(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 199894323 B2
(10) Patent No. 740457

(54) Title
Novel vitamin D analogues

(51)[6] International Patent Classification(s)
C07C 401/00

(21) Application No: 199894323

(22) Application Date: 1998.10.02

(87) WIPO No: WO99/18070

(30) Priority Data

(31) Number	(32) Date	(33) Country
9721156	1997.10.06	GB

(43) Publication Date : 1999.04.27
(43) Publication Journal Date : 1999.06.24
(44) Accepted Journal Date : 2001.11.01

(71) Applicant(s)
Leo Pharmaceutical Products Ltd. A/S (Lovens Kemiske Fabrik Produktionsaktieselskab)

(72) Inventor(s)
Welf Von Daehne; Gunnar Grue-Sorensen; Martin John Calverley; Claus Aage Svensgaard Bretting

(74) Agent/Attorney
CALLINAN LAWRIE,Private Bag 7,KEW VIC 3101

OPI DATE 27/04/99 APPLN. ID 94323/98
AOJP DATE 24/06/99 PCT NUMBER PCT/DK98/00423
AU9894323

T)

(51) International Patent Classification 6 :
C07C 401/00

A1

(11) International Publication Number: WO 99/18070

(43) International Publication Date: 15 April 1999 (15.04.99)

(21) International Application Number: PCT/DK98/00423

(22) International Filing Date: 2 October 1998 (02.10.98)

(30) Priority Data:
9721156.9 6 October 1997 (06.10.97) GB

(71) Applicant (*for all designated States except US*): LEO PHARMACEUTICAL PRODUCTS LTD. A/S (LØVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB) [DK/DK]; Industriparken, DK-2750 Ballerup (DK).

(72) Inventors; and

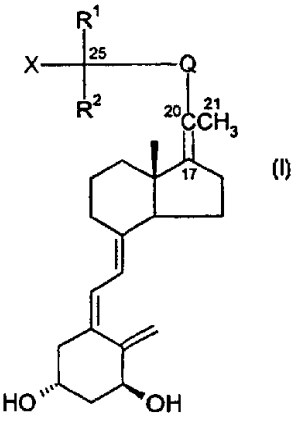
(75) Inventors/Applicants (*for US only*): VON DAEHNE, Welf [DE/DK]; Frihedsvej 4, DK-2960 Rungsted Kyst (DK). GRUE-SØRENSEN, Gunnar [DK/DK]; Thyrasvej 3, DK-4000 Roskilde (DK). CALVERLEY, Martin, John [GB/DK]; Oktobervej 61, DK-2730 Herlev (DK). BRETTING, Claus, Aage, Svensgaard [DK/DK]; Smallegade 42, 4. 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, GH, GM, HR, HU, ID, 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, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL VITAMIN D ANALOGUES



(I)

(57) Abstract

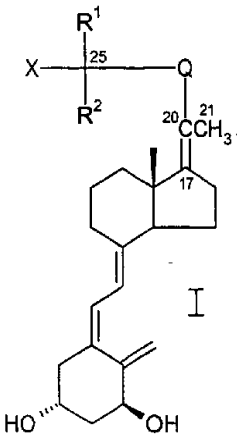
The present invention relates to compounds of formula (I), in which formula X is hydrogen or hydroxy or protected hydroxy; R^1 an R^2 stand for hydrogen, methyl or ethyl, or, when taken together with the carbon atom bearing the group X, R^1 and R^2 can form a C_3–C_5 carbocyclic ring; Q is a C_3–C_6 hydrocarbylene, hydrocarbylene indicating the diradical obtained after removal of 2 hydrogen atoms for a straight or banched, saturated or unsaturated hydrocarbon, in which one of any CH_2 groups may optionally be replaced by an oxygen atom or a carbonyl group, such that the carbon atom (C-22) directly bonded to C-20 is an sp^2 or sp^3 hybridized carbon atom, i.e. bonded to 2 or 3 other atoms; and in which another of the CH_2 groups may be replaced by phenylene, and where Q may optionally be substituted with one or more hydroxy or C_1–C_4-alkoxy groups. These compounds have been discovered to possess exceptionally high immunosuppressive activites together with high tumour cell proliferation inhibiting activities.

NOVEL VITAMIN D ANALOGUES

This invention relates to a hitherto unknown class of compounds that show strong activity in inducing differentiation and inhibiting undesirable proliferation of certain cells, including skin cells and cancer cells, as well as immunomodulating and anti-inflammatory 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 characterised by abnormal cell differentiation and/or cell proliferation such as e.g. psoriasis and other disturbances of keratinisation, 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, as well as a number of other disease states including hyperparathyroidism, particularly secondary hyperparathyroidism associated with renal failure, cognitive impairment or senile dementia (Alzheimer's 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.

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

2



I

in which formula X is hydrogen or hydroxy or protected hydroxy; R^1 and R^2 stand for hydrogen, methyl or ethyl, or, when taken together with the carbon atom bearing the group X, R^1 and R^2 can form a C_3-C_5 carbocyclic ring; Q is a C_3-C_6 hydrocarbylene, hydrocarbylene indicating the diradical obtained after removal of 2 hydrogen atoms from a straight or branched, saturated or unsaturated hydrocarbon, in which one of any CH_2 groups may optionally be replaced by an oxygen atom or a carbonyl group, such that the carbon atom (C-22) directly bonded to C-20 is an sp^2 or sp^3 hybridised carbon atom, i.e. bonded to 2 or 3 other atoms; and in which another of the CH_2 groups may be replaced by phenylene, and where Q may optionally be substituted with one or more hydroxy or C_1-C_4-alkoxy groups.

Examples of I include, illustratively but not limitingly, the horizontal entries in Table 1 (p. 12), where for convenience Q is considered to be a composite of segments Qa through Qf, with any blank spaces being understood as direct bond, such that Qa is directly bonded to C-20, and R^1 is the same as R^2 unless otherwise noted. Thus, segments within Q such as methylene, methene (in contiguous pairs, i.e. carbon atoms connected by double bonds), methyne (in contiguous pairs, i.e. carbon atoms connected by triple bonds), phenylene (illustrated by m-phenylene), alkylidene (illustrated by 1,1-

propylidene), hydroxymethylene, alkoxymethylene (illustrated by ethoxymethylene), keto, and oxa may be combined to produce side chains that are in fact identical (apart from the 17,20-double bond) to those already known from a variety of active vitamin D analogues.

The compounds of the invention can comprise more than one diastereoisomeric form (e.g. *E* or *Z* configuration of the 17,20-double bond and also of any non-ring double bond present in the group Q; *R* and *S* configurations when a hydroxy group or an alkoxy group or a branching atom is present in Q). The invention covers all these diastereoisomers in pure form and also mixtures thereof. In addition, prodrugs of I in which one or more of the hydroxy groups are masked as groups that can be reconverted to hydroxy groups *in vivo* could also be envisaged.

The compounds I may be obtained in crystalline form either directly by concentration from an organic solvent or by crystallisation or recrystallisation from an organic solvent or mixture of said solvent and a co-solvent which may be organic or inorganic, such as water. The crystals may be isolated in essentially solvent-free form or as a solvate, such as a hydrate. The invention covers all crystalline modifications and forms and also mixtures thereof.

A number of vitamin D analogues have been described that show some degree of selectivity in favour of the cell differentiation inducing/cell proliferation inhibiting activity in vitro as compared with the effects on calcium metabolism in vivo (as measured in increased serum calcium concentration and/or increased urinary calcium excretion), which adversely limit the dosage that can safely be administered. One of the first of these to appear, calcipotriol (INN) or calcipotriene (USAN), has been developed on the basis of this selectivity and is now recognised world-wide as an effective and safe drug for the topical treatment of psoriasis.

A study with another analogue selected on this basis supports the concept that systemically administered vitamin D analogues may inhibit breast cancer cell proliferation in vivo at sub-toxic doses (Colston, K.W. et al., Biochem. Pharmacol. 44, 2273-2280 (1992)).

Promising immunosuppressive activities of vitamin D analogues have

been reviewed (Binderup, L., Biochem. Pharmacol. 43, 1885-1892 (1992)). Thus, a series of 20-epi-vitamin D analogues has been identified as potent inhibitors of T-lymphocyte activation *in vitro* (Binderup, L. et al, Biochem. Pharmacol. 42, 1569-1575 (1991)). Two of these analogues, MC 1288 and KH 1060, systemically administered, have shown immunosuppressive activities *in vivo* in experimental animal models. Additive or synergistic effects were observed in combination with low-dose cyclosporin A. KH 1060, alone or in combination with cyclosporin A, has also been shown to prevent autoimmune destruction of transplanted islets in diabetic NOD mice (non-obese diabetic mice) (Bouillon, R. et al. In: Vitamin D, Proceedings of the Ninth Workshop on Vitamin D, Orlando, Florida, Walter de Gruyter, Berlin, 1994, pp 551-552). MC 1288 was able to prolong survival of cardiac and small bowel grafts in rats (Johnsson, C. et al. In: Vitamin D, Proceedings of the Ninth Workshop on Vitamin D, Orlando, Florida, Walter de Gruyter, Berlin, 1994, pp 549-550). However, in all these studies, the dosages of the analogues that produced significant immunosuppression also induced increases in serum calcium levels. There is therefore a continuing need for new analogues with high potency showing an acceptable combination of prolonged therapeutic activity and minimum toxic effects.

The present invention provides a hitherto undisclosed series of vitamin D analogues which is characterised by the presence of a double bond between C-17 and C-20.

21-Nor-17(20)-ene vitamin D analogues are described in EP 0 717 034, but the only previously described vitamin D analogues with a C-17,20 double bond and the C-21 methyl group preserved are those with a C-22,23 triple bond (WO 94/01398). The compounds of the present invention extend the range of side chain types to comprise a more comprehensive selection of side chains known from prior art vitamin D analogues.

These compounds have been discovered to possess exceptionally high immunosuppressive activities together with high tumour cell proliferation inhibiting activities.

The following standard abbreviations are used throughout this disclosure:

18C6 = 18-Crown-6

AIBN = 2,2'-azobisisobutyronitrile

b.p. = boiling point

Bu = n-butyl

Bu^t = tert-butyl

DIBAH = diisobutylaluminium hydride

DMAP = 4-dimethylaminopyridine

DMF = N,N-dimethylformamide

DMR = Dess-Martin-Reagent = 1,1,1-triacetoxy-1,1-dihydro-1,2-benz-iodoxol-3(1H)-one

Et = ethyl

Ether = diethyl ether

Fg = functional group

LDA = lithium diisopropylamide

Lg = leaving group

Me = methyl

m.p. = melting point

PCC = pyridinium chlorochromate

PDC = pyridinium dichromate

Ph = phenyl

PPTS = pyridinium p-toluenesulfonate

Py = pyridine

r.o.s. = "rest of sequence"

TBABr = tetra-n-butylammonium bromide

TBAF = tetra-n-butylammonium fluoride

TBAOH = tetra-n-butylammonium hydroxide

$TBAHSO_4$ = tetra-n-butylammonium hydrogensulfate

TBS = tert-butyldimethylsilyl

Tf = trifluromethansulfonyl

TFA = trifluoroacetic acid

THF = tetrahydrofuran

THP = tetrahydro-4H-pyran-2-yl

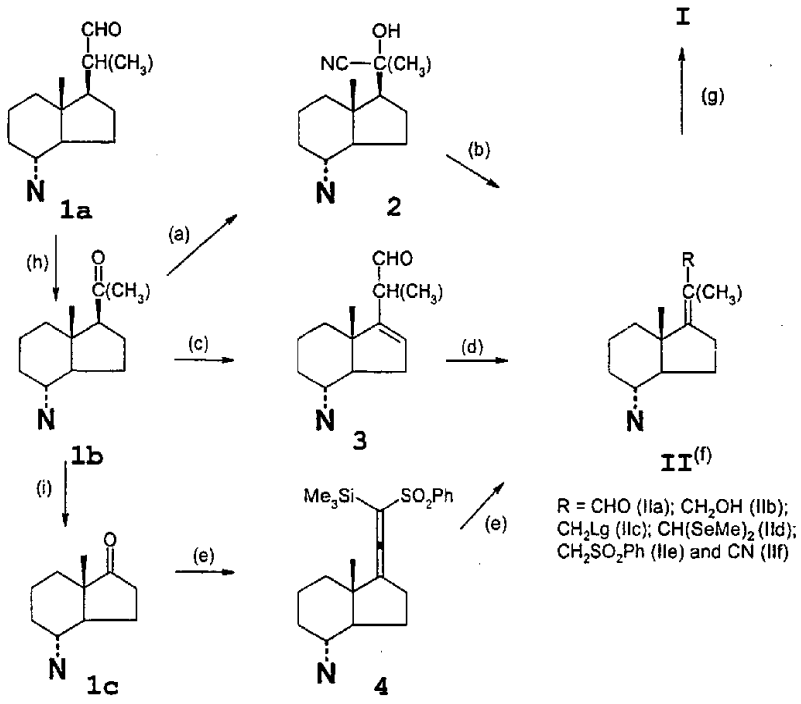
TMS = trimethylsilyl

Tol = toluene

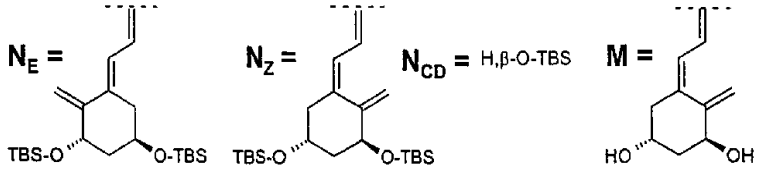
Ts = 4-toluenesulfonyl

Compounds of formula **I**, as illustrated in Table 1, may be prepared by the general methods of Schemes 1 and 3. In Scheme 1, the vitamin D nucleus building block aldehyde **1a**, is converted to a key intermediate of type II (Scheme 2) via the intermediates **2**, **3** or **4**.

