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SYNTHESIS OF MC 903, A BIOLOGICALLY ACTIVE VITAMIN D METABOLITE ANALOGUE

MARTIN J. CALVERLEY

Leo Pharmaceutical Products, DK-2750 Ballerup, Denmark

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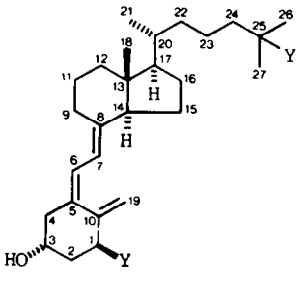
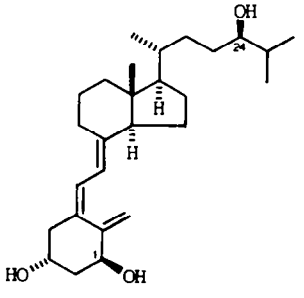
Summary: MC 903 (**4**), a 1,24-dihydroxyvitamin D analogue containing a double bond and a cyclopropane ring in the side chain, was synthesised in 12 steps from vitamin D_2.

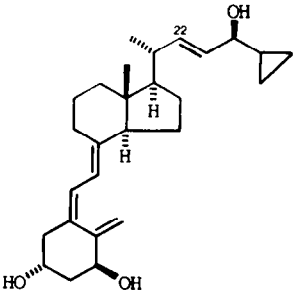
1α,25-Dihydroxyvitamin D_3 (1,25-$(OH)_2$-D_3, **2**) is the hormonally active metabolite of vitamin D_3 (**1**) and mediates its effect on intestinal uptake of calcium and phosphate by binding to a receptor present in intestinal epithelium cells.[1] Recently, specific receptors for 1,25-$(OH)_2$-D_3 have been discovered in various cells, such as skin[2] and certain tumour cells,[3] which are not regarded as participating in mineral metabolism. Furthermore it has been observed[4,5] that the hormone is a potent inhibitor of proliferation and inducer of differentiation of such cells. This has led to the speculation that 1,25-$(OH)_2$-D_3 may find application in the treatment of disease states characterised by excessive cell proliferation and incomplete cell differentiation, such as psoriasis and leukemia. However, the potent effect of the natural hormone on calcium metabolism involves the risk that such treatment may induce hypercalcemia, and this has stimulated the search for analogues having a relatively weak systemic effect on calcium metabolism while maintaining potent regulatory effects on cell proliferation and differentiation.



1 Y = H [VITAMIN D_3]
2 Y = OH [1,25-$(OH)_2$-D_3]



3 [1,24(R)-$(OH)_2$-D_3]



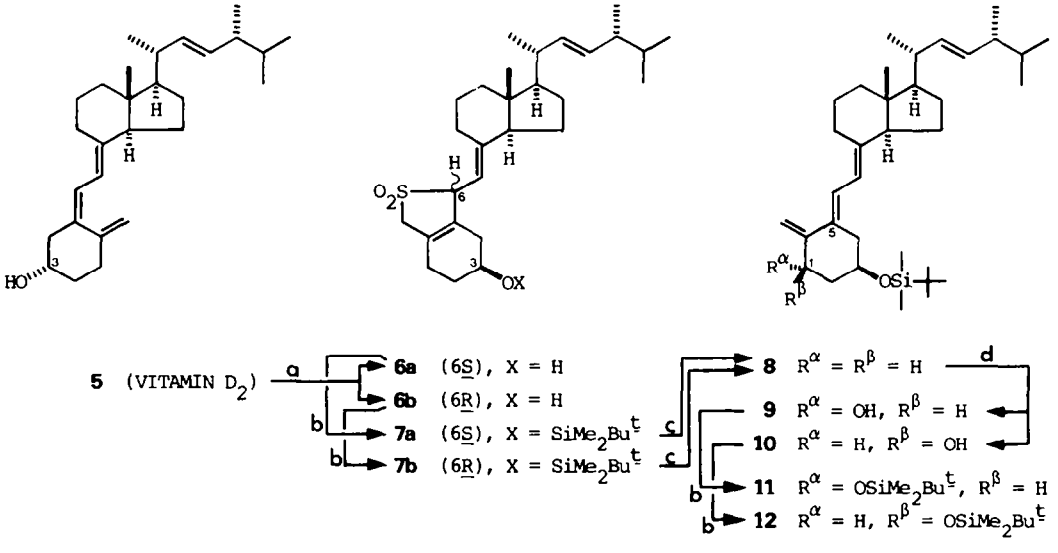
4 [MC 903]

