is C_1 - C_3 alkyl, aryl or aralkyl or YR^4 can be performed by standard methods well known to the specialist. Illustrative, but non limiting, compounds of this sort are listed in Table 3.

In the alkylation reaction use is preferably made of an alkylating agent R^3Z , in which Z stands for a good leaving group, such as for example Cl^- , Br^- , I^- , $CH_3SO_3^-$, $p-CH_3-C_6H_4-SO_3^-$ or $CF_3SO_3^-$; the R^3Z being allowed to react with the anion of the appropriate compound II or III ($R^3 = H$), derived therefrom by means of a suitable strong base, such as an alkali-metal alkoxide, alkyl alkali-metal or alkali-metal hydride. A useful method is described in General Procedure 2, and in more detail in the included preparations; a suitable crown ether may be added as a phase transfer agent to accelerate the alkylation process.

In the acylation reaction producing compounds III where $R^3 = YR^4$, use may advantageously be made of standard acylation procedures, such as reaction of the alcohol II with an acid chloride or acid anhydride (R^4YCl or $(R^4Y)_2O$), or by forming the acylating agent in situ from the corresponding acid R^4YOH and a dehydrating or condensing agent, such as e.g. a carbodiimide or an assisting acid anhydride, forming an intermediary mixed anhydride.

Furthermore, the addition of a suitable base, such as a tertiary amine, may often be profitably applied during the acylation; in many cases addition of a special heterocyclic amine like DMAP may accelerate the acylation process considerably. Examples of acylation procedures are given in General Procedure 3.

Table 3 also contains nonlimiting examples of photoisomerized compounds of general formula IV along with references to the preparation of

each compound.

It should be noted that the preparations and examples of Tables 3 and 4 are illustrative only, the particular synthesis of each step and the order in which each step is performed can be varied greatly. Furthermore, the radical R: $-Q-C(R^1)(R^2)(X^1)$ may optionally be a radical which can be converted to this at any convenient later stage (or over several stages). Thus R in compounds II, III and IV does not necessarily have the same meaning along a particular synthetic sequence. The conversion of R to $-Q-C(R^1)(R^2)X^1$ may well involve several steps and possibly involve a temporary protection of the sensitive triene system of the molecule. Apart from any necessary modification of R^3 or within the side chain (R), the conversion of III to I involves a photoisomerisation step and a deprotection step, analogous to the steps used in the last stages of the synthesis of other vitamin D analogues (see European patent No. 0 227 836).

Table 3

Intermediates of General Formulas II, III & IV

Type	Prep No.	Comp No.	Gen. Proc	Radicals of formulas II, III & IV					
				R^3	Q	R^1	R^2	XR^1	
1)	2)	3)	4)						
IIA	01	201	1	-	$(CH_2)_2$	Me	Me	OTMS	
IIA	02	202	1	-	$(CH_2)_2$	Et	Et	OTMS	
IIA	03	203	1	-	$(CH_3)_2$	Me	Me	OTMS	

Table 3 (continued)

Intermediates of General Formulas II, III & IV

5	Type	Prep	Comp	Gen.	Radicals of formulas II, III & IV				
		No.	No.	Proc	R ³	Q	R ¹	R ²	XR ¹
	1)	2)	3)	4)					
10	IIA	04	204	1	-	(CH ₂) ₃	Et	Et	OTMS
	IIA	05	205	1	-	(CH ₂) ₄	Et	Et	OTMS
	IIIA	06	301	2a	Me	(CH ₂) ₂	Me	Me	OTMS
	IIIA	07	302	2a	Et	(CH ₂) ₂	Me	Me	OTMS
	IIIA	08	303	2	Me	(CH ₂) ₂	Et	Et	OTMS
15	IIIA	09	304	2	Me	(CH ₂) ₃	Me	Me	OTMS
	IIIA	10	305	2	Me	(CH ₂) ₃	Et	Et	OTMS
	IIIA	11	306	2a	Et	(CH ₂) ₃	Et	Et	OTMS
	IIIA	12	307	2	Me	(CH ₂) ₄	Et	Et	OTMS
	IIIA	13	308	2a	Et	(CH ₂) ₄	Et	Et	OTMS
20	IVA	14	401	4	Me	(CH ₂) ₂	Me	Me	OTMS
	IVA	15	402	4	Et	(CH ₂) ₂	Me	Me	OTMS
	IVA	16	403	4	Me	(CH ₂) ₂	Et	Et	OTMS
	IVA	17	404	4	Me	(CH ₂) ₃	Me	Me	OTMS
	IVA	18	405	4	Me	(CH ₂) ₃	Et	Et	OTMS
25	IVA	19	406	4	Et	(CH ₂) ₃	Et	Et	OTMS
	IVA	20	407	4	Me	(CH ₂) ₄	Et	Et	OTMS
	IVA	21	408	4	Et	(CH ₂) ₄	Et	Et	OTMS
	IIB	01	221	1	-	(CH ₂) ₂	Me	Me	OTMS

Table 3 (continued)

Intermediates of General Formulas II, III & IV

5	Type	Prep	Comp	Gen.	Radicals of formulas II, III & IV				
		No.	No.	Proc	R ³	Q	R ¹	R ²	XR ¹
	1)	2)	3)	4)					
10	IIIA	22	310	2	Et	(CH ₂) ₃	Me	Me	OTMS
	IIIA	23	311	2	Me	(CH ₂) ₄	Me	Me	OTMS
	IIIA	24	312	2	Et	(CH ₂) ₄	Me	Me	OTMS
	IIIA	25	314	2a	Pr	(CH ₂) ₂	Me	Me	OTMS
	IIIA	26	315	2	Bn	(CH ₂) ₂	Me	Me	OTMS
15	IIIB	34	321	2	Me	(CH ₂) ₂	Me	Me	OTMS
	IVA	27	410	4	Et	(CH ₂) ₃	Me	Me	OTMS
	IVA	28	411	4	Me	(CH ₂) ₄	Me	Me	OTMS
	IVA	29	412	4	Et	(CH ₂) ₄	Me	Me	OTMS
	IVA	30	414	4	Pr	(CH ₂) ₂	Me	Me	OTMS
20	IVA	31	415	4	Bn	(CH ₂) ₂	Me	Me	OTMS
	IVA	32	416a [*]	4	H	(CH ₂) ₂	Me	Me	OTMS
	IVA	33	416 [*]	3	PhOCS	(CH ₂) ₂	Me	Me	OTMS
	IVB	35	421	4	Me	(CH ₂) ₂	Me	Me	OTMS

Notes to Table 3:

- 1) Type: See Scheme 1
- 2) Prep No. = Preparation Number
- 3) Comp No. = Compound Number

- 4) Gen. Proc = General Procedure Number
* Reversal of steps b) and c) of Scheme 1. Therefore, in compound 416a, R³ stands for H

5

Exemplified and planned Compounds I of the invention are listed in Table 4, the numbered examples giving reference to illustrative methods of synthesis, together with spectroscopic data for these exemplified compounds.

- 10 The planned Compounds, 109, 113, 117-120 and 122-135 are made in a sequence of synthetic steps which is analogous to the sequence used for the preparations of the exemplified Compounds, 101-108, 110-112, 114-116 and 121, Examples 1-15; see Scheme 1, and the notes to Scheme 1.

- In the following, R⁴, R⁵, Hal, Z and Y have the above meanings, and
15 Q, R¹, R² and R³ have same meanings as they have in Table 4, for the corresponding planned compounds of formula I. Compound 1 and the appropriate Compound V, Hal-Q-CR¹R²-OR⁵ (OR⁵ being replaced by H in the case of the synthesis of Compound 131), are reacted, according to General Procedure 1 (GP 1), to give the corresponding compound of formula II.

- 20 The compound of formula II and the appropriate R³Z are reacted, according to GP 2, to give the corresponding compound of formula III, except for the sequence leading to Compounds 134 and 135; in which cases the appropriate Compound II (Compound 201) is acylated, according to GP 3, with the appropriate acylating reagent R⁴YCl or (R⁴Y)₂O to give the corresponding compound of formula III.
25

The compound of formula III is photo-isomerized, according to GP 4, to give the corresponding compound of formula IV. As the last step, the compound of formula IV is deprotected, according to either GP 5, GP 6 or GP 7, to give the Compound I in question.