Scheme 1.



$N = N_E$ or N_Z or N_{CD}



Notes to Scheme 1

(a) HCN

(b) 1) $POCl_3$/Py → IIf; 2) DIBAH → IIa

(c) W. von Daehne et al., poster at X vit. D workshop, Strasbourg 1997; WO 98/24762

(d) NaOH, CH_2Cl_2, TBABr → IIa

(e) Cf. N. Ohmori et al., Tetr. Lett. *1986*, **27**, 71

(f) For IIb, IIc, IId and IIe: See Scheme 2

(g) See Scheme 3, Table 1, and "Methods of Synthesis 1-7"

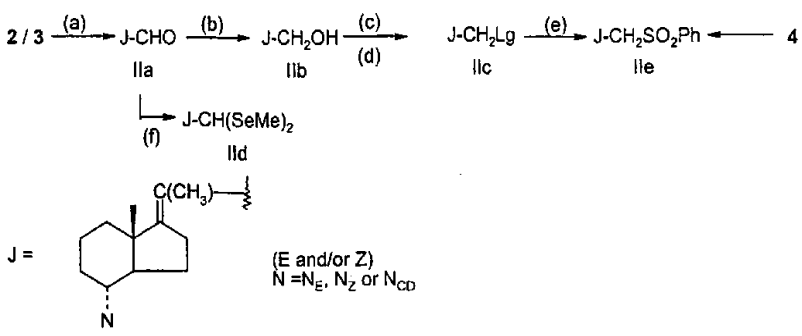
(h) **1b** ($N=N_{CD}$): B. Fernandez et al., J.Org.Chem. *1992*, **57**, 3173

1b ($N=N_E$): K. Hansen et al., in: Vitamin D: Gene Regulation, Structure-Function Analysis and Clinical Application; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; de Gruyter, Berlin, 1991, pp 161-162

(i) Fernandez et al., J.Org.Chem. *1992*, **57**, 3173

In Scheme 2 the method of preparation of each type of compound II, that is IIa, IIb, IIc, IId, and IIe from compound **2**,**3** and **4** is outlined. In Table 2 and preparations 1 to 6, 10 , 18, 31 and 34 the synthesis of some compounds of types IIa, IIb and IIc are described in more detail.

Scheme 2



Notes to Scheme 2

(a) See Table 2, Preparations 1-4, and 31.

(b) $NaBH_4/CeCl_3$

(c) Lg = leaving groups, such as e.g. halide (Cl, Br, I), lower alkanoate, p-toluenesulfonate (tosylate), methanesulfonate (mesylate) or trifluoromethanesulfonate (triflate).

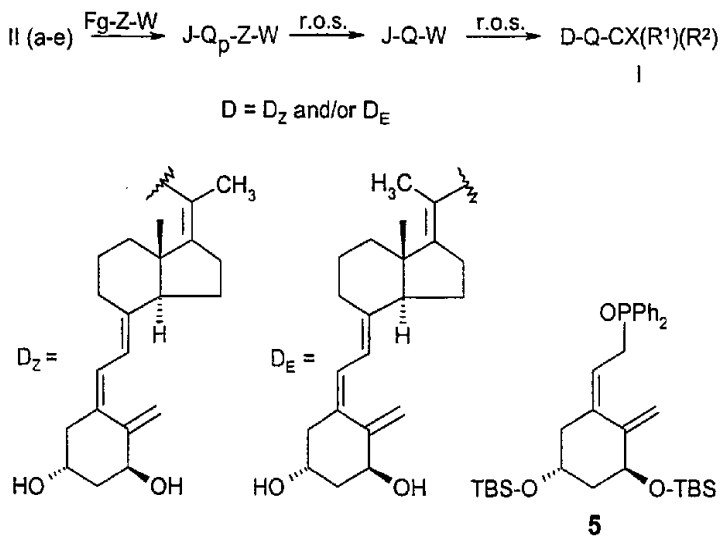
(d) The compounds IIc are obtained from IIb by standard procedures using suitable acid derivatives corresponding to the required Lg.

(e) 1) PhS^-K^+, 2) H_2O_2, $NaWO_4$ (M.J. Calverley, in: Trends in Medicinal Chemistry '90; S. Sarel et al. Eds., Blackwell Scientific Publ., Oxford 1992, pp 299-306).

(f) $B(SeMe)_3$, TFA, CH_2Cl_2, (WO 89/10351; M.J. Calverley, Tetr. Lett. *1987*, **28**, 1337)

In Scheme 3 the synthesis of compounds I from the key intermediates II (a-e) is outlined in a general manner. More detailed descriptions for the synthesis of the preferred compounds I, listed in Table 1, are given in the "Methods of synthesis 1-7", and in further detail in the Preparations (Table 3) and Examples (Table 4).

Scheme 3



Compounds II are first reacted with side chain building blocks Fg-Z-W, to give the intermediates J-Q_p-Z-W. Fg is a reactive functional group, the kind of which is indicated in the Methods of synthesis 1-7; Z is a linking group, which together with Q_p forms a side chain moiety which may either be identical to Q in compound I, or alternatively may be a moiety which can be converted to Q at any subsequent stage in the synthesis; Q_p is a part of Q which may either be identical to Qa, or to Qa,Qb, or to Qa,Qb,Qc, depending on the particular method of synthesis, or Q_p may similarly be converted to Qa, or to Qa,Qb, or to Qa,Qb,Qc later during the synthesis; W is either identical to the group CX(R^1)(R^2) in compound I, or may be similarly converted thereto later during the synthesis.

The remaining steps in the synthesis involve the below mentioned operations 1-4, in the following called "rest of sequence", abbreviated "r.o.s."; these operations may be performed in any desired order, according to the synthetic demands of each particular Compound I to be prepared:

1 Optional conversion of the group Q_p-Z to Q;

2 Optional conversion of the group W to $C(R^1)(R^2)(X)$.

3 Optional conversion of the group N_E / N_{CD} to the group N_Z by:

a Triplet-sensitised photoisomerisation of the vitamin D triene (5*E* to 5Z); or

b Desilylation, oxidation to the ketone and Horner coupling with the A-ring building block **5** of Scheme 3 (see e.g. WO 94/14766);

4 Conversion of the group N_Z to the group M by removal of the vitamin D nucleus silyl protective groups.

Table 1 Preferred Compounds I

Qa	Qb	Qc	Qd	Qe	Qf	R1/R2	X	Method
CH2	CH2	CH2				Me	H	1
CH2	CH2	CH2				Me	OH	1
CH	CH	CH2				Et	OH	5
CH2	O	CH2				Et	OH	7
CH(OH)	CH2	CH2				Me	OH	2
CH(OH)	CH	CH				Me	OH	3
CH	CH	CH(OH)				(CH2)2	H	5
CH(OH)	C	C				Et	OH	4
CH(OC2H5)	CH2	CH2				Et	OH	2
CH(OC2H5)	CH	CH				Me	OH	3
CH(OC2H5)	C	C				Et	OH	4
C(=O)	CH2	CH2				Me	OH	2
C(=O)	CH	CH				Me	OH	3
C(=O)	C	C				Et	OH	4
CH2	CH2	CH2	CH2			Et	OH	1
CH	CH	CH2	CH2			Me	OH	5
CH	CH	CH	CH			Et	OH	6
CH	CH	C	C			Et	OH	5
CH2	O	CH2	CH2			Et	OH	7
CHOH	CH2	CH2	CH2			H	H	2
CH(OH)	CH2	CH2	CH2			Et	OH	2
CH(OH)	CH	CH	CH2			Et	OH	3
CH(OH)	C	C	CH2			Et	OH	4
CH(OC2H5)	CH2	CH2	CH2			Et	OH	2
CH(OC2H5)	CH	CH	CH2			Et	OH	3
CH(OC2H5)	C	C	CH2			Et	OH	4
CH(OC2H5)	C	C	CH2			Et	OTHP	4
C(=O)	CH2	CH2	CH2			Et	OH	2
C(=O)	CH	CH	CH2			Et	OH	3
C(=O)	C	C	CH2			Et	OH	4
CH2	CH2	CH2	CH2	CH2		Me	OH	1
CH	CH	CH2	CH2	CH2		Me	OH	5
CH	CH	CH	CH	CH2		Me	OH	6
CH2	O	CH2	CH2	CH2		Me	OH	7
CH2	O	CH2	CH2	CH2		Et	OH	7
CH	CH	CH2	O	CH2		Me	OH	5
CH(OH)	CH2	CH2	CH2	CH2		Me	OH	2
CH(OH)	CH	CH	CH2	CH2		Me	OH	3
CH(OH)	C	C	CH2	CH2		Me	OH	4
CH(C2H5)	O	CH2	CH2	CH2		Et	OH	7
CH(OC2H5)	CH2	CH2	CH2	CH2		Me	OH	2
CH(OC2H5)	CH	CH	CH2	CH2		Me	OH	3
CH(OC2H5)	C	C	CH2	CH2		Me	OH	4
C(=O)	CH2	CH2	CH2	CH2		Me	OH	2
C(=O)	CH	CH	CH2	CH2		Me	OH	3
C(=O)	C	C	CH2	CH2		Me	OH	4
CH2	O	m-C6H4				Me	OH	7
CH2	O	CH2	m-C6H4			Me	OH	7
CH2	CH2	CH2	CH2	CH2	CH2	Me	OH	1

Note to Table 1

The compounds may have either 17(20)*E* or 17(20)*Z*-configuration, both configurations are included. For compounds with a 22-OH or 22-OR^3 substituent, both 22*R* and 22*S* configurations are included. For compounds with double bonds at C-22, C-23 or C-24, both the *E* and *Z* configurations are included.

Methods of synthesis: 1-7

The methods described in the following are based on procedures described for the preparation of vitamin D analogues having a 17β,20-single bond with either "20-normal" or "20-epi" configuration instead of the 17,20-double bond of the compounds of the present invention.

Reference is given to this prior art, in which experimental details can be found.

The following definitions are used:

R^3 = C_1-C_5 alkyl; Y = Halogen. Other symbols and abbreviations have the above meanings.

Abstracts of the paper and posters, presented at the Tenth Workshop on Vitamin D, Strasbourg, France - May 24 -29, 1997, which are mentioned in this application, are published:

a) Bretting, C. et al., pp. 77-78;

b) Calverley, M. et al., pp. 30 - 31;

c) Hansen, K. et al., pp. 87 -88;

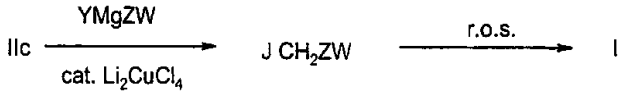
d) von Daehne, W. et al., pp. 81 -82

in *Vitamin D*: Chemistry, Biology and Clinical Applications of the Steroid Hormone (Editors Norman, A. W.; Bouillon, R.; Thomasset, M.), University of California, Riverside, **1997**.