The discovery that transposition of the 25-hydroxyl group of 1,25-$(OH)_2$-D_3 to the 24(R) position results in an unnatural analogue [1α,24(R)-dihydroxyvitamin D_3, **3**] with essentially equal cell differentiating ability *in vitro*,[5,6] but with a slightly reduced tendency to give hypercalcemia *in*

vivo,[7] suggests that other 1α,24-dihydroxylated analogues could also be of interest. We have explored the biological consequences of incorporating carbons 25, 26 and 27 of **3** and related compounds into various cycloalkane rings, a modification which has not been tried before in the vitamin D field, and in this report we describe the synthesis of the novel cyclopropyl, Δ^{22} derivative (MC 903, **4**), in which a dramatic separation of these biological effects has been achieved, and which has been selected as a candidate for clinical evaluation in the treatment of psoriasis.

The availability of steroidal aldehydes by cleavage of the side chain double bond in Δ^{22} steroids (ergosterol, stigmasterol) has made them attractive intermediates for the partial synthesis of analogues possessing a modified side chain,[8] and these analogues can be converted to vitamin D-type seco-steroids.[9] The more direct synthetic strategy we have adopted follows the lead of Hesse's group in taking the readily available vitamin D_2 (**5**) as starting material,[10] and we have already briefly reported on our use of this approach in the modification of the vitamin D_2 side chain via reductive alkylation of a versatile seleno-acetal intermediate.[11] We now report related work based on Wittig methodology, which similarly involves a convenient, late-stage, versatile intermediate for the synthesis of new 1α-hydroxylated vitamin D analogues.

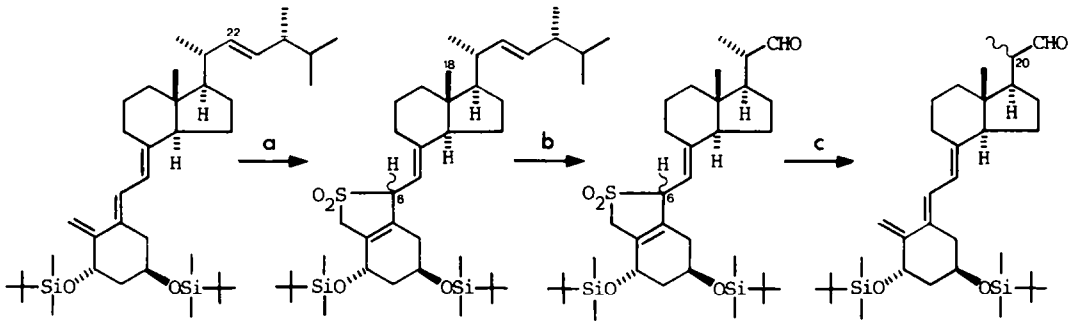
The reactions taking vitamin D_2 (**5**) to the 1α-hydroxylated (5E)-vitamin D_2 derivative **9** were carried out essentially as described by Hesse's group,[12] with certain practical modifications. Thus, vitamin D_2 was converted to its SO_2-adducts using the very convenient procedure used by Takayama's group,[13] in which the vitamin is simply dissolved in liquid sulphur dioxide, and the excess solvent is removed after allowing to react for 30 min at its boiling point. The ca. 1:1 mixture of vitamin D_2 SO_2-adducts[13a] (**6**) obtained by this method as a foam was directly silylated, and each of the crystalline tert-butyldimethylsilyl (TBDMS) ethers (**7a, b**) was isolated and is characterized here for the first time. Cheletropic extrusion of SO_2 in refluxing ethanol containing suspended $NaHCO_3$ converted either isomer to the same (5E)-vitamin derivative **8**, which was submitted as a crude oil directly to a selenite mediated allylic hydroxylation reaction under the conditions developed by Hesse's group. These conditions allow selective introduction of a 1α-hydroxyl group into the (5E)-vitamin D system in ca. 50-60% yields, the major identified by-product being the 1β-hydroxylated compound.[12] In our hands, the ratio of 1α-(**9**) to 1β-(**10**) hydroxylated products was found to be ca. 6:1 by HPLC analysis of the reaction mixture (this ratio being constant during the reaction course), but we have found that the undesired isomer is readily separated after a derivatisation step. Thus, silylation of the crude hydroxylation products and purification involving a