Table 4**Exemplified and Planned Compounds of General Formula I**

Exam	Comp	Isom	Gen.	Radicals of the general formula I					
	No.	No.	C-22	Proc	R ³	Q	R ¹	R ²	X
5	1)	2)	3)	4)					
10	1	101	A	5	Me	(CH ₂) ₂	Me	Me	OH
	2	102	A	5	Et	(CH ₂) ₂	Me	Me	OH
	3	103	A	5	Me	(CH ₂) ₂	Et	Et	OH
	4	104	A	5	Me	(CH ₂) ₃	Me	Me	OH
	5	105	A	5	Me	(CH ₂) ₃	Et	Et	OH
15	6	106	A	6	Et	(CH ₂) ₃	Et	Et	OH
	7	107	A	6	Me	(CH ₂) ₄	Et	Et	OH
	8	108	A	6	Et	(CH ₂) ₄	Et	Et	OH
		109	A	5-7	Et	(CH ₂) ₂	Et	Et	OH
	9	110	A	5	Et	(CH ₂) ₃	Me	Me	OH
20	10	111	A	5	Me	(CH ₂) ₄	Me	Me	OH
	11	112	A	5	Et	(CH ₂) ₄	Me	Me	OH
		113	A	5-7	Me	CH ₂	Me	Me	OH
	12	114	A	5	Pr	(CH ₂) ₂	Me	Me	OH
	13	115	A	5	Bn	(CH ₂) ₂	Me	Me	OH
25	14	116	A	6	PhOCS	(CH ₂) ₂	Me	Me	OH
		117	A	5-7	Me	(CH ₂) ₂	CF ₃	CF ₃	OH
		118	A	5-7	Et	(CH ₂) ₂	CF ₃	CF ₃	OH
		119	A	5-7	Me	(CH ₂) ₂	C ₂ F ₅	C ₂ F ₅	OH

Table 4 (continued)Exemplified and Planned Compounds of General Formula I

5	Exam	Comp	Isom	Gen.	Radicals of the general formula I				
	No.	No.	C-22	Proc	R ³	Q	R ¹	R ²	X
	1)	2)	3)	4)					
10		120	A	5-7	Et	(CH ₂) ₂	C ₂ F ₅	C ₂ F ₅	OH
	15	121	B	5	Me	(CH ₂) ₂	Me	Me	OH
		122	B	5-7	Et	(CH ₂) ₂	Me	Me	OH
		123	A	5-7	Me	(CH ₂) ₃	CF ₃	CF ₃	OH
		124	A	5-7	Et	(CH ₂) ₃	CF ₃	CF ₃	OH
15		125	A	5-7	Me	CH ₂ CF ₂	Me	Me	OH
		126	A	5-7	Et	CH ₂ CF ₂	Me	Me	OH
		127	A	5-7	Me	CH ₂ CF ₂	CF ₃	CF ₃	OH
		128	A	5-7	Et	CH ₂ CF ₂	CF ₃	CF ₃	OH
		129*	A	5-7	Me	(CH ₂) ₂	Me	CF ₃	OH
20		130#	A	5-7	Me	(CH ₂) ₂	CF ₃	Me	OH
		131	A	5-7	Me	(CH ₂) ₂	Me	Me	H
		132	A	5-7	Me	(CH ₂) ₂	-(CH ₂) ₄ -		OH
		133	A	5-7	Me	(CH ₂) ₂	-(CH ₂) ₅ -		OH
		134	A	6	PhSCO	(CH ₂) ₂	Me	Me	OH
25		135	A	6	PhSCS	(CH ₂) ₂	Me	Me	OH

Notes to Table 4

1) Exam No. = Example Number

- 2) Comp No. = Compound Number
- 3) Isom C-22 = Isomer at carbon 22 of the side chain
- 4) Gen. Proc = General Procedure Number
- * R-configuration of the carbon bearing R¹ and R²
- 5 # S-configuration of the carbon bearing R¹ and R²

The present compounds are intended for use in pharmaceutical compositions which are useful in the local or systemic treatment of human and veterinary disorders as described above.

The present compounds may be used in combination with other pharmaceuticals or treatment modalities. In the treatment of psoriasis the present compounds may be used in combination with e.g. steroids or with other treatments e.g. light- or UV-light-treatment or the combined PUVA-treatment. In the treatment of cancer the present compounds may be used in combination with other anti-cancer drugs or anti-cancer treatments, such as radiation treatment. In the prevention of graft rejection and graft versus host reaction, or in the treatment of auto-immune diseases, the present compounds may advantageously be used in combination with other immunosuppressive/immunoregulating drugs or treatments, e.g. with cyclosporin A.

The amount required of a compound of formula I (hereinafter referred to as the active ingredient) for therapeutic effect will, of course, vary both with the particular compound, the route of administration and the mammal under treatment. The compounds of the invention can be administered by the parenteral, intra-articular, enteral or topical routes. They are well absorbed when given enterally and this is the preferred route of administration in the treatment of systemic disorders. In the treatment of dermatological disorders like psoriasis or eye diseases topical or enteral forms are preferred.

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

0.1% by weight of the formulation.

The formulations, both for veterinary and for human medical use, of the present invention thus comprise an active ingredient in association with a pharmaceutically acceptable carrier therefore and optionally other therapeutic ingredient(s). The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

The formulations include e.g. those in a form suitable for oral, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular and intravenous), transdermal, intra-articular and topical, nasal or buccal administration.

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

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

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

Formulations for rectal administration may be in the form of a

suppository incorporating the active ingredient and a carrier, or in the form of an enema.

Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredient which is preferably isotonic with the blood of the recipient. Transdermal formulations may be in the form of a plaster.

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

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

Formulations suitable for administration to the nose or buccal cavity include powder, self-propelling and spray formulations, such as aerosols and atomizers.

In addition to the aforementioned ingredients, the formulations of this invention may include one or more additional ingredients, such as diluents, binders, preservatives etc.

The compositions may further contain other therapeutically active compounds usually applied in the treatment of the above mentioned pathological conditions, such as other immunosuppressants in the treatment of immunological diseases, or steroids in the treatment of dermatological diseases.

The present invention further concerns a method for treating patients suffering from one of the above pathological conditions, said method consisting of administering to a patient in need of treatment an effective amount of one or more compounds of formula I, alone or in combination with one or more other therapeutically active compounds usually applied in

the treatment of said pathological conditions. The treatment with the present compounds and/or with further therapeutically active compounds may be simultaneous or with intervals.

In the systemic treatment daily doses of from 0.001-2 μg per
5 kilogram bodyweight, preferably from 0.002-0.3 $\mu\text{g/kg}$ of mammal
bodyweight, for example 0.003-0.3 $\mu\text{g/kg}$ of a compound of formula I are
administered, typically corresponding to a daily dose for an adult human of
from 0.2 to 25 μg . In the topical treatment of dermatological disorders,
ointments, creams or lotions containing from 0.1-500 $\mu\text{g/g}$, and preferably
10 from 0.1-100 $\mu\text{g/g}$, of a compound of formula I are administered. For topical
use in ophthalmology ointments, drops or gels containing from 0.1-500 $\mu\text{g/g}$,
and preferably from 0.1-100 $\mu\text{g/g}$, of a compound of formula I are
administered. The oral compositions are formulated, preferably as tablets,
capsules, or drops, containing from 0.05-50 μg , preferably from 0.1-25 μg ,
15 of a compound of formula I, per dosage unit.

The invention will now be further described in the following General
Procedures, Preparations and Examples:

General Procedures, Preparations and Examples

20 General

The exemplified compounds I are listed in Table 4.

For ^1H NMR (300 MHz) and ^{13}C NMR (75.6 MHz) spectra chemical
shift values (δ) are quoted, unless otherwise specified, for deuterio-
chloroform solutions relative to internal tetramethylsilane ($\delta = 0.00$) or
25 chloroform ($\delta = 7.25$ for ^1H NMR) or deuteriochloroform ($\delta = 76.81$ for
 ^{13}C NMR). The value for a multiplet, either defined (doublet (d), triplet (t),
quartet (q)) or not (m) at the approximate mid point is given unless a range is
quoted (s = singlet, b = broad).

Ether is diethyl ether, and was dried over sodium. THF was dried
30 over sodium-benzophenone. Petroleum ether refers to the pentane fraction.
Reactions were run at room temperature unless otherwise noted. The
work-up procedure referred to involves dilution with the specified solvent

(otherwise the organic reaction solvent), extraction with water and then brine, drying over anhydrous MgSO_4 , and concentration in vacuo to give a residue. Chromatography was performed on silica gel.

5 General Procedures

General Procedure 1: Reaction of Compound 1 with Grignard reagents, RMgHal , derived from side chain building blocks V (RHal), to give Compounds IIA and IIB (Scheme 1, Table 3) (Preparations 01-05)

To 0.12 g magnesium turnings (Grignard quality) in a dry flask was added, dropwise with stirring and in an argon atmosphere, a solution of the appropriate compound V (5.0 mmol) in a 1:1 mixture of dry THF and dry ether (6 ml). Stirring was continued under heating to reflux for 45 minutes. The resulting Grignard reagent was again cooled to 20°C , and a solution of the aldehyde, compound 1 (0.57 g; 1 mmole) in a 1:1 mixture of dry THF and dry ether (2 ml) was added dropwise, during 5 minutes, followed by stirring at 20°C for 30 minutes. The reaction mixture was poured into a 10% aqueous solution of ammonium chloride and worked up (ether) to yield a crude product containing compounds IIA and IIB which were separated and purified by chromatography (mixture of ether and pet.ether as eluant) to yield the title compounds of the preparation. (If necessary, repeated chromatography of selected fractions were performed, possibly using mixtures of pet.ether, dichlormethane and ethylacetate, e.g. a 80:20:2 mixture, as eluant. Conveniently the purification/separation may take place in the form of PLC or using a preparative HPLC apparatus).