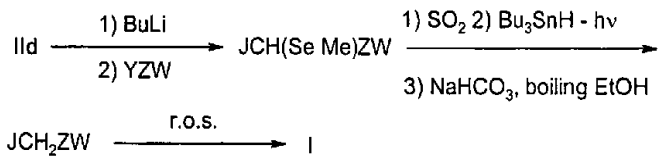
Method 1

I = D-$(CH_2)_{3-6}CR^1R^2X$

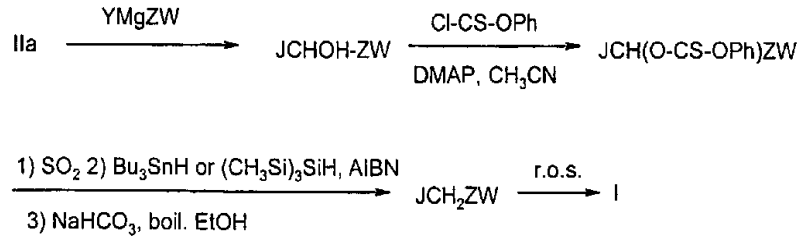
1.1 WO 91/00271



1.2 WO 89/10351



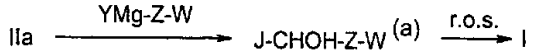
1.3 WO 91/00271; WO 97/46522; M. Robins et al., JACS *1983*, **105**, 4059; D. Schummer et al., Synlett *1990*,705



Method 2

I = D-C^{22}(H,OH / H,OR^3 / O)-$(CH_2)_{2-5}$-CR^1R^2-X

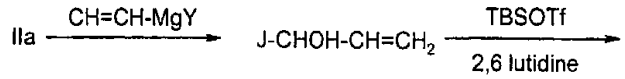
WO 91/00271; WO 97/46522; C. Bretting et al., poster at X vit. D workshop, Strasbourg,1997

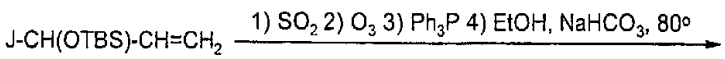


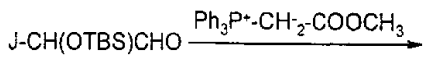
Method 3

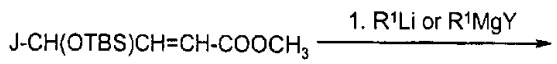
I = D-C^{22}(H,OH / H,OR^3 / O)-CH=CH-$(CH_2)_{0-2}$-CR^{1}R^2-X

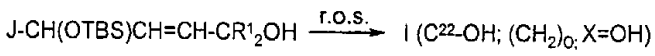
3.1.1 WO 98/18759





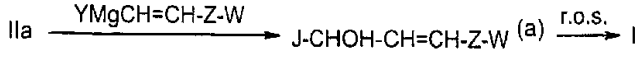




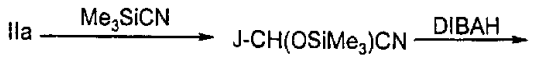


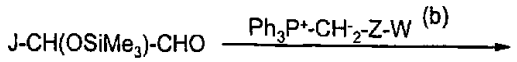
3.1.2. As 3.1.1., but instead of silylation of C^{22}OH in step 2, this group is alkylated to C^{22}OR^3 or oxidized to C^{22}O as described in note (a) to give finally I (C^{22}-OR^3 or C^{22}O; $(CH_2)_0$; X=OH)

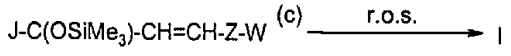
3.2.



3.3

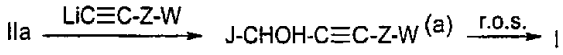






Method 4 I = D-C^{22}(H,OH / H,OR^3 / O)C≡C-(CH$_2$)$_{0-2}$-CR^{1}R^2-X

WO 93/19044



Method 5 I = D-C^{22}H=CH-Z-CR^{1}R^2-X

5.1.1 WO 87/00834

IIa $\xrightarrow{Ph_3P^+\text{-}CH^-\text{-}CO\text{-}C(CH_2)_2}$ (b) J-CH=CH-CO-CH$(CH_2)_2$

$\xrightarrow[CeCl_3]{NaBH_4}$ J-CH=CH-CHOH-CH$(CH_2)_2$

$\xrightarrow{r.o.s.}$ I = D-CH=CH-CHOH-CH$(CH_2)_2$

5.1.2 (e.g. WO 95/02577)

IIa $\xrightarrow{Ph_3P^+\text{-}CH^-\text{-}Z\text{-}W}$ (b) J-CH=CH-Z-W $\xrightarrow{r.o.s.}$ I

5.2 WO 91/00271

IIa $\xrightarrow[2)\ PhCOCl,\ 3)\ Na/Hg]{1)\ Ph\text{-}SO_2\text{-}CH_2\text{-}Z\text{-}W,\ LDA}$ J-CH=CH-Z-W $\xrightarrow{r.o.s.}$ I

5.3 M.J. Calverley, in:Trends in Medicinal Chemistry '90; S. Sarel et al. Eds.; Blackwell Scientific Publ., Oxford 1992, p. 299-306.

IIe $\xrightarrow[3)\ PhCOCl,\ 4)\ Na/Hg]{1)\ LDA,\ 2)\ OHC\text{-}Z\text{-}W}$ J-CH=CH-Z-W $\xrightarrow{r.o.s.}$ I

5.4

IIa $\xrightarrow{YMgCH_2ZW}$ J-CHOH-CH$_2$Z-W $\xrightarrow{Dehydration}$ (d)

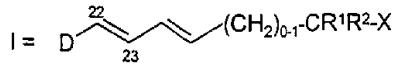
J-CH=CH-Z-W $\xrightarrow{r.o.s.}$ I

5.5 WO 94/10139

IIa $\xrightarrow[2)\ DIBAH]{1)\ Ph_3P^+\text{-}CH_2\text{-}COOMe}$ J-CH=CH-CH$_2$-OH $\xrightarrow[2)\ R^1MgY]{1)\ BrCH_2COO\text{-}Bu^t,\ KOH,\ TBAHSO_4}$

J-CH=CH-CH$_2$-O-CH$_2$-CR$^1{}_2$-OH $\xrightarrow{r.o.s.}$ I = D-CH=CH-CH$_2$-O-CH$_2$-CR$^1{}_2$-OH

Method 6



6.1.1 WO 91/00855

IIa $\xrightarrow{Ph_3P^+\text{-}CH\text{-}CH\text{=}CH\text{-}COOMe}$ J-CH=CH-CH=CH-COOMe $\xrightarrow{R^1Li}$

J-CH=CH-CH=CH-CR^1_2-OH $\xrightarrow{r.o.s.}$ I = D-CH=CH-CH=CH-CR^1_2-OH

6.1.2 WO 91/00855

IIa $\xrightarrow[2)\ DIBAH,\ 3)\ PDC]{1)\ Ph_3P^+\text{-}CH_2^-\text{-}COOMe}$ J-CH=CH-CHO $\xrightarrow[2)\ PhCOCl\ 3)\ Na/Hg]{1)\ PhSO_2\text{-}CH_2CH_2\text{-}CR^1R^2\text{-}X,\ LDA}$

J-CH=CH-CH=CH-CH_2-CR^1R^2-X $\xrightarrow{r.o.s.}$ I = D-CH=CH-CH=CH-CH_2-CR^1R^2-X

6.2 A. Fürstner, Synth. *1989*, 571; Y. Shen et al.,Tetr. Lett. *1988*, **29**, 6119

IIa $\xrightarrow{BrZnCH_2\text{-}CH\text{=}CH\text{-}COOEt,\ Bu_3P}$ (e) J-CH=CH-CH=CH-COOEt

$\xrightarrow{R^1Li}$ J-CH=CH-CH=CH-CR^1_2-OH $\xrightarrow{r.o.s.}$ I = D-CH=CH-CH=CH-CR^1_2-OH

Method 7

I = D-CH(H/R^3)-O-Z-CR^1R^2-X

7.1 WO 91/15475

IIc + OH-Z-W $\xrightarrow[\text{e.g. NaH/DMF}]{\text{base}}$ J-CH_2-O-Z-W $\xrightarrow{\text{r.o.s.}}$ I

7.2

IIb + Lg-Z-W $\xrightarrow[\text{e.g. KOH, KOBu}^t\text{ or KH in e.g. THF (18C6)}]{\text{base}}$ J-CH_2-O-Z-W $\xrightarrow{\text{r.o.s.}}$ I

7.2.1 G. Neef et al., Tetr.Lett. 1991, 32, 5073; M. Calverley, paper at X vit. D workshop,Strasbourg 1997

IIb $\xrightarrow[\text{2) } R^1MgY]{\text{1) } BrCH_2COO\text{-Bu}^t, KOH, TBAHSO_4, H_2O, Tol}$

J-CH_2-O-CH_2-$CR^1{}_2$-OH $\xrightarrow{\text{r.o.s.}}$ I = D-CH_2-O-CH_2-$CR^1{}_2$-OH

7.2.2 N. Kubodera et al., Chem.Pharm.Bull. *1992*, **40**, 1494

IIb $\xrightarrow[NaOH, TBAOH, H_2O, Tol]{CH_2=CH_2\text{-COOEt}}$ J-CH_2-O-CH_2-CH_2-COOEt

$\xrightarrow{R^1Li/R^1MgY}$ J-CH_2-O-$(CH_2)_2$-$CR^1{}_2$-OH $\xrightarrow{\text{r.o.s.}}$

I = D-CH_2-O-$(CH_2)_2$-$CR^1{}_2$-OH

7.3 K. Hansen et al., poster at X vit. D workshop, Strasbourg, 1997

IIa $\xrightarrow{R^3Li \text{ or } R^3MgY}$ J-CHR^3-OH $\xrightarrow{\text{Method 7.2, 7.2.1 or 7.2.2}}$

J-CHR^3-O-Z-W $\xrightarrow{\text{r.o.s.}}$ I = D-CHR^3-O-Z-CR^1R^2-X

Notes to Methods of Synthesis: 1-7

(a) Optional alkylation of C^{22}-OH to C^{22}-OR^3 e.g. with R^3Y+KH+18C6 as in WO 93/19044 or WO 97/46522 or oxidation of C^{22}-OH to C^{22}=O, e.g. with PCC or DMR, as in WO 97/20811.

(b) Optionally other Wittig-type reagents such as $(EtO)_2PO$-CH_2-Z-W + base or Ph_2PO-CH_2-Z-W + base may be used.

(c) Optional desilylation of C^{22}-$OSiMe_3$ to C^{22}-OH followed by alkylation or oxidation as described in note (a).

(d) Standard methods of dehydration, such as acid catalysed dehydration, or treatment with $POCl_3$/pyridine, or treatment with "Martin sulfurane dehydrating agent" may be used.

(e) Alternatively the tributylphosphine may be excluded, resulting in a 22-ol. This may be dehydrated to the 22,23-ene in a separate step, by standard methods, see e.g. M.W. Rathke, Org. React. *1975* **22**, 432.

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 atomisers.

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 kilogram bodyweight, preferably from 0.002-0.3 µg/kg of mammal bodyweight, for example 0.003-0.2 µg/kg of a compound of formula I are administered, typically corresponding to a daily dose for an adult human of from 0.2 to 15 µg. In the topical treatment of dermatological disorders, ointments, creams or lotions containing from 0.1-500 µg/g, and preferably from 0.1-100 µg/g, of a compound of formula I are administered. For topical use in ophthalmology ointments, drops or gels containing from 0.1-500 µg/g, and preferably from 0.1-100 µg/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, of a compound of formula I, per dosage unit.

The invention is further illustrated by the following non-limiting General Procedures, Preparations and Examples:

General Procedures, Preparations and Examples

The exemplified compounds I are listed in Table 4, the intermediates of general formula II are listed in Table 2, and other intermediates are listed in Table 3.

General:

THF was dried over sodium/benzophenone. Reactions were routinely run under an argon atmosphere unless otherwise noted.

In the standard work-up procedure, the organic layer was separated, washed

with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give the product, which was purified by chromatography or crystallisation.

For ^{1}H nuclear magnetic resonance spectra (300 MHz) and ^{13}C NMR (75.6 MHz) chemical shift values (δ) (in ppm) are quoted, for deuteriochloroform solutions relative to internal tetramethylsilane (δ = 0.00) or chloroform (δ = 7.25) or deuteriochloroform (δ = 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).

Table 2. Some compounds of type II

Formula	N	Config. at 17,20	Comp. Type	Comp. No.	Prep. No.
J-CHO	N_E	Z	IIa	201	1,2
J-CHO	N_E	E	IIa	202	1,2,4
J-CH_2OH	N_E	Z	IIb	203	5
J-CH_2OH	N_E	E	IIb	204	6
J-$CH_2OOCC(CH_3)_3$	N_E	Z	IIc	205	10
J-$CH_2OOCC(CH_3)_3$	N_E	E	IIc	206	18
J-CN	N_E	E	IIf	211	3
J-CN	N_E	Z	IIf	212	3
J-CHO	N_Z	Z	IIa	207	31
J-CH_2Cl	N_E	Z	IIc	208	34

J: See Scheme 2

N (N_E / N_Z): See Scheme 1

Table 3. Some intermediate products

Formula	N	Config. at 17(20)	Config. at C22 (A or B)	Comp. No.	Prep. No.
J-CHOH-C_4H_9	N_E	Z	A	301	7
J-CHOH-C_4H_9	N_E	Z	B	302	7
J-CHOH-C_4H_9	N_Z	Z	A	401	8
J-CHOH-C_4H_9	N_Z	Z	B	402	9
J-$(CH_2)_3CH(CH_3)_2$	N_E	Z		303	11
J-$(CH_2)_3CH(CH_3)_2$	N_Z	Z		403	12
J-CHOH-C≡C-CH_2-$C(C_2H_5)_2$OTHP	N_E	Z	A	304	13
J-CHOH-C≡C-CH_2-$C(C_2H_5)_2$OTHP	N_E	Z	B	305	13
J-CHOH-C≡C-CH_2-$C(C_2H_5)_2$OTHP	N_Z	Z	A	404	14
J-CHOH-C≡C-CH_2-$C(C_2H_5)_2$OTHP	N_Z	Z	B	405	15
J-CHOC_2H_5-C≡C-$CH_2C(C_2H_5)_2$OTHP	N_Z	Z	A	406	16
J-CHOC_2H_5-C≡C-$CH_2C(C_2H_5)_2$OTHP	N_Z	Z	B	407	17
J-$(CH_2)_3C(CH_3)_2$-OTMS	N_E	Z		308	19
J-$(CH_2)_3C(CH_3)_2$-OTMS	N_E	E		309	20
J-$(CH_2)_3C(CH_3)_2$OH	N_E	Z		408	21
J-$(CH_2)_3C(CH_3)_2$OH	N_E	E		409	22