a SO_2 (liquid, reflux); b t-$BuMe_2SiCl$, Imidazole (DMF, 20 °C); c $NaHCO_3$ (EtOH, reflux); d SeO_2, N-methylmorpholine N-oxide (MeOH - CH_2Cl_2, reflux).

rapid filtration through silica gel and crystallisation gave the pure bis-TBDMS ether (**11**), leaving the corresponding oily 1β-isomer (**12**) to be isolated from the mother liquor by careful chromatography. The overall yield of the intermediate (**11**) from vitamin D_2 was 35%.

Protection of the conjugated triene system as a dienophile adduct is required to allow selective ozonolysis of Δ^{22} in vitamin D_2,[10] and this is also the case with the derivatised 1α-hydroxy-(5E)-vitamin (**11**). Thus, treatment of **11** (in diethyl ether as a co-solvent) with liquid sulphur dioxide gave quantitatively a crystalline mixture of SO_2-adducts (**13**). In this case the ratio of adducts was found to be ca. 3:1. Takayama's group reported[13b] the positions of the C-18 H_3 singlet in the ^{1}H-NMR spectra of vitamin D (6R) and (6S) SO_2-adducts of known configuration, and these fall into mutually exclusive ranges [viz.(6R), δ ca. 0.55; (6S), δ 0.65-0.70]. These ranges are not exceeded in the 1-substituted analogues of the present work, nor indeed in a variety of other analogues (unpublished data), and therefore the assignments of configuration at C-6 in the major isomer, **13a** (6S; δ 0.66), and the minor isomer, **13b** (6R; δ 0.57), are made on this basis. The mixture of adducts **13** was conveniently used directly in the subsequent steps, but for ease of characterisation the major (less polar) isomer **13a** was separated by chromatography. Ozonolysis of this compound gave the aldehyde **14a** (81%), from which thermal cheletropic extrusion of SO_2 in the presence of $NaHCO_3$ gave the key intermediate **15**, the same product obtained in the minor series from **13b** via **14b**.



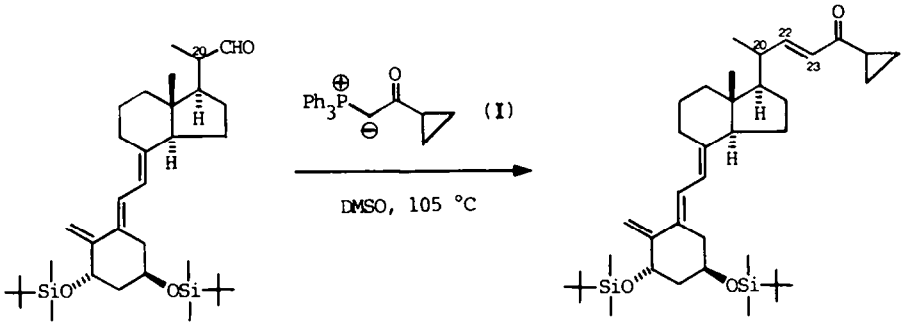
11 **13a** (6S) **14a** (6S) **15** (20S)
13b (6R) **14b** (6R) **16** (20R)

a SO_2 (Et_2O, -10 °C); b i. O_3; ii. PPh_3 (CH_2Cl_2-MeOH, -70 to 0 °C); c $NaHCO_3$ (EtOH, reflux).