General Procedure 2: Alkylation of C-22-hydroxy-compounds of type II or III to the corresponding compound III
where $R^3 = C_1-C_{10}$ hydrocarbyl (Scheme 1, Table 3) (Preparations 06-13 and 22-23)

5 To a solution of the appropriate compound II or III (0.25 mmol) in dry THF (4 ml) was added, while stirring at 20°C under argon, a 20% suspension of potassium hydride in mineral oil (0.1 ml) followed by an alkylating agent, R^3Z (0.75 mmol), and the mixture was stirred for 5 minutes, after which 18-Crown-6 (0.07 g) was added. Stirring at 20°C was
10 continued for 1.5 hours, after which the reaction mixture was worked up (ether). The crude product was purified by chromatography (mixture of ether and pet.ether as eluant) to yield the title compound of the preparation.

Variation: General Procedure 2a

15 The procedure of General Procedure 2 was followed, except that after stirring of the reaction mixture for 1.5 hours as described, another portion of potassium hydride (20% in mineral oil) (0.1 ml), of alkylating agent R^3Z (0.75 mmol), and of 18-crown-6 (0.07 g) was added, and the mixture was stirred for another 1.5 hours.

General Procedure 3: Acylation of C-22-hydroxy-compounds of type II or III to the corresponding compound III where $R^3 = YR^4$ (Scheme 1, Table 3) (Preparation 33)

- 5 To a solution of the appropriate compound II or III (0.25 mmol) in a suitable dry solvent, e.g. dichloromethane, was added, while stirring at 20°C under argon, an acylating reagent (R^4YCl , $(R^4Y)_2O$ or R^4YOH), preferably accompanied by one or two suitable bases, such as triethylamine, pyridine and/or DMAP. In the case where an acid, R^4YOH , was used, the
- 10 addition of a dehydrating or condensing agent such as e.g. dicyclohexyl carbodiimide was desirable. The reaction mixture was then stirred at a suitable temperature (from room temperature up to the boiling point of the solvent) for a sufficient time (typically for 1 to 4 hours). After a suitable work-up the crude product was purified by chromatography to yield the title
- 15 compound of the preparation.

General Procedure 4: Isomerization of Compounds III to the corresponding compound IV (Scheme 1, Table 3) (Preparations 14-21 and 27-35)

- 20 A solution of the appropriate compound III (0.3 mmol), anthracene (120 mg) and triethylamine (0.05 ml) in dichloromethane (20 ml) under argon in a Pyrex flask was irradiated with UV-light from a high pressure ultraviolet lamp, type TQ760Z2 (Hanau) at about 10°C for 20 minutes under stirring. The reaction mixture was concentrated in vacuo and treated with
- 25 pet.ether (2x5 ml). After filtering the filtrate was concentrated in vacuo and purified by chromatography (mixture of ether and pet.ether as eluant) to yield the title compound of the preparation.

General Procedure 5: Deprotection of Compounds IV to the corresponding Compounds I by treatment with tetra-n-butyl-ammoniumfluoride (Scheme 1, Table 4) (Examples 1-5, 9-11, 12-13 and 15)

5 To a solution of the appropriate compound IV (0.16 mmol) in THF (5 ml) was added a solution of tetra-n-butylammonium fluoride (300 mg) in THF (5 ml) while stirring at 60°C under argon. Stirring was continued for one hour at 60°C, and the reaction mixture was worked up (ethyl acetate with an additional extraction with aqueous sodium hydrogen carbonate). The
10 residue after evaporation was purified by chromatography (50% to 0% pet.ether in ethyl acetate as eluant) to yield the title compound of the example.

General Procedure 6: Deprotection of Compounds IV to the corresponding Compound I by treatment with HF (Scheme 1, Table 4) (Examples 6-8 and 14)

15 To a solution of the appropriate compound IV (0.07 mmol) in ethyl acetate (0.2 ml) was added acetonitrile (2 ml) followed by a 5% solution of hydrofluoric acid in acetonitrile:water, 7:1 (1.2 ml) under argon and with
20 stirring. Stirring was continued for 45 minutes at 20°C. Saturated aqueous sodium bicarbonate solution (10 ml) was added, and the reaction mixture was worked up (ethyl acetate) The residue was purified by chromatography (50% to 0% pet.ether in ethyl acetate as eluant) to yield the title compound of the example.

General Procedure 7: Deprotection of Compounds IV to the corresponding Compounds I by treatment with tetra-n-butylammoniumfluoride followed by pyridine-p-toluenesulfonate ² (Scheme 1, Table 4)

To a solution of the appropriate compound IV (0.16 mmol) in THF (5 ml) was added a solution of tetra-n-butylammonium fluoride (300 mg) in THF (5 ml) while stirring at 60°C under argon. Stirring was continued for one hour at 60°C, and the reaction mixture was worked up (ethyl acetate with an additional extraction with aqueous sodium hydrogen carbonate). The residue after evaporation was purified by chromatography (50% to 0% pet.ether in ethyl acetate as eluant) and then dissolved in absolute ethyl alcohol (2 ml). PPTS (2 mg) was added, and the mixture was stirred for one hour at 50°C under argon. After work-up (ethyl acetate with an additional aqueous sodium bicarbonate extraction) the residual crude product was purified by chromatography (50% to 0% pet.ether in ethyl acetate as eluant) to yield the title compound of the example.

Preparations

Preparation 01: Compounds 201 and 221

Method: General Procedure 1.

Starting material V: Compound 501

Chromatography eluant: 0% to 5% ether in pet.ether.

¹H NMR for 201: δ = 0.06 (m, 12H), 0.11 (s, 9H), 0.54 (s, 3H), 0.85 (d, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.23 (s, 6H), 1.20-2.15 (m, 19H), 2.31 (bd, 1H), 2.55 (dd, 1H), 2.88 (m, 1H), 3.80 (m, 1H), 4.21 (m, 1H), 4.52 (m, 1H), 4.94 (m, 1H), 4.98 (m, 1H), 5.82 (d, 1H), 6.45 (d, 1H).

² or in the reverse order

^{13}C NMR for 221: 153.4, 142.8, 135.3, 121.5, 116.3, 106.5, 74.1, 73.8, 70.1, 67.0, 56.1, 52.7, 45.7, 43.8, 41.8, 41.2, 39.8, 36.4, 29.9, 29.5, 28.7, 26.7, 25.7, 25.6, 25.2, 23.3, 21.9, 18.1, 17.9, 12.4, 12.2, 2.3, -5.0, -5.1, -5.1

5 Preparation 02: Compound 202

Method: General Procedure 1.

Starting material V: Compound 502

Chromatography eluant: 5% ether in pet.ether.

^1H NMR: δ = 0.05 (m, 12H), 0.11 (s, 9H), 0.54 (s, 3H), 0.82 (t, 6H),
10 0.83 (d, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.15-2.15 (m, 23H), 2.31 (m, 1H),
2.55 (dd, 1H), 2.88 (m, 1H), 3.77 (m, 1H), 4.21 (m, 1H), 4.52 (m, 1H), 4.93
(m, 1H), 4.98 (m, 1H), 5.82 (d, 1H), 6.45 (d, 1H).

Preparation 03: Compound 203

15 Method: General Procedure 1.

Starting material V: Compound 503

Chromatography eluant: 5% ether in pet.ether.

^1H NMR: δ = 0.06 (m, 12H), 0.10 (s, 9H), 0.55 (s, 3H), 0.83 (d,
3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.20 (s, 6H), 1.15-2.15 (m, 21H), 2.31 (bd,
20 1H), 2.55 (dd, 1H), 2.88 (m, 1H), 3.85 (m, 1H), 4.21 (m, 1H), 4.52 (m, 1H),
4.94 (m, 1H), 4.98 (m, 1H), 5.83 (d, 1H), 6.45 (d, 1H).

Preparation 04: Compound 204

Method: General Procedure 1.

25 Starting material V: Compound 504

Chromatography eluant: 10% ether in pet.ether.

^1H NMR: δ = 0.06 (m, 12H), 0.09 (s, 9H), 0.55 (s, 3H), 0.81 (t, 6H),
0.83 (d, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.45 (q, 4H), 1.15-2.15 (m, 21H),
2.31 (bd, 1H), 2.55 (dd, 1H), 2.88 (m, 1H), 3.85 (m, 1H), 4.22 (m, 1H), 4.53
30 (m, 1H), 4.94 (m, 1H), 4.98 (m, 1H), 5.83 (d, 1H), 6.45 (d, 1H).

Preparation 05: Compound 205

Method: General Procedure 1.

Starting material V: Compound 505

Chromatography eluant: 0% to 5% ether in pet.ether.

5 ¹H NMR: δ = 0.05 (m, 12H), 0.08 (s, 9H), 0.54 (s, 3H), 0.79 (t, 6H), 0.83 (d, 3H), 0.85 (s, 9H), 0.89 (s, 9H), 1.10-2.10 (m, 27H), 2.31 (bd, 1H), 2.55 (dd, 1H), 2.88 (m, 1H), 3.84 (m, 1H), 4.21 (m, 1H), 4.53 (m, 1H), 4.94 (m, 1H), 4.98 (m, 1H), 5.82 (d, 1H), 6.45 (d, 1H).

10 Preparation 06: Compound 301

Method: General Procedure 2a.

Alkylating agent R³Z: Methyl iodideStarting material II: Compound 201

Chromatography eluant: 0% to 20% ether in pet.ether.