Table 3, continued

Formula	N	Config. at 17(20)	Config. at C22 (A or B)	Comp. No.	Prep. No.
J-$(CH_2)_3C(CH_3)_2OH$	N_Z	Z		508	23
J-$(CH_2)_3C(CH_3)_2OH$	N_Z	E		509	24
$HC\equiv C-CH_2-C(C_2H_5)_2-OSiMe_3$					25
J-CHOH-$C\equiv C-CH_2-C(C_2H_5)_2-OSiMe_3$	N_E	Z	A	310	26
J-CHOH-$C\equiv C-CH_2-C(C_2H_5)_2-OSiMe_3$	N_E	Z	B	311	26
J-CHOH-$C\equiv C-CH_2-C(C_2H_5)_2-OSiMe_3$	N_Z	Z	A	410	27
J-CHOH-$C\equiv C-CH_2-C(C_2H_5)_2-OSiMe_3$	N_Z	Z	B	411	28
J-CHOEt-$C\equiv C-CH_2-C(C_2H_5)_2-OSiMe_3$	N_Z	Z	A	510	29
J-CHOEt-$C\equiv C-CH_2-C(C_2H_5)_2-OSiMe_3$	N_Z	Z	B	511	30
$JC^{22}H=CHC^{24}H=CH-COOEt$, 22E,24E	N_Z	Z		312	32
$JC^{22}H=CHC^{24}H=CH-CEt_2-OH$, 22E,24E	N_Z	Z		412	33
J-CH_2O-(m)-$C_6H_4-C(CH_3)_2-OH$	N_E	Z		313	35
J-CH_2O-(m)-$C_6H_4-C(CH_3)_2-OH$	N_Z	Z		413	36

Formula	N	Config. at 17(20)	Config. at C22 (A or B)	Comp. No.	Prep. No.
J- CH_2-O-$(CH_2)_3$-$C(C_2H_5)_2$-$OSiMe_3$	N_E	Z		314	37
J- CH_2-O-$(CH_2)_3$-$C(C_2H_5)_2$-$OSiMe_3$	N_Z	Z		414	38
J-CH_2OH-$(CH_2)_3$-$C(C_2H_5)_2$-$OSiMe_3$	N_E	Z	A	315	39
J-CH_2OH-$(CH_2)_3$-$C(C_2H_5)_2$-$OSiMe_3$	N_E	Z	B	316	39
J-CH_2OH-$(CH_2)_3$-$C(C_2H_5)_2$-$OSiMe_3$	N_Z	Z	A	415	40
J-CH_2OH-$(CH_2)_3$-$C(C_2H_5)_2$-$OSiMe_3$	N_Z	Z	B	416	41
J-CH^{22}=CH^{23}-CO-$C(CH_2)_2$, 22E	N_Z	Z		317	42
J-CH^{22}=CH^{23}CHOH-$C(CH_2)_2$, 22E	N_Z	Z		417	43

J: See Scheme 2

N (N_E / N_Z): See Scheme 1

Configuration at C22: Isomer A is, or is derived from, the less polar A isomer at the N_E -intermediate stage; isomer B is, or is derived from, the corresponding more polar B isomer at the N_E -intermediate stage.

Table 4. Exemplified Compounds I

Formula	Config. at C22	Comp. No.	Exam. No.	General Method of Synthesis
D_Z-CHOH-C_4H_9	A	101	1	2
D_Z-CHOH-C_4H_9	B	102	2	2
D_Z-$(CH_2)_3CH(CH_3)_2$		103	3	1
D_Z-CHOH-C≡C-CH_2-$C(C_2H_5)_2OH$	A	104	4	4
D_Z-CHOH-C≡C-CH_2-$C(C_2H_5)_2OH$	B	105	5	4
D_Z-$CHOC_2H_5$-C≡C-CH_2-$C(C_2H_5)_2$OTHP	A	106	6	4
D_Z-$CHOC_2H_5$-C≡C-CH_2-$C(C_2H_5)_2$OTHP	B	107	7	4
D_Z-$(CH_2)_3C(CH_3)_2OH$		108	8	1
D_E-$(CH_2)_3C(CH_3)_2OH$		109	9	1
D_Z-$CHOC_2H_5$-C≡C-CH_2-$C(C_2H_5)_2OH$	A	110	10	4
D_Z-$CHOC_2H_5$-C≡C-CH_2-$C(C_2H_5)_2OH$	B	111	11	4
D_Z-$C^{22}H$=$CHC^{24}H$=CH-$C(C_2H_5)_2OH$, 22E,24E		112	12	6
D_Z-CH_2-O-(m)C_6H_4-$C(CH_3)_2OH$		113	13	7
D_Z-CH_2-O-$(CH_2)_3$-$C(C_2H_5)_2OH$		114	14	7
D_Z-CH_2OH-$(CH_2)_3$-$C(C_2H_5)_2OH$	A	115	15	2
D_Z-CH_2OH-$(CH_2)_3$-$C(C_2H_5)_2OH$	B	116	16	2
D_Z- CH^{22}=CH^{23}CHOH-$C(CH_2)_2$, 22E		117	17	5

D (D_Z / D_E): See Scheme 3

Configuration at C22: Isomer A is the 22 isomer of compound I derived from the less polar A isomer at the N_E -intermediate stage; isomer B is the 22 isomer of compound I derived from the corresponding more polar B isomer at the N_E -intermediate stage, (cf. Table 3).

General Procedure 1 Photoisomerisation

A solution of the appropriate compound ($N=N_E$) (0.28 mmol), anthracene (0.1 g) and triethylamine (0.20 ml, 1.4 mmol) in dichloromethane (16 ml) in a 25 ml round-bottomed Pyrex flask was irradiated at ca. 10°C with UV-light from a high pressure ultraviolet lamp, type TQ760Z2 (Hanau), at 700 W, for 30 minutes (15 minutes at 0.08 mmol scale) while stirring. The reaction mixture was evaporated *in vacuo*, and the residue was treated with petroleum ether (2 x 2 ml) and filtered. The filtrate was concentrated and purified by chromatography to afford the compound where $N=N_Z$.

Variation: General Procedure 1a

The procedure of General Procedure 1 was followed, except that 9-acetylanthracene was used instead of anthracene, and 45 minutes with a TQ150Z2 lamp (Hanau) was used, instead of the lamp and time in General Procedure 1.

Variation: General Procedure 1b

The procedure of General Procedure 1 was followed, except that 9-acetylanthracene (25 mg) was used instead of anthracene, toluene (20 ml) was used instead of dichloromethane, and the lamp was used at 500 W for 10 minutes (5 minutes at 0.05 mmol scale) instead of 700 W for 30 minutes.

General Procedure 2 Deprotection with HF

To a stirred solution of the appropriate silyl-protected compound (0.25 mmol) in ethyl acetate (1.5 ml) was added acetonitrile (6 ml) followed by a 5% solution of hydrofluoric acid in acetonitrile-H_2O 7:1 (2.0 ml). After stirring for a further 45-60 minutes, 1 M potassium hydrogen carbonate (10 ml) was added, and the reaction mixture was worked up (ethyl acetate). The residue was purified by chromatography (eluant: 30% pentane in ethyl acetate) to give the desired compound I.

General Procedure 3 Deprotection with TBAF

To a solution of the appropriate silyl-protected compound (0.18 mmol) in THF (4.5 ml) was added TBAF trihydrate (0.29 g, 0.9 mmol), and the mixture was

heated to reflux for one hour with stirring. After addition of 0.2 M sodium hydrogen carbonate (5 ml), the mixture was worked up (ethyl acetate). The residue was purified by chromatography (eluant: 30% pentane in ethyl acetate) to yield the desired compound I.

General Procedure 4
(C.f. Method 4)

Reaction of a Compound IIa with an acetylenic side chain building block

To a solution of the appropriate acetylenic side chain building block (3.0 mmol) in dry THF (5 ml), cooled to -78°C and stirred under argon, was added dropwise, during 2 minutes, a solution of n-butyllithium (1.6 M in hexane; 1.5 ml). Stirring was continued at -78°C for 15 minutes and then at 20°C for another 15 minutes. The mixture was again cooled to -78°C, and a solution of the appropriate aldehyde, compound IIa, (1.5 mmol) in dry THF (5 ml) was added dropwise during 4 minutes, and after that, stirring was continued at -78°C for 30 minutes. The reaction mixture was worked up (ether) to yield a crude product containing the isomeric 22-hydroxy compounds A (less polar) and B (more polar). These were separated by chromatography (mixture of ethyl acetate and petroleum ether as eluant) to yield the pure compounds.

General Procedure 5
(C.f. Method 4)

Alkylation of an acetylenic C-22-hydroxy-compound (R^3=H) to the corresponding compound where R^3=C_1-C_5

To a solution of the appropriate 22-hydroxy compound (R^3=H) (0.5 mmol) in dry THF (5 ml) was added, while stirring at 20°C under argon, a 20% suspension of potassium hydride in mineral oil (0.2 ml) followed by an alkylating agent, R^3Y (1.5 mmol). Then, a solution of 18-Crown-6 (0.13 g) in dry THF (2 ml) was added, during 5 minutes. Stirring at 20°C was continued for two hours, after

which the reaction mixture was worked up (ether). The crude product was purified by chromatography (mixture of ether and petroleum ether as eluant) to yield the desired alkoxy compound.

Preparation 1

Compounds 201 and 202

To a solution of 1(S),3(R)-di(tert-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(E),7(E),10(19),16-tetraene (W. von Daehne et al., poster at X vit. D workshop, Strasbourg 1997; WO 98/24762) (**3**; N=N_E, 20*S*-isomer) (2.28 g, 4 mmol) in dichloromethane (20 ml) was added with stirring TBABr (258 mg, 0.8 mmol) followed by 2N aqueous sodium hydroxide (10 ml). After stirring at room temperature for 40 minutes, the mixture was diluted with dichloromethane (20 ml) and water (30 ml). The organic phase was separated and the aqueous layer extracted with dichloromethane (40 ml). The combined organic extracts were washed with water (4 x 25 ml) and brine (25 ml), dried over magnesium sulfate end evaporated *in vacuo* to yield a mixture of compounds 201 (Z-form) and 202 (E-form) in an approximate molar ratio of 95:5. Separation of the two compounds was performed by chromatography on silica gel (eluant: 2.5 to 5% ether in petroleum ether) to give the less polar Z-isomer 201 and the more polar E-isomer 202 , both as colourless crystals (from ether-methanol).

Compound 201

^{1}H NMR δ 0.06 (m,12H), 0.85 (s,9H), 0.90 (s,9H), 0.95 (s,3H), 1.70 (bs,3H), 1.50-2.70 (m,14H), 2.87 (m,1H), 4.23 (m,1H), 4.53 (m,1H), 4.96 (m,1H), 4.99 (m,1H), 5.92 (d,1H), 6.43 (d,1H), 10.2 (s,1H).

M.p. 113-114°C

Anal. Calcd. for $C_{34}H_{58}O_3Si_2$: C 71.52, H 10.24. Found: C 71.51, H 10.19

UV (EtOH, nm): λ_{max} 265 (ε 35900)

IR (KBr) 1665, 1620 cm^{-1}

Compound 202

^{1}H NMR δ 0.06 (m,12H), 0.83 (s,3H), 0.84 (s,9H), 0.89 (s,9H), 1.80 (bs, 3H), 1.50-2.0 (m,8H), 2.23 (dd, 1H), 2.33 (m,2H) 2.57 (dd, 1H), 2.88 (m.2H), 3.09

(dd,1H), 4.22 (m,1H), 4.53 (m,1H), 4.96 (m,1H), 4.99 (m,1H), 5.91 (d,1H), 6.44 (d,1H), 9.99 (s,1H).

M.p. 109-110°C

EIMS calcd. for $C_{34}H_{58}O_3Si_2$ + 570.3925, found 570.39

UV (EtOH, nm): λ_{max} 268 (ε 37500)

IR (KBr) 1670, 1620 cm^{-1}

Preparation 2

Compounds 201 and 202

By substituting 1(S),3(R)-di(tert-butyldimethylsilyloxy)-20(R)-formyl-9-10-secopregna-5(E),7(E),10(19),16-tetraene (W. von Daehne et al., poster at X vit. D workshop, Strasbourg 1997; WO 98/24762) (**3**; N=N_E, 20*R*-isomer) for the corresponding 20*S* isomer in the procedure of Preparation 1, a similar mixture of compounds 201 and 202 (approximate molar ratio 95:5) was obtained.