The slightly less polar C-20 epimer **16** was an unavoidable by-product of these reactions, and control of the reaction conditions was necessary to obtain high yields of **15**. It was established that progressive epimerisation at C-20 occurred under the mildly basic conditions necessary[14] to stabilise the acid-sensitive conjugated triene system of the product in the SO_2-extrusion reaction.[15] The extent of epimerisation depended on the solvent: reactions in refluxing methanol rapidly gave a ca. 1:1 mixture of **15** and **16** (together with considerable degradation), while the proportion of 16 was reduced to ca. 6% (HPLC control) (and degradation was negligible) in refluxing ethanol. However, if the latter reactions were prolonged over the 60-90 min required for essentially complete consumption of starting materials **14**, serious epimerisation ensued (ca. 50% at 5 h). The use of n-butanol (at 80°C) instead of ethanol gave a similar initial proportion of epimer (5%) but an increased stability to extended reaction times. On the other hand, the use of N,N-dimethylformamide (at 80°C) as solvent gave a slightly higher initial proportion of epimer.

As implied above, the undesired (20R) aldehyde (**16**) could be removed by chromatography for the characterisation of the pure (20S) isomer (**15**). However, it was found expedient to defer separation of the by-product series until after the next step, since the crude product obtained conveniently and without material loss from the reaction run in ethanol as described above crystal-

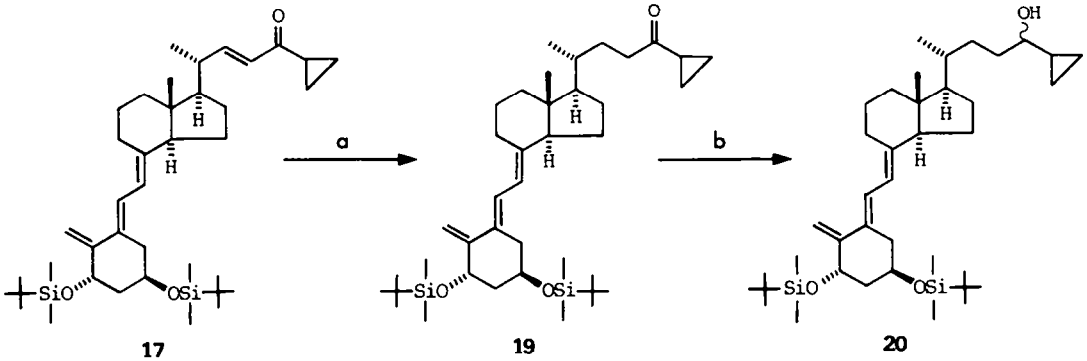
lised directly in a form which contained ca. 90% of **15** and could be stored for considerable periods.[16] Treatment of this product with about a molar excess of cyclopropylcarbonylmethylene-triphenylphosphorane (**I**, readily obtained from cyclopropyl methyl ketone; see Experimental) in dimethyl sulphoxide at 105°C for 4 h led to the isolation of the pure enone (**17**) in overall 60–63% yields from **14a** or the mixture **14a/14b**. The (20S) epimer (**18**) was also isolated (4%) and characterised. The proportion of "natural" and "unnatural" C-20 epimers in the starting material for the Wittig reaction was found to be equal to that in the product and also to remain constant over the reaction period (HPLC control). Only products containing the (E)-configurated Δ^{22} were obtained from these reactions (^{1}H-NMR analysis: $J_{22,23}$ ca. 16 Hz).[17]



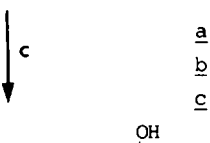
15 (20S)
16 (20R)

17 (20R)
18 (20S)

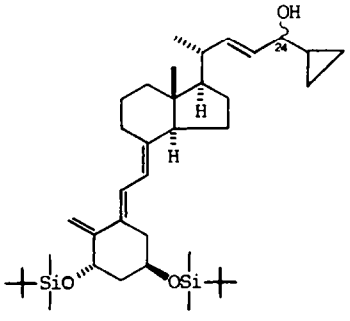
The next step in the synthesis required a selective 1,2-reduction of the conjugated carbonyl group of **17**. To facilitate the identification of possible products of over-reduction in this reaction and (not least) to allow the synthesis of the side chain saturated target compound corresponding to **4**, the enone **17** was converted to the saturated ketone **19**, by reduction with $Na_2S_2O_4$ under



17 **19** **20**



a $Na_2S_2O_4$, $NaHCO_3$, $(C_{10}H_{21})_3NMe^+ Cl^-$ (PhH–H_2O, reflux);
b $NaBH_4$ (THF–MeOH, 5 °C);
c $NaBH_4$, $CeCl_3 \cdot 6H_2O$ (THF–MeOH, 5 °C).