15 ¹H NMR: δ = 0.06 (m, 12H), 0.10 (s, 9H), 0.51 (s, 3H), 0.83 (d, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.20 (s, 3H), 1.21 (s, 3H), 1.25-2.10 (m, 18H), 2.31 (bd, 1H), 2.55 (dd, 1H), 2.88 (m, 1H), 3.18 (m, 1H), 3.33 (s, 3H), 4.21 (m, 1H), 4.52 (m, 1H), 4.94 (m, 1H), 4.98 (m, 1H), 5.82 (d, 1H), 6.45 (d, 1H).

20

Preparation 07: Compound 302

Method: General Procedure 2a.

Starting material II: Compound 201Alkylating agent R³Z: Ethyl iodide

25 Chromatography eluant: 0% to 3% ether in pet.ether.

30 ¹H NMR: δ = 0.05 (m, 12H), 0.09 (s, 9H), 0.50 (s, 3H), 0.84 (d, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.17 (t, 3H), 1.20 (s, 3H), 1.21 (s, 3H), 1.10-2.10 (m, 18H), 2.31 (bd, 1H), 2.55 (dd, 1H), 2.88 (m, 1H), 3.20 (m, 1H), 3.47 (m, 2H), 4.22 (m, 1H), 4.52 (m, 1H), 4.93 (m, 1H), 4.98 (m, 1H), 5.81 (d, 1H), 6.45 (d, 1H).

Preparation 08: Compound 303

Method: General Procedure 2.

Starting material II: Compound 202Alkylating agent R³Z: Methyl iodide

5 Chromatography eluant: 0% to 20% ether in pet.ether.

¹H NMR: δ = 0.06 (m, 12H), 0.10 (s, 9H), 0.52 (s, 3H), 0.82 (t, 6H), 0.83 (d, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.20-2.15 (m, 22H), 2.31 (bd, 1H), 2.55 (dd, 1H), 2.88 (m, 1H), 3.18 (m, 1H), 3.33 (s, 3H), 4.21 (m, 1H), 4.53 (m, 1H), 4.93 (m, 1H), 4.98 (m, 1H), 5.82 (d, 1H), 6.46 (d, 1H).

10

Preparation 09: Compound 304

Method: General Procedure 2.

Starting material II: Compound 203Alkylating agent R³Z: Methyl iodide

15 Chromatography eluant: 0% to 2% ether in pet.ether.

¹H NMR: δ = 0.06 (m, 12H), 0.09 (s, 9H), 0.52 (s, 3H), 0.83 (d, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.19 (s, 3H), 1.20 (s, 3H), 1.10-2.15 (m, 20H), 2.31 (bd, 1H), 2.55 (dd, 1H), 2.88 (m, 1H), 3.22 (m, 1H), 3.33 (s, 3H), 4.21 (m, 1H), 4.52 (m, 1H), 4.93 (m, 1H), 4.98 (m, 1H), 5.82 (d, 1H), 6.45 (d, 1H).

20

Preparation 10: Compound 305

Method: General Procedure 2.

Starting material II: Compound 20425 Alkylating agent R³Z: Methyl iodide

Chromatography eluant: 0% to 20% ether in pet.ether.

¹H NMR: δ = 0.06 (m, 12H), 0.10 (s, 9H), 0.52 (s, 3H), 0.81 (t, 6H), 0.83 (d, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.15-2.10 (m, 24H), 2.31 (bd, 1H), 2.55 (dd, 1H), 2.88 (m, 1H), 3.21 (m, 1H), 3.33 (s, 3H), 4.21 (m, 1H), 4.52 (m, 1H), 4.93 (m, 1H), 4.98 (m, 1H), 5.82 (d, 1H), 6.45 (d, 1H).

30

Preparation 11: Compound 306

Method: General Procedure 2a.

Starting material II: Compound 204Alkylating agent R³Z: Ethyl bromide

5 Chromatography eluant: 0% to 20% ether in pet.ether.

¹H NMR: δ = 0.06 (m, 12H), 0.08 (s, 9H), 0.50 (s, 3H), 0.81 (t, 6H),
0.83 (d, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.17 (t, 3H), 1.10-2.10 (m, 24H),
2.31 (bd, 1H), 2.55 (dd, 1H), 2.88 (m, 1H), 3.24 (m, 1H), 3.47 (m, 2H), 4.21
10 (m, 1H), 4.53 (m, 1H), 4.93 (m, 1H), 4.98 (m, 1H), 5.82 (d, 1H), 6.45 (d,
1H).

Preparation 12: Compound 307

Method: General Procedure 2.

Starting material II: Compound 20515 Alkylating agent R³Z: Methyl iodide

Chromatography eluant: 0% to 20% ether in pet.ether.

¹H NMR: δ = 0.06 (m, 12H), 0.09 (s, 9H), 0.51 (s, 3H), 0.80 (t, 6H),
0.83 (d, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.44 (q 4H), 1.15-2.10 (m, 22H),
2.31 (bd, 1H), 2.55 (dd, 1H), 2.88 (m, 1H), 3.22 (m, 1H), 3.33 (s, 3H), 4.21
20 (m, 1H), 4.53 (m, 1H), 4.93 (m, 1H), 4.98 (m, 1H), 5.82 (d, 1H), 6.45 (d,
1H).

Preparation 13: Compound 308

Method: General Procedure 2a.

25 Starting material II: Compound 205Alkylating agent R³Z: Ethyl bromide

Chromatography eluant: 0% to 20% ether in pet.ether.

¹H NMR: δ = 0.05 (m, 12H), 0.09 (s, 9H), 0.50 (s, 3H), 0.80 (t, 6H),
0.83 (d, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 1.17 (t, 3H), 1.44 (q, 4H), 1.15-2.10
30 (m, 22H), 2.31 (bd, 1H), 2.55 (dd, 1H), 2.88 (m, 1H), 3.22 (m, 1H), 3.47 (m,
2H), 4.21 (m, 1H), 4.53 (m, 1H), 4.93 (m, 1H), 4.98 (m, 1H), 5.82 (d, 1H),

6.45 (d, 1H).

Preparation 14: Compound 401

Method: General Procedure 4.

5 Starting material III: Compound 301

Chromatography eluant: 5% ether in pet.ether.

^1H NMR: δ = 0.06 (m, 12H), 0.11 (s, 9H), 0.50 (s, 3H), 0.82 (d, 3H), 0.87 (s, 18H), 1.20 (s, 3H), 1.21 (s, 3H), 1.15-2.10 (m, 18H), 2.21 (dd, 1H), 2.44 (dd, 1H), 2.82 (m, 1H), 3.18 (m, 1H), 3.32 (s, 3H), 4.18 (m, 1H),
10 4.37 (m, 1H), 4.86 (m, 1H), 5.17 (m, 1H), 6.01 (d, 1H), 6.23 (d, 1H).

Preparation 15: Compound 402

Method: General Procedure 4.

Starting material III: Compound 302

15 Chromatography eluant: 2.5% ether in pet.ether.

^1H NMR: δ = 0.06 (m, 12H), 0.10 (s, 9H), 0.49 (s, 3H), 0.83 (d, 3H), 0.88 (s, 18H), 1.17 (t, 3H), 1.20 (s, 3H), 1.21 (s, 3H), 1.10-2.10 (m, 18H), 2.21 (dd, 1H), 2.44 (dd, 1H), 2.83 (m, 1H), 3.20 (m, 1H), 3.47 (m, 2H), 4.18 (m, 1H), 4.37 (m, 1H), 4.86 (m, 1H), 5.17 (m, 1H), 6.01 (d, 1H),
20 6.23 (d, 1H).

Preparation 16: Compound 403

Method: General Procedure 4.

Starting material III: Compound 303

25 Chromatography eluant: 0% to 2% ether in pet.ether.

^1H NMR: δ = 0.06 (m, 12H), 0.10 (s, 9H), 0.50 (s, 3H), 0.82 (m, 9H), 0.87 (s, 9H), 0.88 (s, 9H), 1.20-2.10 (m, 22H), 2.21 (dd, 1H), 2.44 (dd, 1H), 2.82 (m, 1H), 3.18 (m, 1H), 3.32 (s, 3H), 4.18 (m, 1H), 4.38 (m, 1H), 4.86 (m, 1H), 5.18 (m, 1H), 6.01 (d, 1H), 6.23 (d, 1H).

Preparation 17: Compound 404

Method: General Procedure 4.

Starting material III: Compound 304

Chromatography eluant: 2% ether in pet.ether.

- 5 ¹H NMR: δ = 0.05 (m, 12H), 0.09 (s, 9H), 0.50 (s, 3H), 0.81 (d, 3H), 0.86 (s, 18H), 1.19 (s, 3H), 1.20 (s, 3H), 1.15-2.07 (m, 20H), 2.21 (dd, 1H), 2.44 (dd, 1H), 2.82 (m, 1H), 3.22 (m, 1H), 3.32 (s, 3H), 4.18 (m, 1H), 4.37 (m, 1H), 4.86 (m, 1H), 5.17 (m, 1H), 6.00 (d, 1H), 6.23 (d, 1H).

10 Preparation 18: Compound 405

Method: General Procedure 4.