Preparation 3

Compounds 211 and 212

Potassium cyanide (7.0 g) (toxic) was stirred in an ice cold solution of 1(S),3(R)-di(tert-butyldimethylsilyloxy)-20-oxo-9,10-secopregna-5(E),7(E),10(19)-triene; **1b** (N=N_E) (K. Hansen et al., in: Vitamin D: Gene Regulation, Structure-Function Analysis and Clinical Application; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; de Gruyter, Berlin, 1991, pp 161-162)(3.0 g) in a mixture of ethanol (30 ml) and acetic acid (15 ml) for 30 min. After stirring for 21 h at room temperature the mixture was filtered. Water (45 ml) was added to the filtrate and the precipitate was collected and dried *in vacuo*. The precipitate was dissolved in dry pyridine (5 ml) and phosphorous oxychloride (1.3 g) was added at 0°C. After stirring for 22 h at room temperature the reaction mixture was partitioned between water (150 ml) and ether (150 ml). The organic phase was washed with water (150 ml) and brine (100 ml), dried with magnesium sulfate and evaporated to dryness *in vacuo*. Chromatography on silica gel with methylene chloride/petroleum ether 2:1 gave the separated products, compound

211 (E-form) and compound 212 (Z-form), in the ratio of approximately 3:1.

Compound 211

^{13}C NMR δ 169.7, 153.3, 140.1, 136.5, 121.0, 120.0, 117.6, 106.7, 99.8, 69.9, 67.0, 55.9, 48.8, 43.7, 36.4, 36.2, 32.7, 28.2, 25.6, 25.6, 22.9, 22.5, 18.0, 17.9, 15.8, 15.3, -5.0, -5.1, -5.1

Compound 212

^{13}C NMR δ 170.4, 153.3, 140.6, 136.3, 121.1, 119.2, 117.3, 106.8, 97.2, 70.0, 67.0, 55.5, 48.4, 43.7, 36.5, 35.2, 30.5, 28.4, 25.6, 25.6, 22.9, 22.0, 18.0, 17.9, 17.8, 16.7, -5.0, -5.1, -5.1

Preparation 4

Compound 202

A solution of compound 211 (50 mg) in toluene (2 ml) was cooled to -78°C and a solution of DIBAH (83 µl, 20% in hexane) was added. After stirring at -78°C for 30 min and at room temperature for 27 h the mixture was stirred with saturated aqueous ammonium chloride (4 ml) for 30 min. The mixture was extracted with ethyl acetate (30 ml). The organic phase was washed with water (20 ml) and brine (20 ml), dried with magnesium sulfate and evaporated to dryness *in vacuo*. Chromatography on silica gel with ether/petroleum ether 1:10 gave the title compound.

^{13}C NMR δ 193.4, 171.9, 153.3, 140.6, 136.3, 127.9, 121.1, 117.5, 106.7, 70.0, 67.0, 54.6, 49.8, 43.7, 36.5, 36.4, 28.3, 28.2, 25.7, 25.6, 23.0, 18.0, 17.9, 15.4, 10.0, -5.0, -5.1, -5.1.

Preparation 5

Compound 203

To a stirred solution of compound 201 (366 mg, 0.64 mmol) in THF (3 ml) was subsequently added at 0°C 0.4 M methanolic cerium (III) chloride heptahydrate (1.6 ml), methanol (3 ml) and sodium borohydride (60.8 mg, 1.6 mmol). After stirring at 0°C for 40 minutes, the reaction mixture was diluted with ethyl acetate (40 ml) and water (15 ml) was added. The organic phase was separated, washed with water (10 ml) and brine (10 ml), dried over magnesium sulfate and

evaporated *in vacuo*. The residual oil was purified by chromatography on silica gel (eluant: 5% ethyl acetate in petroleum ether) to give the title compound as a colourless oil.

^{1}H NMR δ 0.05 (m,12H), 0.75 (s,3H), 0.85 (s,9H), 0.89 (s,9H), 1.69 (bs, 3H), 2.46-0.60 (m,14H), 2.56 (dd,1H), 2.84 (dd,1H), 3.95 (d,1H), 4.22 (m,1H), 4.34 (d,1H), 4.53 (m,1H), 4.94 (m,1H), 4.98 (m,1H), 5.87 (d,1H), 6.44 (d,1H).

Preparation 6

Compound 204

By substituting compound 202 for the compound 201 in the procedure of Preparation 5, the isomeric compound 204 was obtained.

^{1}H NMR δ 6.44(d,1H), 5.86(d,1H), 4.98(m,1H), 4.94(m,1H), 4.53(m,1H), 4.22(m,1H), 4.04(s,2H), 2.84(m,1H), 2.56(dd,1H), 2.60-0.60(m,14H), 1.79(bs,3H), 0.89(s,9H), 0.85(s,9H), 0.75(s,3H), 0.05(m,12H)

Preparation 7

Compounds 301 and 302

A stirred solution of compound 201 (17.1 mg, 0.03 mmol) in dry THF (2 ml) was cooled to -78°C and 1.6 M butyl lithium in hexane (0.04 mmol) was added via a syringe. After stirring at -78°C for a further 20 minutes, the reaction was quenched with a few drops of water and warmed to room temperature. The reaction mixture was diluted with ether (20 ml), washed with water (4 x 5 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a mixture of the compounds 301 (less polar, isomer A) and 302 (more polar, isomer B) in an approximate molar ratio of 1:2. The two isomers could be separated by chromatography on silica gel (eluant: 10% ether in petroleum ether).

Compound 301

^{1}H NMR δ 0.05 (m,12H), 0.80 (s,3H), 0.85 (s,9H), 0.89 (s,9H), 1.55 (bs,3H), 2.45-0.62 (m,23H), 2.57 (m,1H), 2.85 (m,1H), 4.22 (m,1H), 4.53 (m,1H), 4.70 (m,1H), 4.94 (m,1H), 4.98 (m,1H), 5.87 (d,1H), 6.44 (d,1H).

Compound 302

^{1}H NMR δ 0.05 (m,12H), 0.73 (s,3H), 0.85 (s,9H), 0.89 (s,9H), 1.55 (bs,3H),

2.45-0.62 (m,23H), 2.57 (m,1H), 2.85 (m,1H), 4.22 (m,1H), 4.53 (m,1H), 4.70 (m,1H), 4.94 (m,1H), 4.98 (m,1H), 5.87 (d,1H), 6.44 (d,1H).

Preparation 8

Compound 401

Method: General Procedure 1

Starting material: Compound 301

Preparation 9

Compound 402

Method: General Procedure 1

Starting material: Compound 302

Preparation 10

Compound 205

To a solution, maintained at about 5°C, of pyridine (0.2 ml), DMAP (15 mg) and compound 203 (0.070 g, 0.12 mmol) in dry dichloromethane (2 ml) was added in one portion pivaloyl chloride (0.060 g, 0.5 mmol). After stirring at the same temperature for 1 h, the reaction mixture was quenched with water and partitioned between ether and 5% sodium hydrogen carbonate solution. The organic layer was separated, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give an oil. Purification by chromatography on silica gel (15 g) (eluant: 5% ether in petroleum ether) gave the title compound as a foam.

^{13}C NMR δ 178.6, 153.4, 150.4, 142.0, 135.7, 121.4, 120.3, 116.8, 106.5, 70.0, 67.0, 64.8, 56.3, 47.3, 43.8, 38.6, 38.0, 36.4, 30.1, 28.4, 27.0, 25.7, 25.6, 23.4, 22.7, 18.1, 18.1, 18.0, 17.9, -5.0, -5.1, -5.1

Preparation 11

Compound 303

To a solution, maintained at about 5°C, of the Grignard reagent prepared from magnesium (1.1 atomic equivalents) and the side chain building block 3-methyl-

1-bromobutane (0.300 g, 2 mmol) in dry THF (3 ml) was added via a syringe lithium tetrachlorocuprate (1 ml of a 0.1 M solution in dry THF) followed by compound 205 (0.055 g, 0.083 mmol) in dry THF (2 ml). After stirring at the same temperature for 16 h, the reaction mixture was quenched with water and partitioned between ether and saturated ammonium chloride solution. The organic layer was separated, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give an oil. Purification by chromatography on silica gel (15 g) (eluant: 2% ether in petroleum ether) gave the title compound as an oil.

^{13}C NMR δ 153.5, 142.8, 142.8, 135.3, 126.0, 121.5, 116.4, 106.4, 70.1, 67.1, 56.7, 46.9, 43.8, 39.3, 38.3, 36.4, 34.2, 29.9, 28.6, 27.8, 26.8, 25.7, 25.6, 23.6, 22.9, 22.5, 22.4, 19.8, 18.1, 17.9, 17.7, -4.9, -5.1

Preparation 12

Compound 403

Method: General Procedure 1a

Starting material: Compound 303

Chromatography eluant: 2% ether in petroleum ether.

Preparation 13

Compounds 304 and 305

Method: General Procedure 4

Starting material: Compound 201

Acetylenic side chain building block: 3-Ethyl-3-(tetrahydro-4H-pyran-2-yl-oxy)-5-hexyne (WO 93/19044)

Chromatography eluant: 0% to 10% ethyl acetate in petroleum ether.

Compound 304 (isomer 22A)

^{1}H NMR δ 6.42(d,1H), 5.86(d,1H), 5.44(m,1H), 4.98(m,1H), 4.94(m,1H), 4.81(m,1H), 4.53(m,1H), 4.21(m,1H), 3.96(m,1H), 3.44(m,1H), 2.83(m,1H), 2.56(dd,1H), 2.46(m,2H), 1.70(bs,3H), 2.42-1.37(m,24H), 0.89(s,9H), 0.84(s,9H), 0.93-0.80(t,6H), 0.80(s,3H), 0.05(m,12H)

Compound 305 (isomer 22B)

^{1}H NMR δ 6.42(d,1H), 5.86(d,1H), 5.49(m,1H), 4.98(m,1H), 4.94(m,1H), 4.80(m,1H), 4.52(m,1H), 4.21(m,1H), 3.95(m,1H), 3.43(m,1H), 2.83(m,1H), 2.56(dd,1H), 2.46(m,2H), 1.72(bs,3H), 2.41-1.36(m,24H), 0.89(s,9H), 0.84(m,9H), 0.93-0.80(t,6H), 0.75(s,3H), 0.05(m,12H)

Preparation 14

Compound 404

Method: General Procedure 1

Starting material: Compound 304

Chromatography eluant: 0% to 5% ethyl acetate in petroleum ether.

^{13}C NMR δ 148.1, 147.4, 139.5, 135.4, 125.1, 122.7, 118.3, 111.1, 93.0, 82.4, 81.8, 79.9, 71.9, 67.3, 62.8, 61.8, 56.3, 46.9, 45.9, 44.6, 38.8, 32.0, 30.3, 28.4, 28.3, 26.8, 25.7, 25.6, 25.3, 23.4, 22.7, 20.1, 18.0, 17.9, 13.8, 7.7, 7.6, -4.9, -5.0, -5.3

Preparation 15

Compound 405

Method: General Procedure 1

Starting material: Compound 305

Chromatography eluant: 0% to 5% ethyl acetate in petroleum ether.

^{13}C NMR δ 148.6, 148.1, 139.5, 135.4, 124.8, 122.8, 118.4, 111.1, 93.0, 82.4, 81.6, 79.8, 72.0, 67.3, 62.8, 61.3, 56.3, 47.0, 45.9, 44.6, 38.3, 32.0, 30.4, 28.4, 28.3, 26.7, 25.7, 25.6, 25.3, 23.3, 22.7, 20.1, 18.3, 18.0, 17.9, 14.5, 7.7, 7.6, -4.9, -5.0, -5.3

Preparation 16

Compound 406

Method: General Procedure 5

Starting material: Compound 404

Alkylating agent: Ethyl bromide

Chromatography eluant: 0% to 2.5% ethyl acetate in petroleum ether.

^{13}C NMR δ 148.1, 147.6, 139.6, 135.4, 124.4, 122.8, 118.4, 111.2, 93.1, 93.0, 82.3, 80.3, 80.0, 72.0, 68.6, 67.3, 63.0, 62.9, 56.4, 46.9, 45.9, 44.6, 38.9, 32.1, 30.2, 28.5, 28.4, 28.3, 26.8, 25.7, 25.6, 25.4, 23.4, 22.7, 20.2, 20.2, 18.0, 17.9, 17.7, 15.1, 14.1, 7.7, 7.6, -4.8, -4.9, -5.0, -5.3

Preparation 17

Compound 407

Method: General Procedure 5

Starting material: Compound 405

Alkylating agent: Ethyl bromide

Chromatography eluant: 0% to 2.5% ethyl acetate in petroleum ether.

^{13}C NMR δ 148.5, 148.1, 139.7, 135.3, 123.9, 122.8, 118.3, 111.2, 93.0, 82.5, 80.2, 79.9, 72.0, 67.9, 67.3, 62.9, 62.8, 56.3, 47.0, 45.9, 44.6, 38.0, 32.0, 30.4, 28.5, 28.4, 26.7, 25.7, 25.6, 25.3, 23.4, 22.7, 20.1, 18.3, 18.0, 17.9, 17.7, 15.2, 14.9, 7.7, 7.6, -4.9, -5.0, -5.3

Preparation 18

Compound 206

By substituting compound 204 for compound 203 in the procedure of preparation 10, the isomeric compound 206 was obtained as a foam.