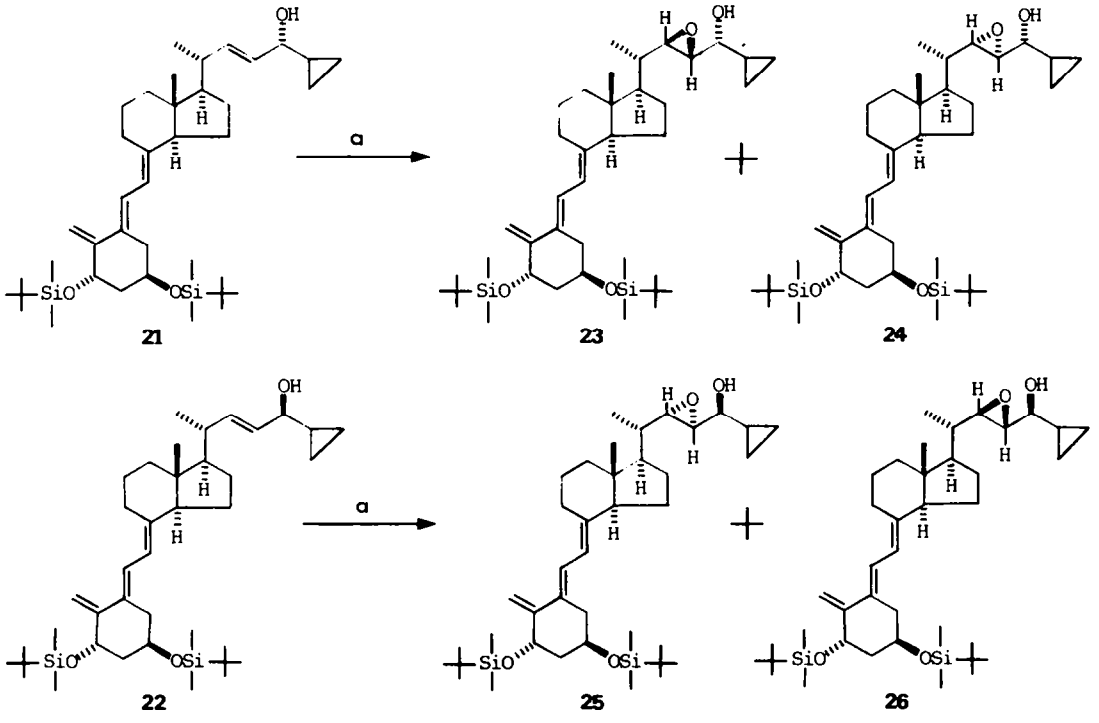
21 (less polar isomer)
22 (more polar isomer)

phase transfer conditions.[18] Further reduction of **19** with $NaBH_4$ in tetrahydrofuran–methanol then gave a mixture of alcohols (**20**), which was not resolvable on analytical HPLC.[19] Reduction of the enone (**17**) under similar conditions gave a TLC-resolvable mixture of the two C-24 epimeric allylic alcohols (**21** and **22**), together with some **20**, which ran on TLC with the less polar isomer (**21**), but was resolvable on analytical HPLC (ratio:- **20**, 13 : **21**, 48 : **22**, 39). Performing this reaction in the presence of an equivalent amount of $CeCl_3 \cdot 6H_2O$[20] reduced the proportion of side chain saturated

alcohols (20) to ca. 1% of the mixture, and this modification was used preparatively. Isolation of practically pure samples of **21** and **22** was achieved after chromatography and recrystallisation. The integrity of the (E)-configuration of Δ^{22} in **21** and **22** was confirmed by their reconversions to **17** by MnO_2 oxidation in dichloromethane. The configurations at C-24 were assigned on the basis of the results of epoxidation reactions of the side chain allylic alcohol moiety under Sharpless' "kinetic resolution" conditions.[21]