Starting material III: Compound 305

Chromatography eluant: 0% to 3% ether in pet.ether.

- 15 ¹H NMR: δ = 0.06 (m, 12H), 0.09 (s, 9H), 0.51 (s, 3H), 0.81 (m, 9H), 0.88 (s, 18H), 1.15-2.10 (m, 24H), 2.21 (dd, 1H), 2.43 (dd, 1H), 2.82 (m, 1H), 3.21 (m, 1H), 3.32 (s, 3H), 4.18 (m, 1H), 3.37 (m, 1H), 4.86 (m, 1H), 5.17 (m, 1H), 6.01 (d, 1H), 6.23 (d, 1H).

Preparation 19: Compound 406

20 Method: General Procedure 4.

Starting material III: Compound 306

Chromatography eluant: 0% to 2% ether in pet.ether.

- 25 ¹H NMR: δ = 0.06 (m, 12H), 0.08 (s, 9H), 0.49 (s, 3H), 0.81 (t, 6H), 0.82 (d, 3H), 0.87 (s, 18H), 1.17 (t, 3H), 1.10-2.10 (m, 24H), 2.21 (dd, 1H), 2.44 (dd, 1H), 2.82 (m, 1H), 3.23 (m, 1H), 3.47 (q, 2H), 4.18 (m, 1H), 4.37 (m, 1H), 4.86 (m, 1H), 5.18 (m, 1H), 6.01 (d, 1H), 6.23 (d, 1H).

Preparation 20: Compound 407

Method: General Procedure 4.

30 Starting material III: Compound 307

Chromatography eluant: 0% to 2% ether in pet.ether.

^1H NMR: δ = 0.06 (m, 12H), 0.09 (s, 9H), 0.50 (s, 3H), 0.80 (t, 6H), 0.81 (d, 3H), 0.87 (s, 18H), 1.44 (q, 4H), 1.10-2.10 (m, 22H), 2.21 (dd, 1H), 2.44 (dd, 1H), 2.83 (m, 1H), 3.21 (m, 1H), 3.32 (s, 3H), 4.18 (m, 1H), 4.36 (m, 1H), 4.86 (m, 1H), 5.17 (m, 1H), 6.01 (d, 1H), 6.23 (d, 1H).

5

Preparation 21: Compound 408

Method: General Procedure 4.

Starting material III: Compound 308

Chromatography eluant: 0% to 2% ether in pet.ether.

10

^1H NMR: δ = 0.06 (m, 12H), 0.09 (s, 9H), 0.49 (s, 3H), 0.79 (t, 6H), 0.80 (d, 3H), 0.87 (s, 18H), 1.17 (t, 3H), 1.44 (q, 4H), 1.07-2.10 (m, 22H), 2.21 (dd, 1H), 2.44 (dd, 1H), 2.83 (m, 1H), 3.22 (m, 1H), 3.47 (m, 2H), 4.18 (m, 1H), 4.36 (m, 1H), 4.86 (m, 1H), 5.17 (m, 1H), 6.01 (d, 1H), 6.23 (d, 1H).

15

Preparation 22: Compound 310

Method: General Procedure 2.

Starting material II: Compound 203

Alkylating agent R^3Z : Ethyl bromide

20

Chromatography eluant: 0% to 5% ether in pet.ether.

^{13}C NMR: 153.4, 143.3, 135.1, 121.6, 116.1, 106.4, 82.6, 73.8, 70.1, 67.0, 64.2, 55.6, 50.7, 46.1, 44.9, 43.8, 39.2, 36.4, 35.0, 31.1, 29.7, 29.6, 28.9, 25.7, 25.6, 25.0, 23.2, 22.1, 21.1, 18.1, 17.9, 15.6, 12.8, 12.7, 2.4, -4.9, -5.0, -5.1, -5.1.

25

Preparation 23: Compound 311

Method: General Procedure 2.

Starting material II: Compound 114j of WO91/00271

Alkylating agent R^3Z : Methyl iodide

30

Chromatography eluant: 0% to 20% ether in pet.ether.

^{13}C NMR: 153.4, 143.2, 135.1, 121.6, 116.2, 106.4, 83.4, 73.8, 70.1,

67.0, 56.4, 55.8, 51.2, 45.9, 44.8, 43.8, 39.6, 36.4, 35.4, 30.2, 29.7, 29.6, 28.8, 26.7, 25.8, 25.7, 25.6, 24.5, 23.3, 22.0, 18.1, 17.9, 12.6, 12.3, 2.4, -4.9, -5.0, -5.1, -5.1

5 Preparation 24: Compound 312

Method: General Procedure 2.

Starting material II: Compound 114j of WO91/00271

Alkylating agent R³Z: Ethyl bromide

Chromatography eluant: 0% to 20% ether in pet.ether.

10 ¹³C NMR: 153.4, 143.3, 135.1, 121.6, 116.1, 106.4, 82.5, 73.8, 70.1, 67.0, 64.2, 55.7, 50.8, 46.1, 44.8, 43.8, 39.2, 36.4, 35.1, 30.8, 29.7, 29.6, 28.9, 26.9, 25.7, 25.6, 25.1, 24.5, 23.3, 22.1, 18.1, 17.9, 15.6, 12.8, 12.6, 2.4, -4.9, -5.0, -5.1, -5.1

15 Preparation 25: Compound 314

Method: General Procedure 2a.

Starting material II: Compound 201

Alkylating agent R³Z: n-Propyl bromide

Chromatography eluant: 0% to 5% ether in pet.ether.

20 ¹³C NMR: 153.5, 143.3, 135.1, 121.6, 116.1, 106.4, 83.0, 73.8, 70.6, 70.1, 67.0, 55.7, 50.9, 46.1, 43.8, 41.2, 39.4, 36.4, 35.3, 29.8, 29.6, 28.9, 25.7, 25.6, 25.3, 25.2, 23.4, 23.3, 22.1, 18.1, 17.9, 12.6, 10.7, 2.4, -4.9, -5.0, -5.1, -5.1

Preparation 26: Compound 315

25 Method: General Procedure 2.

Starting material II: Compound 201

Alkylating agent R³Z: Benzyl bromide

Chromatography eluant: 0% to 5% ether in pet.ether.

30 ¹³C NMR: 153.4, 143.2, 138.1, 135.1, 128.0, 127.4, 127.0, 121.6, 116.2, 106.4, 82.7, 73.7, 70.4, 70.1, 67.0, 55.7, 51.1, 46.0, 43.8, 41.2, 39.5, 36.4, 35.5, 29.8, 29.6, 28.8, 25.7, 25.6, 25.5, 25.2, 23.2, 22.0, 18.1, 17.9, 12.6, 12.5,

2.4, -4.9, -5.0, -5.1, -5.1

Preparation 27: Compound 410

Method: General Procedure 4.

5 Starting material III: Compound 310

Chromatography eluant: 0% to 5% ether in pet.ether.

^{13}C NMR: 148.1, 140.9, 134.7, 123.0, 117.6, 111.0, 82.7, 73.8, 71.8, 67.3, 64.2, 55.5, 50.7, 46.0, 45.8, 44.9, 44.6, 39.2, 35.0, 31.2, 29.7, 29.6, 28.8, 25.7, 25.6, 25.0, 23.2, 22.0, 21.1, 18.1, 18.0, 15.6, 12.9, 12.6, 2.4, -4.9, -5.0, -5.3

10

Preparation 28: Compound 411

Method: General Procedure 4.

Starting material III: Compound 311

Chromatography eluant: 0% to 5% ether in pet.ether.

15 ^{13}C NMR: 148.1, 140.8, 134.8, 123.0, 117.6, 111.0, 83.4, 73.7, 71.8, 67.3, 56.4, 55.6, 51.2, 45.8, 45.7, 44.7, 44.6, 39.7, 35.4, 30.1, 29.7, 29.6, 28.7, 26.7, 25.8, 25.7, 25.6, 24.5, 23.3, 21.9, 18.0, 17.9, 12.5, 12.3, 2.4, -4.9, -5.0, -5.3

Preparation 29: Compound 412

20 Method: General Procedure 4.

Starting material III: Compound 312

Chromatography eluant: 0% to 5% ether in pet.ether.

^{13}C NMR: 148.1, 140.9, 134.7, 123.0, 117.6, 111.0, 82.6, 73.8, 71.8, 67.3, 64.2, 55.5, 50.7, 46.0, 45.8, 44.8, 44.6, 39.3, 35.1, 30.8, 29.7, 29.6, 28.8, 25 26.9, 25.7, 25.7, 25.6, 25.1, 24.5, 23.2, 22.0, 18.1, 15.6, 12.8, 12.6, 2.4, -4.9, -5.0, -5.3

Preparation 30: Compound 414

Method: General Procedure 4.

30 Starting material III: Compound 314

Chromatography eluant: 0% to 1% ether in pet.ether.

^{13}C NMR: 148.1, 140.9, 134.7, 123.0, 117.6, 111.0, 83.0, 73.8, 71.8,

70.6, 67.3, 55.6, 50.9, 45.9, 45.8, 44.6, 41.2, 41.2, 39.5, 35.3, 29.8, 29.6, 27.5,
25.7, 25.6, 25.3, 25.2, 23.4, 22.4, 20.2, 19.2, 14.1, 12.6, 10.7, 2.4, -4.9, -5.0, -5.3

Preparation 31: Compound 415

5

Method: General Procedure 4.