^{13}C NMR δ 178.5, 153.4, 148.5, 142.1, 135.6, 121.4, 120.2, 116.7, 106.5, 70.0, 67.2, 67.0, 55.9, 47.4, 43.8, 38.7, 37.4, 36.4, 28.7, 28.5, 27.1, 25.7, 25.6, 23.4, 22.9, 18.1, 17.9, 16.4, 15.3, -4.9, -5.0, -5.1, -5.1

Preparation 19

Compound 308

By substituting 1-bromo-3-methyl-3-trimethyl-silyloxybutane for 3-methyl-1-bromobutane in the procedure of preparation 11, compound 308 was obtained.

Preparation 20

Compound 309

By substituting compound 206 for compound 205 in the procedure of preparation 19, compound 309 was obtained.

Preparation 21

Compound 408

To a solution of compound 308 (1 mmol) in THF (5 ml) and ethyl alcohol (10 ml) PPTS (30 mg) was added, and the mixture was stirred for 1 hour at 25°C under argon. After work up (ethyl acetate with an additional aqueous sodium bicarbonate extraction), the residual crude product was purified by chromatography with 30 % ether in petroleum ether as eluant to give compound 408.

^{13}C NMR δ 153.4, 143.3, 142.7, 135.3, 125.5, 121.5, 116.5, 106.4, 70.9, 70.0, 67.0, 56.7, 46.9, 44.0, 43.7, 38.3, 36.4, 34.2, 29.9, 29.0, 28.9, 28.5, 25.7, 25.6, 23.8, 23.6, 22.9, 19.7, 18.1, 17.9, -5.0, -5.1

Preparation 22

Compound 409

By substituting compound 309 for compound 308 in the procedure of preparation 21, compound 409 was obtained.

^{1}H NMR δ 6.44 (d,1H), 5.85 (d,1H), 4.98 (bs,1H), 4.93 (bs,1H),4.54 (m,1H), 4.21 (m,1H), 2.83 (dd,1H), 2.58 (dd,1H),2.4-1.10 (m,20H), 1.68 (bs,3H), 1.21 (bs,6H), 0.89 (s,9H),0.86 (s,9H), 0.77 (s,3H), 0.05 (bs,12H)

Preparation 23

Compound 508

Method: General Procedure 1

Starting material: Compound 408

Preparation 24

Compound 509

Method: General Procedure 1

Starting material: Compound 409

Preparation 25

3-Ethyl-3-trimethylsilyloxy-5-hexyne

To a solution of 3-ethyl-3-hydroxy-5-hexyne (12.6 g) (WO 93/19044), triethylamine (67 ml) and DMAP (0.47 g) in dichloromethane (150 ml) was added, with stirring at 0°C, trimethylchlorosilane (38 ml), during 10 min. Stirring was continued at 0°C for 15 min. and at 25°C for 45 min. The reaction mixture was worked up, and the crude product was purified by distillation *in vacuo* to give the title compound as an oil, b.p. 83-85°C/25 mm Hg.

^{13}C NMR δ 81.6, 77.9, 69.7, 31.4, 28.9, 7.9, 2.3

Preparation 26

Compounds 310 (isomer 22A) and 311 (isomer 22B)

Method: General Procedure 4

Starting material: Compound 201

Acetylenic side chain building block: 3-Ethyl-3-trimethylsilyloxy-5-hexyne

Chromatography eluant: 2.5% ethyl acetate in petroleum ether.

Compound 310 (isomer 22A)

^{13}C NMR δ 153.4, 147.3, 141.9, 135.7, 125.2, 121.3, 116.8, 106.5, 82.6, 81.7, 78.1, 70.0, 67.0, 61.8, 56.4, 47.1, 43.7, 38.7, 36.4, 31.5, 30.3, 29.3, 28.4, 25.7, 25.6, 23.4, 22.8, 18.2, 18.1, 17.9, 13.9, 7.9, 2.3, -5.0, -5.1

Compound 311 (isomer 22B)

^{13}C NMR δ 153.4, 148.5, 141.9, 135.7, 124.9, 121.3, 116.8, 106.5, 82.6, 81.7, 78.1, 70.0, 67.0, 61.4, 56.4, 47.1, 43.8, 38.2, 36.4, 31.5, 30.3, 29.3, 28.4, 25.7, 25.6, 23.4, 22.7, 18.4, 18.1, 17.9, 14.5, 7.9, 2.3, -5.0, -5.1, -5.1

Preparation 27

Compound 410 (isomer 22A)

Method: General Procedure 1b

Starting material: Compound 310

Chromatography eluant: 2.5% to 5% ether in petroleum ether.

^{13}C NMR δ 148.1, 147.5, 139.6, 135.4, 125.1, 122.8, 118.3, 111.2, 82.6, 81.8, 78.1, 72.0, 67.3, 61.9, 56.3, 47.0, 45.9, 44.6, 38.8, 31.5, 30.3, 29.3, 28.3, 25.7, 25.6, 23.4, 22.8, 18.1, 18.0, 18.0, 13.9, 7.9, 2.3, -4.9, -5.0, -5.3

Preparation 28

Compound 411 (isomer 22B)

Method: General Procedure 1b

Starting material: Compound 311

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

^{13}C NMR δ 148.7, 148.1, 139.6, 135.4, 124.8, 122.8, 118.3, 111.1, 82.6, 81.6, 78.1, 71.9, 67.3, 61.4, 56.3, 47.0, 45.9, 44.6, 38.3, 31.5, 30.4, 29.2, 28.3, 25.7, 25.6, 23.3, 22.6, 18.3, 18.0, 17.9, 14.5, 7.9, 2.3, -4.9, -5.0, -5.3

Preparation 29

Compound 510 (isomer 22A)

Method: General Procedure 5

Starting material: Compound 410

Alkylating agent: Ethyl bromide

Chromatography eluant: 0% to 6% ether in petroleum ether.

^{13}C NMR δ 148.1, 147.6, 139.7, 135.3, 124.3, 122.8, 118.3, 111.1, 82.5, 80.4, 78.2, 72.0, 68.6, 67.3, 63.0, 56.3, 46.9, 45.9, 44.6, 38.9, 31.6, 31.6, 30.1, 29.4, 28.3, 25.7, 25.6, 23.4, 22.7, 18.0, 17.9, 17.7, 15.1, 14.2, 7.9, 2.3, -4.9, -5.0, -5.3

Preparation 30

Compound 511 (isomer 22B)

Method: General Procedure 5

Starting material: Compound 411

Alkylating agent: Ethyl bromide

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

^{13}C NMR δ 148.5, 148.0, 139.7, 135.3, 123.9, 122.8, 118.3, 111.2, 82.7, 80.2, 78.2, 72.0, 68.0, 67.3, 62.9, 56.3, 47.0, 45.9, 44.6, 38.0, 31.6, 30.4, 29.2, 28.3, 25.7, 25.6, 23.4, 22.7, 18.3, 18.0, 17.9, 15.2, 14.9, 7.9, 2.3, -4.9, -5.0, -5.3

Preparation 31

Compound 207

Method: General Procedure 1b

Starting material: Compound 201

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

^{13}C NMR δ 190.9, 174.0, 148.1, 138.2, 136.2, 130.0, 122.5, 119.2, 111.1, 71.8, 67.3, 56.0, 48.8, 45.8, 44.6, 40.4, 32.4, 28.1, 25.6, 25.6, 23.3, 22.4, 19.5, 18.0, 17.9, 11.8, -4.9, -5.0, -5.2

Preparation 32

Compound 312

A solution of compound 207 (0.144 g, 0.25 mmol) and 3-(methoxycarbonyl)-2-propenyl-1-idene-triphenylphosphorane in dry toluene (3 ml) was heated at 100°C for 18 hours. After concentration *in vacuo* the residue was purified by chromatography , eluant: 0% to 2.5 % ether in petroleum ether, to give the title compound as an oil.

^{13}C NMR δ 167.7, 157.5, 148.1, 146.3, 140.6, 139.3, 135.6, 124.2, 122.7, 118.6, 118.0, 111.1, 71.9, 67.3, 56.3, 51.2, 48.0, 45.8, 44.6, 39.1, 31.8, 28.3, 25.7, 25.6, 23.4, 22.7, 18.0, 18.0, 15.6, -4.9, -5.0, -5.3

Preparation 33

Compound 412

To a stirred solution of compound 312 (20 mg, 0.031 mmol) in THF (2 ml), cooled to -78°C, was added a freshly prepared 1.16 M solution of ethyl lithium in ether (0.08 ml, 0.093mmol). Stirring at -78°C was continued for one hour, after which water (15 ml) was added. The reaction mixture was worked up

(ether) to give a crude product which was purified by chromatography, eluant: 0% to 5 % ether in petroleum ether, to give the title compound as an oil.
^{1}H NMR δ 6.81 (d,1H), 6.3-6.0 (m,4H), 5.61 (d,1H), 5.18 (bs,1H), 4.87 (bs,1H), 4.36 (m,1H), 4.18 (m,1H), 2.80 (bd,1H), 2.5-0.9 (m,17H), 1.72 (bs,1H), 1.57 (bq,4H), 0.90 (bt,6H), 0.88 (bs,18H), 0.83 (s,3H), 0.06 (bs,12H)

Preparation 34

Compound 208

To a solution of N-chlorosuccinimide (21 mg) in dry dichloromethane (1.5 ml) was added a solution of dimethylsulfide (12.2 µl) in dry dichloromethane (0.9 ml), during 5 minutes, at 0°C, with stirring. Stirring was continued for 10 minutes at 0°C and for 20 minutes at -20°C. To the reaction mixture was added a solution of compound 203 (77mg, 0.134 mmol) in dry dichloromethane (2.0 ml) during 5 minutes, at -20°C. Stirring was continued for 45 minutes at -20°C to -30°C. Work-up: The reaction mixture was partitioned between ethyl acetate (20 ml) and. water (20 ml). The aqueous phase was extracted with another (15 ml) portion of ethyl acetate, and the combined organic phases were extracted with water (20 ml) and saturated aqueous sodium chloride solution (10 ml), dried with sodium sulfate, and evaporated at (0-10°C) *in vacuo*; all work-up-liquids were ice-cold. The crude compound 208 was used without further purification in the following step (preparation 35).

Preparation 35

Compound 313

To solution of 3-(2-hydroxy-2-propyl)-phenol (46 mg, 0.30 mmol)(WO 91/15475) in dry DMF (3ml) was added a 50% sodium hydride-in-oil-dispersion (15 mg), and the mixture was stirred at 20°C for 90 minutes. After this, it was added to the crude compound 208 of preparation 34 and the mixture was stirred at 20°C for 3 hours, after which it was worked up (ethyl acetate). Purification by chromatography on silica gel (eluant: 0% to 20% ether in petroleum ether) gave the title compound as an oil.
^{1}H NMR δ 159.2, 153.4, 150.7, 150.5, 142.0, 135.6, 129.0, 121.4, 121.2, 116.8,

116.5, 112.1, 111.3, 106.6, 72.4, 70.1, 68.3, 67.0, 56.2, 47.4, 43.8, 38.1, 36.4, 31.5, 30.2, 28.4, 25.7, 25.6, 23.4, 22.7, 18.6, 18.3, 18.1, 17.9, -5.0, -5.1

Preparation 36

Compound 413

Method: General Procedure 1

Starting material: Compound 313

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

^{1}H NMR δ 7.25(m,1H), 7.09 (m,1H), 7.04 (m,1H), 6.81 (m,1H), 6.21(d,1H), 6.06 (d,1H), 5.18 (bd,1H), 4.87 (bd,1H), 4.65 (d,1H), 4.36 (d,1H), 4.35 (m,1H), 4.19 (m,1H), 2.78 (bd,1H), 2.5-0.9 (m,15H), 1.74 (bt,3H),1.57 (s,6H), 0.87 (s,18H), 0.78 (s,3H), 0.05 (bs,12H)

Preparation 37

Compound 314

To a solution of compound 203 (80 mg, 0.140 mmol) in dry THF was added, while stirring at 20°C under argon, a 20% suspension of potassium hydride in mineral oil (54 µl) followed by 6-bromo-3-ethyl-3-trimethylsilyloxy-hexane (WO 89/10351) (111 µl). After 5 minutes, 18-Crown-6 (39 mg) was added, and stirring at 20°C was continued for one and a half hours, after which the reaction mixture was worked up (ether). The crude product was purified by chromatography (0% to 5% ether in petroleum ether as eluant) to yield the title compound as an oil.

^{13}C NMR δ 153.4, 148.5, 142.4, 135.5, 123.0, 121.4, 116.7, 106.5, 78.5, 70.7, 70.5, 70.0, 67.0, 56.3, 47.2, 43.8, 38.2, 36.4, 34.8, 31.2, 30.0, 28.4, 25.7, 25.6, 24.0, 23.5, 22.8, 18.2, 18.2, 18.1, 17.9, 8.0, 2.5, -5.0, -5.1

Preparation 38

Compound 414

Method: General Procedure 1; except that the crude product was used in the following step (Example 14) without previous purification by chromatography.