Sharpless' group has demonstrated[22] that for chiral secondary allylic alcohols,[23] the Katsuki and Sharpless[24] chiral oxidation system derived from a (+)-tartrate ester reacts faster with the S enantiomer* than with the R enantiomer (and vice versa), the faster reactions proceeding with high anti selectivity and the slower reactions proceeding with poor selectivity. These results reflect the combined effects of an enantiofacial discrimination of the (+)- or (-)-reagent on the one hand, and an anti selectivity for both on the other hand, which effects can either be consonant or dissonant. Thus, one of the enantiomers of the allylic alcohol was selectively removed from a mixture (the racemate) by allowing the reaction to proceed to the desired conversion.[22]

It was hoped that the diastereoisomeric allylic alcohols (**21** and **22**) could be regioselectively epoxidised under similar conditions and moreover that they would exhibit sufficiently different reaction rates to enable a clear comparison with Sharpless' experiments, and this proved to be the case. Thus, treatment of **21** and **22** with a deficiency (ca. 0.9 molar equiv.) of t-BuOOH in the presence of $Ti(OPr^i)_4$ (1.2 equiv.) and optically active diethyl tartrate (DET) (1.5 equiv.) in dichloromethane at -20°C resulted in clean partial conversion to two different pairs of more polar products. These four products each gave the UV-spectrum characteristic of the 5(E)-vitamin D conjugated triene system and (distinguishable) high field ^1H- and ^{13}C-NMR spectra consistent with the gross epoxy-alcohol structures **23** to **26**. The reaction courses of comparative experiments on mixtures of **21** and **22** with the (+)- or (-)-DET reagent were followed over several days by HPLC

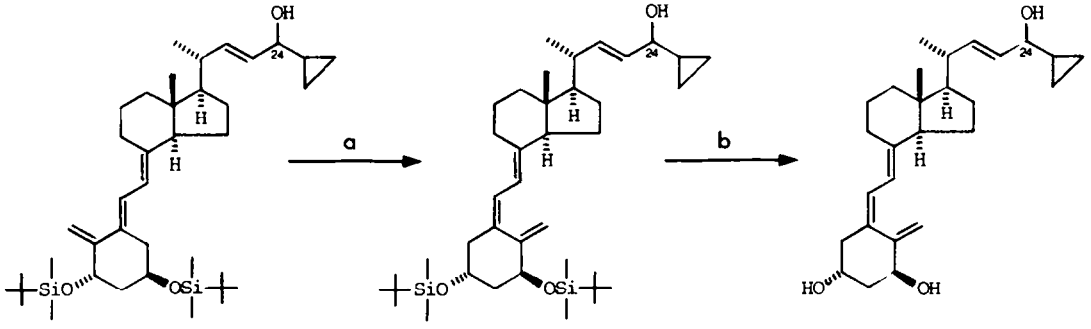


a t-BuOOH, $Ti(OPr^i)_4$, diethyl tartrate (CH_2Cl_2, -20 °C).

* Assignment of configuration here assumes the alkenyl group to have a higher priority than the (cyclo-) alkyl substituent of the carbinol, as is the case for **21** and **22**.

and showed (see Experimental) that: (i) the (-)-DET system reacted considerably faster with **21** than with **22**; (ii) the (+)-DET system reacted considerably faster with **22** than with **21**. From these observations, **21** is assigned the (24R) configuration and **22** the (24S) configuration by juxtaposition with Sharpless' results. Furthermore, in close correspondance with the model (see Note 23): (iii) the relatively fast reaction of **21** (with (-)-DET) gave almost exclusively (96:4) one of the two possible isomers, which is thus assigned the anti stereochemistry, **23**, while the slower reaction of **21** (with (+)-DET) gave a ca. 1:2 mixture of **23** and **24**; and (iv) the relatively fast reaction of **22** (with (+)-DET) gave almost exclusively (98:2) one of the two other possible isomers, also assigned the anti stereochemistry, **25**, while the slower reaction of **22** (with (-)-DET) gave a ca. 1:1 mixture of **25** and **26**.[25] (All these ratios were approximately constant over the observed reaction period).