Starting material III: Compound 315

Chromatography eluant: 0% to 1% ether in pet.ether.

^{13}C NMR: 148.1, 140.8, 139.3, 134.8, 128.0, 127.2, 127.0, 123.0,
117.6, 111.0, 82.7, 73.7, 71.8, 70.4, 67.3, 55.6, 51.1, 45.9, 45.8, 44.6, 41.2, 39.5,
10 35.5, 29.8, 29.6, 28.7, 25.7, 25.6, 25.5, 25.2, 23.2, 21.9, 18.1, 18.0, 12.6, 12.5,
2.4, -4.8, -4.9, -5.0, -5.3

Preparation 32: Compound 416a

Method: General Procedure 4.

15

Starting material II: Compound 201

Chromatography eluant: 0% to 10% ether in pet.ether.

^{13}C NMR: 148.1, 140.6, 134.9, 122.9, 117.8, 111.0, 73.9, 73.0, 71.9,
67.3, 56.0, 52.3, 45.8, 45.3, 44.6, 41.6, 40.0, 39.8, 29.8, 29.7, 29.6, 28.7, 27.2,
25.7, 25.6, 23.2, 21.8, 18.0, 17.9, 12.2, 11.2, 2.4, -4.9, -5.0, -5.3

20

Preparation 33: Compound 416

Method: General Procedure 3.

Starting material IV: Compound 416a

Acylating reagent: Phenyl chlorothionoformate (125 mg)

25

Bases: Pyridine (0.2 ml); 4-Dimethylaminopyridine (115 mg)

Solvent: Dichloromethane (4 ml).

Reaction temperature: 20 °C.

Reaction time: 7 hours.

Chromatography eluant: 5% ether in pet.ether.

30

^{13}C NMR: 194.3, 153.1, 148.2, 140.4, 135.0, 129.2, 126.2, 122.9,
121.9, 117.8, 111.0, 89.2, 73.3, 71.8, 67.3, 55.5, 51.3, 45.8, 45.6, 44.6, 40.2,
39.1, 34.9, 29.9, 29.4, 28.7, 25.7, 25.6, 25.4, 24.3, 23.1, 21.9, 18.1, 18.0, 12.6,

12.4, 2.4, -4.9, -5.0, -5.3

Preparation 34: Compound 321

Method: General Procedure 2.

5 Alkylating agent R³ Z: Methyl iodide

Starting material II: Compound 221

Reaction time: 15 minutes

Chromatography eluant: 15% ether in pet.ether: PLC.

¹H NMR: δ = 6.45(d,1H), 5.83(d,1H), 4.98(m,1H), 4.93(m,1H),
10 4.53(m,1H), 4.22(m,1H), 3.30(s,3H), 3.24(m,1H), 2.88(m,1H), 2.55(dd,1H),
2.31(m,1H), 2.08-1.15(m,18H), 1.22(s,3H), 1.19(s,3H), 0.89(s,9H), 0.86(s,9H),
0.81(d,3H), 0.58(s,3H), 0.10(s,9H), 0.05(m,12H)

Preparation 35: Compound 421

15 Method: General Procedure 4.

Starting material III: Compound 321

Chromatography eluant: 0% to 1% ether in pet.ether.

¹H NMR: δ = 6.24(d,1H), 6.03(d,1H), 5.18(m,1H), 4.87(m,1H),
4.37(m,1H), 4.19(m,1H), 3.31(s,3H), 3.24(m,1H), 2.83(m,1H), 2.45(dd,1H),
20 2.22(dd,1H), 2.07-1.00(m,18H), 1.23(s,3H), 1.20(s,3H), 0.88(s,18H), 0.83(d,3H),
0.58(s,3H), 0.11(s,9H), 0.06(m,12H)

Examples

25 Example 1: 1(S),3(R)-Dihydroxy-20(R)-(1-methoxy-4-
hydroxy-4-methyl-1-pentyl)-9,10-seco-pregna-
5(Z),7(E),10(19)-triene; isomer A (Compound
101)

Method: General Procedure 5.

30 Starting material IV: Compound 401.

Chromatography eluant: 50% to 0% pet.ether in ethylacetate.

¹H NMR: δ = 0.52 (s, 3H), 0.84 (d, 3H), 1.22 (s, 3H), 1.23 (s, 3H),

1.15-2.10 (m, 21H), 2.31 (dd, 1H), 2.59 (dd, 1H), 2.84 (m, 1H), 3.17 (m, 1H), 3.34 (s, 3H), 4.22 (m, 1H), 4.42 (m, 1H), 5.00 (m, 1H), 5.33 (m, 1H), 6.02 (d, 1H), 6.37 (d, 1H).

5 Example 2: 1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-4-hydroxy-4-methyl-1-pentyl)-9,10-seco-pregna-5(Z),7(E),-10(19)-triene; isomer A (Compound 102)

Method: General Procedure 5.

Starting material IV: Compound 402.

10 Chromatography eluant: 50% to 0% pet.ether in ethylacetate.

^1H NMR: δ = 0.51 (s, 3H), 0.85 (d, 3H), 1.19 (t, 3H), 1.22 (s, 3H), 1.23 (s, 3H), 1.10-2.10 (m, 21H), 2.31 (dd, 1H), 2.60 (dd, 1H), 2.85 (dd, 1H), 3.19 (m, 1H), 3.49 (m, 2H), 4.23 (m, 1H), 4.43 (m, 1H), 5.00 (m, 1H), 5.33 (m, 1H), 6.02 (d, 1H), 6.39 (d, 1H).

15

Example 3: 1(S),3(R)-Dihydroxy-20(R)-(4-ethyl-4-hydroxy-1-methoxy-1-hexyl)-9,10-seco-pregna-5(Z),7(E),-10(19)-triene; isomer A (Compound 103)

Method: General Procedure 5.

20 Starting material IV: Compound 403.

Chromatography eluant: 50% to 0% pet.ether in ethylacetate.

^1H NMR: δ = 0.52 (s, 3H), 0.86 (m, 9H), 1.20-2.10 (m, 25H), 2.32 (dd, 1H), 2.60 (dd, 1H), 2.85 (m, 1H), 3.16 (m, 1H), 3.34 (s, 3H), 4.23 (m, 1H), 4.43 (m, 1H), 5.00 (m, 1H), 5.33 (m, 1H), 6.02 (d, 1H), 6.38 (d, 1H).

25

Example 4: 1(S),3(R)-Dihydroxy-20(R)-(5-hydroxy-1-methoxy-5-methyl-1-hexyl)-9,10-seco-pregna-5-(Z),7(E),10(19)-triene; isomer A (Compound 104)

30 Method: General Procedure 5.

Starting material IV: Compound 404.

Chromatography eluant: 50% to 0% pet.ether in ethylacetate.

^1H NMR: δ = 0.52 (s, 3H), 0.83 (d, 3H), 1.22 (s, 6H), 1.20-2.10 (m,

23H), 2.32 (dd, 1H), 2.60 (dd, 1H), 2.85 (m, 1H), 3.20 (m, 1H), 3.34 (s, 3H), 4.23 (m, 1H), 4.43 (m, 1H), 5.00 (m, 1H), 5.33 (m, 1H), 6.02 (d, 1H), 6.38 (d, 1H).

5 Example 5: 1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-1-methoxy-1-heptyl)-9,10-seco-pregna-5(Z),7(E),-10(19)-triene; isomer A (Compound 105)

Method: General Procedure 5.

Starting material IV: Compound 405.

10 Chromatography eluant: 50% to 0% pet.ether in ethylacetate.

^1H NMR: δ = 0.52 (s, 3H), 0.82 (d, 3H), 0.86 (t, 6H), 1.46 (q, 4H), 1.20-2.15 (m, 23H), 2.31 (dd, 1H), 2.60 (dd, 1H), 2.84 (m, 1H), 3.20 (m, 1H), 3.33 (s, 3H), 4.23 (m, 1H), 4.43 (m, 1H), 5.00 (m, 1H), 5.33 (m, 1H), 6.02 (d, 1H), 6.38 (d, 1H).

15

Example 6: 1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-1-heptyl)-9,10-seco-pregna-5(Z),7(E),-10(19)-triene; isomer A (Compound 106)

Method: General Procedure 6.

20 Starting material IV: Compound 406.

Chromatography eluant: 50% to 0% pet.ether in ethylacetate.

^1H NMR: δ = 0.51 (s, 3H), 0.83 (d, 3H), 0.86 (t, 6H), 1.18 (t, 3H), 1.46 (q, 4H), 1.15-2.15 (m, 23H), 2.31 (dd, 1H), 2.60 (dd, 1H), 2.85 (m, 1H), 3.23 (m, 1H), 3.48 (m, 2H), 4.23 (m, 1H), 4.43 (m, 1H), 5.00 (m, 1H),
25 5.33 (m, 1H), 6.02 (d, 1H), 6.38 (d, 1H).