Starting material: Compound 314

^{1}H NMR δ 6.22(d,1H), 6.05 (d,1H), 5.18 (m,1H), 4.86 (m,1H), 4.36(m,1H), 4.18 (m,1H), 4.10 (d,1H), 3.85 (d,1H), 3.37(t,2H), 2.78 (d,1H), 2.44 (dd,1H), 2.4-2.1 (m,5H), 1.9-1.4 (m,8H), 1.63 (s,3H), 1.45 (q,4H), 0.9-0.7 (m,4H), 0.87(d,18H), 0.81 (t,6H), 0.74 (s,3H), 0.08 (s,9H) 0.06 (s,12H)

Preparation 39

Compound 315 and Compound 316

A solution of 6-bromo-3-ethyl-3-trimethylsilyloxy-hexane (WO 89/10351) (1.375 g, 4.9 mmol) in dry THF (5 ml), was added dropwise, during 5 minutes, to magnesium turnings (118 mg, 4.9 mgAt) (previously stirred "dry" during 20 hours under argon) together with ether (1 ml), while stirring under argon at 20°C. Stirring was continued under reflux (oil bath, 75°C) for one and a half hours to finish the formation of the Grignard reagent, and 1.0 ml of the solution was taken out by means of a syringe, while still warm (40 - 50 °C). This was added to a solution of compound 201 (171mg, 0.30 mmol) in THF (2 ml), while stirring under argon at 0-5°C. Stirring was continued for 40 minutes at 20°C, after which the reaction mixture was poured onto a mixture of ether (25 ml) and water (25 ml), containing ammonium chloride (2.5 g), while stirring. The reaction mixture was worked up (ether) to yield a crude product containing the isomeric 22-hydroxy compounds: A (less polar) and B (more polar). These were separated by chromatography (0% to 10% ether in petroleum ether as eluant) to give the pure title compounds.

Compound 315 (isomer 22A)

^{13}C NMR δ 153.5, 146.4, 142.1, 135.6, 128.0, 121.4, 116.7, 106.5, 78.7, 70.7, 70.0, 67.0, 56.8, 47.0, 43.8, 39.6, 38.5, 36.4, 35.9, 31.4, 30.9, 30.4, 28.4, 25.7, 25.6, 23.5, 22.9, 20.2, 18.4, 18.1, 17.9, 13.0, 8.0, 2.5, -5.0, -5.1

Compound 316 (isomer 22B)

^{13}C NMR δ 153.4, 148.2, 142.1, 135.7, 127.5, 121.4, 116.9, 106.5, 78.6, 70.0, 70.0, 67.0, 56.6, 46.9, 43.8, 38.5, 38.5, 36.4, 35.1, 31.3, 31.0, 30.3, 28.5, 25.7, 25.6, 23.5, 22.8, 20.3, 18.9, 18.1, 17.9, 12.9, 8.1, 8.0, 2.5, -5.0, -5.1

Preparation 40

Compound 415 (isomer 22A)

Method: General Procedure 1

Starting material: Compound 315

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

Preparation 41

Compound 416 (isomer 22B)

Method: General Procedure 1

Starting material: Compound 316

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

Preparation 42

Compound 317

A solution of compound 207 (0.25 mmol) and cyclopropylcarbonyl-methylene-triphenylphosphorane (0.5 mmol) in dry toluene (3 ml) was heated at 100°C for 18 hours. After concentration in vacuo the residue was purified by chromatography , eluant: 0% to 2.5 % ether in petroleum ether, to give the title compound as an oil.

Preparation 43

Compound 417

To a stirred solution of compound 317 (0.3 mmol) in THF (1 ml) was added at 0°C 0.4 M methanolic cerium (III) chloride heptahydrate (1 ml), methanol (1 ml) and sodium borohydride (60 mg, 1.6 mmol). After stirring at 0°C for 40 minutes, the reaction mixture was diluted with ethyl acetate (40 ml) and water (15 ml) was added. The organic phase was separated, washed with water (10 ml) and brine (10 ml), dried over magnesium sulfate and evaporated in vacuo. The residual oil was purified by chromatography on silica gel (eluant: 5% ethyl acetate in petroleum ether) to give the title compound as a mixture of epimers at the side

chain hydroxyl position which was used as such in the subsequent step (Example 17).

Example 1: 1(S),3(R)-Dihydroxy-20-(1-hydroxy-1-pentyl)-9,10-secopregna-5(Z),7(E),10(19),17(20)(Z)-tetraene, isomer 22A

Compound 101

Method: General Procedure 2 or 3

Starting material: Compound 401

Example 2: 1(S),3(R)-Dihydroxy-20-(1-hydroxy-1-pentyl)-9,10-secopregna-5(Z),7(E),10(19),17(20)(Z)-tetraene, isomer 22B

Compound 102

Method: General Procedure 2 or 3

Starting material: Compound 402

Example 3: 1(S),3(R)-Dihydroxy-20-(4-methyl-1-pentyl)-9,10-secopregna-5(Z),7(E),10(19),17(20)(Z)-tetraene

Compound 103

Method: General Procedure 2

Starting material: Compound 403

^{1}H NMR δ 6.37(d,1H), 6.04(d,1H), 5.34(bs,1H), 5.01(bs,1H), 4.44(m,1H), 4.23(m,1H), 2.80(dd,1H), 2.61(dd,1H), 1.56(bs,3H), 1.10-2.35 (m,22H), 0.87(d,6H), 0.73(s,3H)

Example 4: 1(S),3(R)-Dihydroxy-20-(1,5-dihydroxy-5-ethyl-2-heptyn-1-yl)-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene, isomer 22A

Compound 104

Method: General Procedure 3

Starting material: Compound 410

Chromatography eluant: 50% to 100% ethyl acetate in petroleum ether.

^{13}C NMR δ 149.8, 147.5, 141.5, 136.2, 127.5, 124.7, 119.6, 112.1, 83.5, 82.4, 75.3, 71.5, 67.4, 62.4, 58.0, 46.2, 43.7, 40.5, 32.0, 31.2, 29.7, 29.5, 24.8, 24.2,

18.3, 14.5, 8.1,

Example 5: 1(S),3(R)-Dihydroxy-20-(1,5-dihydroxy-5-ethyl-2-heptyn-1-yl)-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene, isomer 22B

Compound 105

Method: General Procedure 3

Starting material: Compound 411

Method of purification: Crystallisation from ether.

M.p. 161-175°C

^{1}H NMR δ 6.34(d,1H), 6.05 (d,1H), 5.51 (bs,1H), 5.33 (bs,1H), 4.99 (bs,1H), 4.43 (bs,1H), 4.22 (bs,1H), 2.79 (d,1H), 2.59 (dd,1H), 2.37 (d,2H), 2.35-1.0 (m,17H), 1.71 (s,3H), 1.55 (bq,4H), 0.86 (bt,6H), 0.76 (s,3H)

Example 6: 1(S),3(R)-Dihydroxy-20-(1-ethoxy-5-ethyl-5-(tetrahydro-4H-pyran-2-yl)oxy-2-heptyn-1-yl)-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene, isomer 22A

Compound 106

Method: General Procedure 3

Starting material: Compound 406

^{13}C NMR δ 147.6, 147.6, 141.9, 133.6, 124.7, 117.8, 111.9, 93.2, 82.6, 80.5, 80.2, 70.8, 68.8, 66.8, 63.3, 63.0, 56.6, 47.2, 45.2, 42.9, 39.0, 32.3, 30.3, 28.7, 28.6, 27.0, 25.6, 23.8, 23.1, 20.3, 17.9, 15.3, 14.4, 7.9, 7.8

Example 7: 1(S),3(R)-Dihydroxy-20-(1-ethoxy-5-ethyl-5-(tetrahydro-4H-pyran-2-yl)oxy -2-heptyn-1-yl)-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene, isomer 22B

Compound 107

Method: General Procedure 3

Starting material: Compound 407

^{13}C NMR δ 148.4, 147.6, 142.0, 133.5, 124.8, 124.3, 117.7, 111.9, 93.2, 82.8, 80.3, 80.1, 70.8, 68.1, 66.8, 63.1, 63.0, 56.4, 47.3, 45.3, 42.9, 38.1, 32.2, 30.5, 28.7, 28.6, 26.9, 25.5, 23.7, 23.0, 20.3, 18.5, 15.4, 15.1, 7.9, 7.8

Example 8: 1(S),3(R)-Dihydroxy-20-(4-hydroxy-4-methyl-1-pentyl)-9,10-secopregna-5(Z),7(E),10(19),17(20)(Z)-tetraene

Compound 108

Method: General Procedure 2 or 3

Starting material: Compound 508

^{13}C NMR δ 147.6, 143.4, 142.8, 133.1, 125.7, 125.0, 117.3, 111.9, 70.8, 66.9, 56.8, 47.1, 45.3, 44.2, 42.9, 38.5, 34.4, 30.1, 29.3, 29.2, 28.9, 24.0, 23.9, 23.1, 19.9, 17.8

Example 9: 1(S),3(R)-Dihydroxy-20-(4-hydroxy-4-methyl-1-pentyl)-9,10-secopregna-5(Z),7(E),10(19),17(20)(E)-tetraene

Compound 109

Method: General Procedure 2 or 3

Starting material: Compound 509

^{1}H NMR δ 6.37 (bd,1H), 6.04 (bd,1H), 5.34 (bs,1H), 5.02 (bs,1H), 4.44 (bm,1H), 4.23 (bm,1H), 2.80 (bd,1H), 2.60 (m,2H), 2.4-1.0 (m,21H), 1.70 (bs,3H), 1.21 (s,6H), 0.73 (s,3H)

Example 10: 1(S),3(R)-Dihydroxy-20-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene, isomer 22A

Compound 110

Method: General Procedure 3

Starting material: Compound 510

Chromatography eluant: 50% to 100% ethyl acetate in petroleum ether.

^{13}C NMR δ 148.1, 147.6, 141.8, 133.6, 124.7, 124.5, 117.8, 111.9, 82.1, 81.6, 74.0, 70.8, 68.8, 66.8, 63.4, 56.6, 47.2, 45.3, 42.9, 39.1, 30.8, 30.3, 29.9, 28.7, 23.7, 23.1, 17.9, 15.3, 14.3, 7.9

Example 11: 1(S),3(R)-Dihydroxy-20-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene, isomer 22B

Compound 111

Method: General Procedure 3

Starting material: Compound 511

Chromatography eluant: 0% to 100% ethyl acetate in petroleum ether.

^{13}C NMR δ 148.8, 147.6, 141.8, 133.5, 124.7, 124.0, 117.7, 111.9, 81.9, 81.8, 74.0, 70.8, 68.0, 66.8, 63.2, 56.4, 47.3, 45.2, 42.9, 38.1, 30.8, 30.5, 29.7, 28.7, 23.7, 23.0, 18.6, 15.4, 15.1, 7.9

Example 12: 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),17(20)Z-tetraene

Compound 112

Method: General Procedure 3

Starting material: Compound 412

Chromatography eluant: 25% to 50% ethyl acetate in petroleum ether.

^{1}H NMR δ 6.81 (d,1H), 6.37 (d,1H), 6.28 (dd,1H), 6.12 (dd,1H), 6.08 (bd,1H), 5.63 (d,1H), 5.34 (bs,1H), 5.01 (bs,1H), 4.44 (m,1H), 4.24 (m,1H), 2.80 (bd,1H), 2.60 (dd,1H), 2.5-0.90 (m,16H), 1.74 (bs,3H), 1.58 (bq,4H), 0.90 (t,6H), 0.82 (s,3H)

Example 13: 1(S),3(R)-Dihydroxy-20-[3-(2-hydroxy-2-propyl)-phenoxymethyl]-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene

Compound 113

Method: General Procedure 3

Starting material: Compound 413

Chromatography eluant: 50% to 100% ethyl acetate in petroleum ether.

^{1}H NMR δ 7.24(m,1H), 7.10 (m,1H), 7.04 (m,1H), 6.80 (m,1H), 6.39(d,1H), 6.06 (d,1H), 5.34 (bs,1H), 5.01 (bs,1H), 4.66 (d,1H), 4.44 (m,1H), 4.37 (d,1H), 4.23 (m,1H), 2.79 (bd,1H), 2.60 (dd,1H), 2.4-0.9 (m,16H), 1.75 (bs,3H), 1.58 (s,6H), 0.80 (s,3H)

Example 14: 1(S),3(R)-Dihydroxy-20-[(3-ethyl-3-hydroxy-6-hexyl)-oxymethyl]-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene

Compound 114

Method: General Procedure 3

Starting material: Compound 414

Chromatography eluant: 50% to 100% ethyl acetate in petroleum ether.

^{13}C NMR δ 148.8, 147.6, 142.3, 133.4, 124.8, 122.9, 117.6, 111.9, 74.1, 70.8, 70.8, 66.8, 56.4, 47.3, 45.3, 42.9, 38.4, 35.4, 31.0, 30.1, 28.8, 23.9, 23.7, 23.0, 18.4, 7.9

Example 15: 1(S),3(R)-Dihydroxy-20-(1,5-dihydroxy-5 ethyl-1-heptyl)-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene, isomer 22A

Compound 115

Method: General Procedure 3

Starting material: Compound 415

Chromatography eluant: 50% to 100% ethyl acetate in petroleum ether.

Example 16: 1(S),3(R)-Dihydroxy-20-(1,5-dihydroxy-5 ethyl-1-heptyl)-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene, isomer 22B

Compound 116

Method: General Procedure 3

Starting material: Compound 416

Chromatography eluant: 50% to 100% ethyl acetate in petroleum ether.