Example 7: 1(S),3(R)-Dihydroxy-20(R)-(6-ethyl-6-hydroxy-1-methoxy-1-octyl)-9,10-seco-pregna-5(Z),7(E),-10(19)-triene; isomer A (Compound 107)

30 Method: General Procedure 6.

Starting material IV: Compound 407.

Chromatography eluant: 50% to 0% pet.ether in ethylacetate.

^1H NMR: δ = 0.52 (s, 3H), 0.82 (d, 3H), 0.86 (t, 6H), 1.46 (q, 4H),

1.15-2.10 (m, 25H), 2.31 (dd, 1H), 2.60 (m, 1H), 2.84 (m, 1H), 3.21 (m, 1H), 3.33 (s, 3H), 4.23 (m, 1H), 4.43 (m, 1H), 5.00 (m, 1H), 5.33 (m, 1H), 6.02 (d, 1H), 6.38 (d, 1H).

5 Example 8: 1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-6-ethyl-6-hydroxy-1-octyl)-9,10-seco-pregna-5(Z),7(E),-10(19)-triene; isomer A (Compound 108)

Method: General Procedure 6.

Starting material IV: Compound 408.

10 Chromatography eluant: 50% to 0% pet.ether in ethylacetate.

^1H NMR: δ = 0.51 (s, 3H), 0.82 (d, 3H), 0.85 (t, 6H), 1.18 (t, 3H), 1.46 (q, 4H), 1.10-2.10 (m, 25H), 2.31 (dd, 1H), 2.60 (dd, 1H), 2.84 (m, 1H), 3.22 (m, 1H), 3.47 (q, 2H), 4.23 (m, 1H), 4.43 (m, 1H), 5.00 (m, 1H), 5.33 (m, 1H), 6.02 (d, 1H), 6.38 (d, 1H).

15

Example 9: 1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-5-hydroxy-5-methyl-1-hexyl)-9,10-seco-pregna-5(Z),7(E),-10(19)-triene; isomer A (Compound 110)

Method: General Procedure 5.

20 Starting material IV: Compound 410.

Chromatography eluant: 50% to 0% pet.ether in ethylacetate.

^{13}C NMR: 147.7, 143.0, 133.2, 124.8, 117.0, 111.7, 83.1, 71.0, 70.7, 66.7, 64.5, 55.7, 50.6, 46.4, 45.2, 44.1, 42.9, 39.2, 34.9, 31.4, 29.4, 29.2, 29.1, 24.9, 23.5, 22.3, 21.3, 15.8, 13.2, 12.9

25

Example 10: 1(S),3(R)-Dihydroxy-20(R)-(6-hydroxy-1-methoxy-6-methyl-1-heptyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene; isomer A (Compound 111)

30 Method: General Procedure 5.

Starting material IV: Compound 411.

Chromatography eluant: 50% to 0% pet.ether in ethylacetate.

^{13}C NMR: 147.7, 143.1, 133.0, 124.9, 117.0, 111.8, 83.8, 71.0, 70.8,

66.8, 56.7, 55.8, 51.2, 46.1, 45.3, 44.0, 42.9, 39.6, 35.4, 30.3, 29.3, 29.2, 29.1, 27.0, 25.8, 24.7, 23.5, 22.2, 12.8, 12.6

5 Example 11: 1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-6-
 -hydroxy-6-methyl-1-heptyl)-9,10-seco-pregna-
 5(Z),7(E),10(19)-triene; isomer A (Compound
 112)

Method: General Procedure 5.

Starting material IV: Compound 412.

10 Chromatography eluant: 50% to 0% pet.ether in ethylacetate.

^1H NMR: δ = 6.38(d,1H), 6.01(d,1H), 5.33(m,1H), 5.00(m,1H),
4.43(m,1H), 4.23(m,1H), 3.48(q,2H), 3.22(m,1H), 2.84(dd,1H), 2.60(dd,1H),
2.32(dd,1H), 2.08-1.09(m,25H), 1.21(s,6H), 1.18(t,3H), 0.82(d,3H), 0.51(s,3H)

15 Example 12: 1(S),3(R)-Dihydroxy-20(R)-(4-hydroxy-4-
 -methyl-1-n-propoxy-1-pentyl)-9,10-seco-
 pregna-5(Z),7(E),10(19)-triene; isomer A
 (Compound 114)

Method: General Procedure 5.

20 Starting material IV: Compound 414.

Chromatography eluant: 50% to 0% pet.ether in ethylacetate.

^1H NMR: δ = 6.39(d,1H), 6.02(d,1H), 5.33(m,1H), 5.00(m,1H),
4.43(m,1H), 4.23(m,1H), 3.38(m,2H), 3.19(m,1H), 2.84(dd,1H), 2.60(dd,1H),
2.32(dd,1H), 2.10-1.13(m,23H), 1.22(s,6H), 0.92(t,3H), 0.85(d,3H), 0.51(s,3H)

25

Example 13: 1(S),3(R)-Dihydroxy-20(R)-(1-benzyloxy-
 -4-hydroxy-4-methyl-1-pentyl)-9,10-seco-
 pregna-5(Z),7(E),10(19)-triene; isomer A
 (Compound 115)

30 Method: General Procedure 5.

Starting material IV: Compound 415

Chromatography eluant: 50% to 0% pet.ether in ethylacetate.

^1H NMR: δ = 7.41-7.23(m,5H), 6.38(d,1H), 6.02(d,1H), 5.33(m,1H),

5.00(m,1H), 4.53(m,2H), 4.43(m,1H), 4.23(m,1H), 3.42(m,1H), 2.83(dd,1H),
2.60(dd,1H), 2.31(dd,1H), 2.11-1.13(m,21H), 1.22(s,6H), 0.90(d,3H), 0.53(s,3H)

5 Example 14 1(S),3(R)-Dihydroxy-20(R)-(4-hydroxy-4-
 -methyl-1-phenoxythiocarbonyloxy-1-pentyl)-
 -9,10-seco-pregna-5(Z),7(E),10(19)-triene;
 isomer A (Compound 116)

Method: General Procedure 6.

Starting material IV: Compound 416.

10 Chromatography eluant: 50% to 0% pet.ether in ethylacetate.

^1H NMR: δ = 7.42(t,2H), 7.29(t,1H), 7.08(d,2H), 6.39(d,1H), 6.03(d,1H),
5.34(t,1H), 5.24(m,1H), 5.01(m,1H), 4.44(m,1H), 4.24(m,1H), 2.85(dd,1H),
2.61(dd,1H), 2.32(dd,1H), 2.15-1.20(m,21H), 1.26(s,6H), 0.97(d,3H), 0.54(s,3H)

15 Example 15: 1(S),3(R)-Dihydroxy-20(R)-(1-methoxy-4-
 hydroxy-4-methyl-1-pentyl)-9,10-seco-pregna-
 5(Z),7(E),10(19)-triene; isomer B (Compound
 121)

Method: General Procedure 5.

20 Starting material IV: Compound 421.

Chromatography eluant: 50% to 0% pet.ether in ethylacetate.

^1H NMR: δ = 6.38(d,1H), 6.03(d,1H), 5.34(m,1H), 5.00(m,1H),
4.44(m,1H), 4.24(m,1H), 3.32(s,3H), 3.30(m,1H), 2.84(m,1H), 2.61(dd,1H),
2.32(dd,1H), 2.16(s,1H), 2.09-1.11(m,20H), 1.22(s,3H), 1.21(s,3H), 0.82(d,3H),
25 0.60(s,3H)

Example 16 Capsules containing Compound 101

Compound 101 was dissolved in arachis oil to a final concentration
30 of 1 μg of Compound 101/ml oil. 10 Parts by weight of gelatine, 5 parts by
weight glycerine, 0.08 parts by weight potassium sorbate, and 14 parts by
weight distilled water were mixed together with heating and formed into soft
gelatine capsules. These were then filled each with 100 μl of Compound

101 in oil solution, such that each capsule contained 0.1 μg of Compound 101.

Example 17

Dermatological Cream Containing Compound 102

- 5 In 1 g almond oil was dissolved 0.05 mg of Compound 102. To this solution was added 40 g of mineral oil and 20 g of self-emulsifying beeswax. The mixture was heated to liquify. After the addition of 40 ml hot water, the mixture was mixed well. The resulting cream contains approximately 0.5 μg of Compound 102 per gram of cream.

The following scientific articles and references have been cited throughout this application and the entire contents of each article or reference is hereby incorporated by reference.