Example 17: 1(S),3(R)-Dihydroxy-20-(3-cyclopropyl-3-hydroxy-prop-1(E)-en-1-yl)-9,10-secopregna-5(Z),7(E),10(19),17(20)(Z)-tetraene

Compound 117

Method: General Procedure 3

Starting material: Compound 417

Chromatography eluant: 50% to 100% ethyl acetate in petroleum ether.

Example 18: Capsules containing Compound 105

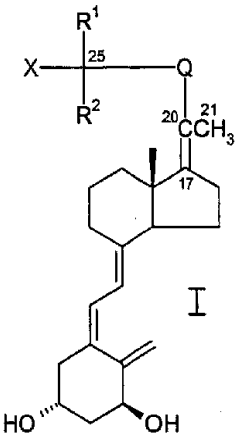
Compound 105 was dissolved in arachis oil to a final concentration of 1 µg of Compound 105/ml oil. 10 Parts by weight of gelatine, 5 parts by weight glycerine, 0.08 parts by weight potassium sorbate, and 14 parts by weight distilled water were mixed together with heating and formed into soft gelatine capsules. These were then filled each with 100 µl of Compound 105 in oil solution, such that each capsule contained 0.1 µg of Compound 105.

Example 19: Dermatological Cream Containing Compound 108

In 1 g almond oil was dissolved 0.05 mg of Compound 108. To this solution was added 40 g of mineral oil and 20 g of self-emulsifying beeswax. The mixture was heated to liquefy. After the addition of 40 ml hot water, the mixture was mixed well. The resulting cream contains approximately 0.5 µg of Compound 108 per gram of cream.

WHAT WE CLAIM IS:

1. A compound of the formula I



I

in which formula X is hydrogen or hydroxy or protected hydroxy; R^1 and R^2 stand for hydrogen, methyl or ethyl, or, when taken together with the carbon atom bearing the group X, R^1 and R^2 can form a C_3-C_5 carbocyclic ring; Q is a C_3-C_6 hydrocarbylene, hydrocarbylene indicating the diradical obtained after removal of 2 hydrogen atoms from a straight or branched, saturated or unsaturated hydrocarbon, in which one of any CH_2 groups may optionally be replaced by an oxygen atom or a carbonyl group, such that the carbon atom (C-22) directly bonded to C-20 is an sp^2 or sp^3 hybridized carbon atom, i.e. bonded to 2 or 3 other atoms; and in which another of the CH_2 groups may be replaced by phenylene, and where Q may optionally be substituted with one or more hydroxy or C_1-C_4-alkoxy groups.

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

3. A compound according to claim 1 which is:

a) 1(S),3(R)-Dihydroxy-20-(4-methyl-1-pentyl)-9,10-secopregna-5(Z),7(E),10(19),17(20)(Z)-tetraene

b) 1(S),3(R)-Dihydroxy-20-(4-hydroxy-4-methyl-1-pentyl)-9,10-secopregna-5(Z),7(E),10(19),17(20)(Z)-tetraene

c) 1(S),3(R)-Dihydroxy-20-(4-hydroxy-4-methyl-1-pentyl)-9,10-secopregna-5(Z),7(E),10(19),17(20)(E)-tetraene

d) 1(S),3(R)-Dihydroxy-20-(1,5-dihydroxy-5-ethyl-2-heptyn-1-yl)-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene, both 22-isomers

e) 1(S),3(R)-Dihydroxy-20-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene, both 22-isomers

f) 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),17(20)Z-tetraene

g) 1(S),3(R)-Dihydroxy-20-[3-(2-hydroxy-2-propyl)-phenoxymethyl]-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene

h) 1(S),3(R)-Dihydroxy-20-[(3-ethyl-3-hydroxy-6-hexyl)-oxymethyl]-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene

i) 1(S),3(R)-Dihydroxy-20-(1,5-dihydroxy-5 ethyl-1-heptyl)-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene, both 22-isomers

j) 1(S),3(R)-Dihydroxy-20-(3-cyclopropyl-3-hydroxy-prop-1(E)-en-1-yl)-9,10-secopregna-5(Z),7(E),10(19),17(20)(Z)-tetraene

4. A method for producing a compound of formula I of claim 1 by which:

a) the side chain attached to C-20 (or an alcohol protected form of this) in compound I is elaborated from 1(S),3(R)-bis-(tert-butyldimethylsilyloxy)-20-formyl-9,10-secopregna-5(E),7(E),10(19),17(20)(Z)-tetraene, or from 1(S),3(R)-bis-(tert-butyldimethylsilyloxy)-20-formyl-9,10-secopregna-5(E),7(E),10(19),17(20)(E)-tetraene, or their corresponding 5(Z) isomers, either

(i) by reaction with the lithium salt of the side chain building block $HC{\equiv}C(CH_2)_nCR_2$-OPG (PG= protecting group), where n is 0, 1 or 2, R is methyl or ethyl and PG is trimethylsilyl or tetrahydropyranyl, prepared by reaction with butyllithium, in a solvent, or

(ii) by reaction with the Grignard reagent $BrMg(CH_2)_nC(R)O$-$Si(CH_3)_3$, where n = 2, 3 or 4 and R = methyl or ethyl, in a solvent, and

b) the compound from step a), above, is optionally (i) separated from diastereoisomers, (ii) subjected to triplet-sensitized photo-isomerisation to the 5(Z) isomer, (iii) alkylated at the 22-hydroxy group with a C_1-C_3 alkyl bromide or iodide in the presence of a base and a phase transfer catalyst, in a solvent, and (iv) desilylated.

5. A method for producing a compound of formula I of claim 1 by which:

a) The side chain attached to C-20 is elaborated from 1(S),3(R)-bis-(tert-butyldimethylsilyloxy)-20-formyl-9,10-secopregna-5(Z),7(E),10(19),17(20)(Z)-tetraene, or its corresponding 17(20)(E)- isomer, by reaction with a Wittig-type reagent $(C_6H_5)_3P$=CH-CH=CH-COOR, where R is methyl or ethyl, in a solvent, and

b) the compound from step a) above is reacted with an organometallic

reagent R^1Li (R^1=methyl or ethyl), followed by desilylation.

6. A method for producing a compound of formula I of claim 1, by which the side chain attached to C-20 in compound I is elaborated from 1(S),3(R)-bis-(tert-butyldimethylsilyloxy)-20-formyl-9,10-secopregna-5(E),7(E),10(19),-17(20)(Z)-tetraene, or 1(S),3(R)-bis-(tert-butyldimethylsilyloxy)-20-formyl-9,10-secopregna-5(E),7(E),10(19),17(20)(E)-tetraene, or their corresponding 5(Z) isomers, by

a) reducing the 20-CHO group to the corresponding 20-CH_2OH group, and either

b) alkylating the 20-CH_2OH group with a side chain building block Hal-$(CH_2)_n$-CR_2-$OSi(CH_3)_3$, where Hal is Cl, Br or I, n is 2, 3 or 4 and R is methyl or ethyl, in the presence of a base and a phase transfer catalyst in a solvent, or

c) converting the hydroxy group of the 20-CH_2OH compound of step a) above, into a leaving group, either

(i) to a lower alkanoate, such as a pivalate, by reaction, with pivaloyl-chloride, pyridine and 4-dimethylaminopyridine in dichloromethane; which lower alkanoate is reacted with a Grignard reagent $HalMg(CH_2)_nCR_2X$, where Hal is Cl, Br or I, n is 2, 3 or 4, R is methyl or ethyl, and X is H or $OSi(CH_3)_3$, in the presence of Li_2CuCl_4, in tetrahydrofuran; followed, if X is $OSi(CH_3)_3$, by removal of the side chain silyl group by partial desilylation with pyridinium p-toluenesulfonate in ethanol, or

(ii) to a chloride or bromide, by reaction with N-chlorosuccinimide or N-bromosuccinimide, and dimethylsulfide in dichloromethane; which chloride or bromide is reacted with sodium 3-(2-hydroxy-2-propyl)-phenolate in N,N-dimethylformamide, and

d) the compound of step b) or c), above, is (i) subjected to triplet-sensitized photoisomerisation to the 5(Z) isomer, and (ii) desilylated with tetra-n-butylammonium fluoride.

7. Intermediate for the synthesis of compounds of formula I and analogues thereof which is:

a) 1(S),3(R)-bis-(tert-butyldimethylsilyloxy)-20-formyl-9,10-secopregna-5(E),7(E),10(19),17(20)(Z)-tetraene, and the corresponding 5(Z) isomer,

b) 1(S),3(R)-bis-(tert-butyldimethylsilyloxy)-20-formyl-9,10-secopregna-5(E),7(E),10(19),17(20)(E)-tetraene, and the corresponding 5(Z) isomer,

c) 1(S),3(R)-bis-(tert-butyldimethylsilyloxy)-20-hydroxymethyl-9,10-secopregna-5(E),7(E),10(19),17(20)(Z)-tetraene, and the corresponding 5(Z) isomer,

d) 1(S),3(R)-bis-(tert-butyldimethylsilyloxy)-20-hydroxymethyl-9,10-secopregna-5(E),7(E),10(19),17(20)(E)-tetraene, and the corresponding 5(Z) isomer,

8. A pharmaceutical composition containing an effective amount of one or more of the compounds of any one of claims 1-3, together with pharmaceutically acceptable, non-toxic carriers and/or auxiliary agents.

9. A pharmaceutical composition according to claim 8 in dosage unit form containing from 0.1 ppm to 0.1% by weight of the dosage unit of a compound of formula I.

10. A method for the treatment and/or prophylaxis of diseases characterized by abnormal cell differentiation and/or cell proliferation

HIV-associated dermatoses, wound healing, cancer, including skin cancer, and of diseases of, or imbalance in, the immune system, and autoimmune diseases, diabetes mellitus and chronic dermatoses of autoimmune type, and inflammatory diseases, as well as a number of other disease states including hyperparathyroidism, particularly secondary hyperparathyroidism associated with renal failure, cognitive impairment or senile dementia (Alzheimer's disease) and other neurodegenerative diseases, hypertension, acne, alopecia, skin atrophy, skin ageing, including photo-ageing, and to their use for promoting osteogenesis and treating/preventing osteoporosis and osteomalacia consisting in administering to a patient in need thereof a pharmaceutical composition according to claim 8.

11. A method of claim 10, wherein diseases characterised by abnormal cell differentiation and/or cell proliferation include psoriasis and other disturbances of keratinisation.

12. A method of claim 10, wherein diseases of, or unbalance in the immune system include host versus graft and graft versus host reaction and transplant rejection.

13. A method of claim 10, wherein autoimmune diseases include discoid and systemic lupus erythematosus.

14. A method of claim 10, wherein chronic dermatoses of autoimmune type include scleroderma and pemphigus vulgaris.

15. A method of claim 10, wherein inflammatory diseases include rheumatoid arthritis.

16. A method of claim 10, wherein skin atrophy includes steroid induced skin atrophy.

17. The use of any one of claim 1-3 in the manufacture of a medicament for the treatment and/or prophylaxis of diseases characterised by abnormal cell differentiation and/or cell proliferation such as HIV-associated dermatoses, wound

healing, cancer, including skin cancer, and of diseases of, or imbalance in, the immune system, and autoimmune diseases, diabetes mellitus and chronic dermatoses of autoimmune type, and inflammatory diseases, as well as a number of other disease states including hyperparathyroidism, particularly secondary hyperparathyroidism associated with renal failure, cognitive impairment or senile dementia (Alzheimer's disease) and other neurodegenerative diseases, hypertension, acne, alopecia, skin atrophy, skin ageing, including photo-ageing, and to their use for promoting osteogenesis and treating/preventing osteoporosis and osteomalacia.

18. The use of claim 17, wherein diseases characterised by abnormal cell differentiation and/or cell proliferation include psoriasis and other disturbances of keratinisation.

19. The use of claim 17, wherein diseases of, or imbalance in the immune system include host versus graft and graft versus host reaction and transplant rejection.

20. The use of claim 17, wherein autoimmune diseases include discoid and systemic lupus erythematosus.

21. The use of claim 17, wherein chronic dermatoses of autoimmune type include scleroderma and pemphigus vulgaris.

22. The use of claim 17, wherein inflammatory diseases include rheumatoid arthritis.

23. The use of claim 17, wherein skin atrophy includes steroid induced skin atrophy.

24. A compound according to claim 1, substantially as herein described with reference to any one of the Examples.

25. A method according to any one of claims 4 to 6 for producing a compound of claim 1 which method is substantially as herein described with reference to any one of the Examples.

26. An intermediate according to claim 7, substantially as herein described with reference to any one of the Examples.

27. A pharmaceutical composition according to claim 8, substantially as herein described with reference to any one of the Examples.

28. A method according to claim 10 which method is substantially as herein described with reference to any one of the Examples.

29. The use according to claim 17, substantially as herein described with reference to any one of the Examples.

DATED this 11th day of July, 2001.

LEO PHARMACEUTICAL PRODUCTS LTD. A/S
(LØVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB)
By their Patent Attorneys:
CALLINAN LAWRIE