5 Scientific Articles and References

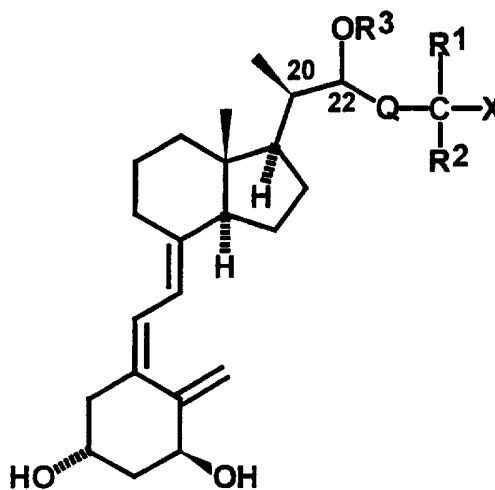
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WHAT WE CLAIM IS:

- 5 1. A compound of the formula



I

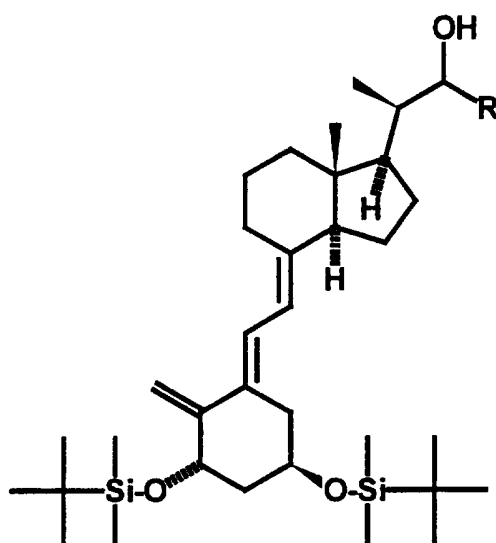
- in which formula X is hydrogen or hydroxy; R^1 and R^2 , which may be the same or different, stand for hydrogen or a C_1 - C_3 alkyl radical; or R^1 and R^2 ,
 10 taken together with the carbon atom bearing the group X, can form a C_3 - C_6 carbocyclic ring; R^3 stands for a C_1 - C_3 alkyl radical, an aryl or an aralkyl radical, or for YR^4 , in which Y stands for the radicals -CO-S-, -CS-O- or -CS-S-, and R^4 stands for a C_1 - C_3 alkyl radical or an aryl or an aralkyl
 radical; Q is $(CH_2)_n$, n being 1 - 4; R^1 , R^2 and Q independently may optio-
 15 nally be substituted with one or more fluorine atoms.

2. A compound of formula I according to claim 1 in which Q is $(CH_2)_n$, n being 2 or 3, in which X is hydroxy, R^1 and R^2 are methyl or ethyl, and R^3 is methyl or ethyl.

3. A diastereoisomer of a compound according to any one of claims 1 and 2, in pure form; or a mixture of such diastereoisomers.
4. A diastereoisomer of a compound according to claim 3 having the
5 "A" -configuration at C-22.
5. A compound according to claim 1 which is :
1(S),3(R)-Dihydroxy-20(R)-(1-methoxy-4-hydroxy-4-methyl-1-pentyl)-
9,10-seco-pregna-5(Z),7(E),10(19)-triene; isomer A, or
10 1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-4-hydroxy-4-methyl-1-pentyl)-
9,10-seco-pregna-5(Z),7(E),10(19)-triene; isomer A.
6. A method for producing a compound of formula I of claim 1 in
which
15 a) 1(S),3(R)-bis-(tert)-butyldimethylsilyloxy)-20(R)-formyl-9,10-seco-
pregna-5(E),7(E),10(19)-triene is reacted with an organometallic
reagent R-Met-Hal or R-Met, in which Met is a suitable metal, such
as magnesium or lithium, Hal is Cl, Br or I, and R is
$$-Q-CR^1R^2-X^1$$

20 in which X^1 is H, OH or OR^5 , R^5 being an alcohol protective
group, and R^1 , R^2 and Q have the above meanings, to form a
mixture of two C-22-epimers IIA and IIB

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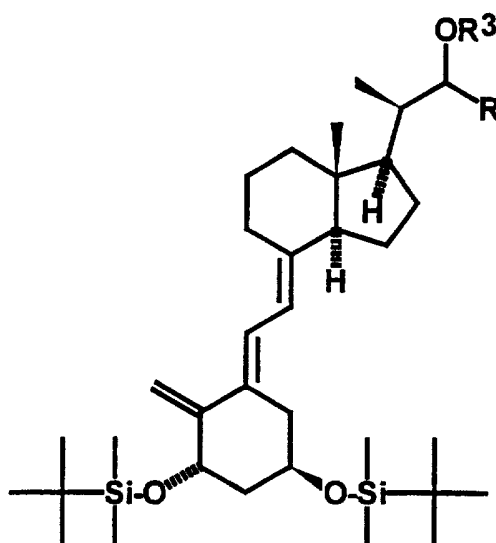


IIA/IIB

which epimers are separated;

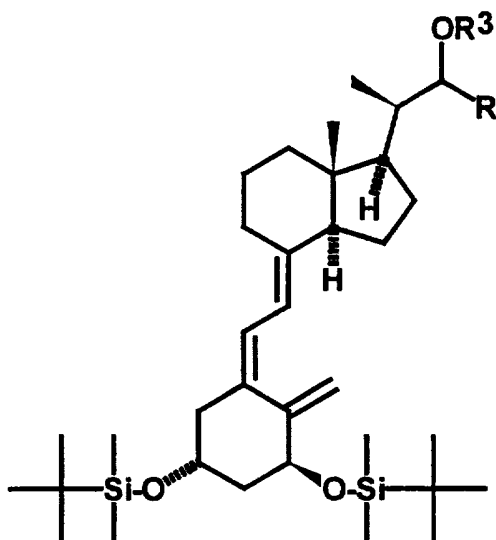
- 5 b) a compound of formula IIA or IIB of step a), is alkylated to the corresponding compound IIIA or IIIB, in which R and R³ have the above meanings or optionally acylated to the corresponding compound IIIA or IIIB, where R³ = YR⁴, Y and R⁴ having the meanings defined in claim 1

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IIIA/IIIB

- c) a compound of formula IIIA or IIIB of step b) is isomerized to the corresponding compound IVA or IVB by means of UV-light in the presence of a triplet sensitizer, such as anthracene,



IVA/IVB

in which R and R³ have the above meanings;

d) a compound of formula IVA or IVB is deprotected to the corresponding compound of the general formula I.

7. A method according to claim 6 in which steps b) and c) are
5 performed in the reverse order.

8. A method according to claim 6 in which steps c) and d) are performed in the reverse order.

10 9. A pharmaceutical composition containing an effective amount of one or more of the compounds of claims 1-5, together with pharmaceutically acceptable, non-toxic carriers and/or auxiliary agents.

10. A pharmaceutical composition according to claim 9 in dosage unit
15 form containing from 0.1 ppm to 0.1% by weight of the dosage unit of a compound of formula I.

11. A method for the treatment and/or prophylaxis of a number of disease states characterized by abnormal cell differentiation and/or cell pro-
20 liferation such as psoriasis and other disturbances of keratinization, HIV-associated dermatoses, wound healing, cancer, including skin cancer, and of diseases of, or imbalance in, the immune system, such as host versus graft and graft versus host reaction and transplant rejection, and autoimmune diseases, such as discoid and systemic lupus erythematosus, diabetes mellitus
25 and chronic dermatoses of autoimmune type, e.g. scleroderma and pemphigus vulgaris, and inflammatory diseases, such as rheumatoid arthritis and asthma, as well as a number of other disease states including hyperparathyroidism, particularly secondary hyperparathyroidism associated with renal failure, cognitive impairment or senile dementia (Alzheimers disease) and
30 other neurodegenerative diseases, hypertension, acne, alopecia, skin atrophy, e.g. steroid induced skin atrophy, skin ageing, including photo-ageing, and to their use for promoting osteogenesis and treating/preventing osteo-

porosis and osteomalacia, consisting in administering to a patient in need thereof an effective amount of a pharmaceutical composition according to claim 9.

- 5 12. The use of a compound of any one of claim 1-5 in the manufacture of a medicament for the treatment and prophylaxis of a number of disease states characterized by abnormal cell differentiation and/or cell proliferation such as psoriasis and other disturbances of keratinization, HIV-associated dermatoses, wound healing, cancer, including skin cancer, and of diseases
10 of, or imbalance in, the immune system, such as host versus graft and graft versus host reaction and transplant rejection, and autoimmune diseases, such as discoid and systemic lupus erythematosus, diabetes mellitus and chronic dermatoses of autoimmune type, e.g. scleroderma and pemphigus vulgaris, and inflammatory diseases, such as rheumatoid arthritis and
15 asthma, as well as a number of other disease states including hyperparathyroidism, particularly secondary hyperparathyroidism associated with renal failure, cognitive impairment or senile dementia (Alzheimers disease) and other neurodegenerative diseases, hypertension, acne, alopecia, skin atrophy, e.g. steroid induced skin atrophy, skin ageing, including photo-ageing,
20 and to their use for promoting osteogenesis and treating/preventing osteoporosis and osteomalacia.

INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/DK 97/00225

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C401/00 A61K31/59

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 5 585 369 A (H.F. DELUCA ET AL) 17 December 1996 see claim 1	1
A	--- EP 0 296 800 A (YAMANOUCI PHARMACEUTICAL CO. LTD.) 28 December 1988 cited in the application see claim 1	1
A	--- WO 94 10139 A (LEO PHARMACEUTICAL PRODUCTS LTD.) 11 May 1994 see claims 1,10	1,12
A	--- WO 93 19044 A (LEO PHARMACEUTICAL PRODUCTS LTD.) 30 September 1993 cited in the application see claims 1,9 -----	1,12

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

1 September 1997

Date of mailing of the international search report

15 -09- 1997

Name and mailing address of the ISA

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Authorized officer

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00225

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 11
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 97/00225

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