It was therefore assumed[21] that the intermediate **22** would lead to the target compound having the required projection of the 24-hydroxyl group, as represented in 1,24(R)-$(OH)_2$-D_2 (**3**),[26] and this was supported by the observed greater biological activity of the target compound (**4**) derived from **22** than of that (**29**) derived from **21**. Thus, clean photoisomerisation[27] in toluene (using anthracene as triplet-sensitiser) of **21** and **22** to the oily (5Z)-vitamin derivatives **27** and **28**, respectively, followed by removal of the alcohol protective groups with tetrabutylammonium fluoride in tetrahydrofuran completed the syntheses of the crystalline 1α,24-dihydroxyvitamin D analogues **29** and **4**.



21 (24R)
22 (24S)

27 (24R)
28 (24S)

29 (24R)
4 (24S)

a Anthracene - hν (toluene, 20 °C); b n-Bu_4N^+ F^- (THF, 60 °C).

Compound **4** (which has been given our company code MC 903) mediates effects on cell proliferation and differentiation comparable to those of 1,25-$(OH)_2$-D_3 (**2**),[28] while **29** is at least 10 times less active.[29] In vivo studies in rats show that **4** is 100-200 times less potent than 1,25-$(OH)_2$-D_3 in its effects on calcium metabolism. The details of the biological testing will be published elsewhere.[28] MC 903 is currently undergoing clinical trials in the therapy of psoriasis.

EXPERIMENTAL

Melting points were determined with a Büchi-Tottoli apparatus and are uncorrected. UV spectra (λ) were measured for solutions in 96% EtOH on a Perkin-Elmer model Lambda 5 spectrophotometer. IR spectra (ν) were obtained on a Perkin Elmer model 783 spectrophotometer for KBr discs unless indicated otherwise ($CHCl_3$), in which case $CHCl_3$ solutions were employed. δ refers to ^{1}H-NMR spectra run at 100 MHz on a Jeol FX100 spectrometer unless otherwise stated. ^{13}C-NMR and high field ^{1}H-NMR were run on a Bruker AC-300 spectrometer. Samples were run in $CDCl_3$ solution using Me_4Si as internal standard. Coupling constants (J) are given in Hertz and are usually approximated to the nearest unit. Where assignments of signals are given, the numbering of carbon atoms is that used in the Discussion Section (see diagram 1), which may differ from that in the Titles. Mass spectra were run on a VG 7070S. It should be noted that the (6S) and (6R) series SO_2-adducts of vitamin D-type derivatives give the same mass spectra, which is that of the corresponding desulphonated compound.

Analytical TLC (to which R_f values refer) was performed on Merck plates pre-coated with silica gel 60 F_{254}. Analytical HPLC (to which T_R values refer) was performed on a Lichrosorb Si 60 column (25 cm x 4 mm) at a flow rate of 3 ml/min. Chromatography was performed on silica gel. In general, the separations were performed on a Waters Associates Prep LC/System 500A, but when a weight of silica gel is given, then this refers to flash chromatography using Merck Kieselgel 60. Organic solutions were dried over anhyd. $MgSO_4$. Petroleum ether refers to the fraction b.p. < 50°C. Reactions were performed routinely under a nitrogen atmosphere.

3(S)-(tert-Butyldimethylsilyloxy)-9,10-seco-ergosta-5,7(E),10(19),22(E)-tetraene (6S) (7a) and (6R) (7b) SO_2-adducts. Vitamin D_2 (12.5 g, 31.5 mmol) was dissolved in liquid SO_2 (50 ml). The solution was stirred under reflux for 30 min. The SO_2 was distilled off, and the residue was dried in vacuo to give a mixture of the known[13a] vitamin D_2 (6S) and (6R) SO_2-adducts (6) as a foam. This was dissolved in DMF (100 ml), and imidazole (4.5 g, 66 mmol) and TBDMS chloride (5.0 g, 33 mmol) were added. The mixture was stirred at 20°C for 90 min and then partitioned between EtOAc (500 ml) and water (200 ml). The organic layer was washed twice with water and brine, dried and concentrated to give a crude product which was separated by chromatography (30% ether in petroleum ether as eluant) to give the (6S) SO_2-adduct (7a), less polar isomer, as needles (9.4 g, 52%), m.p. 117-118°C dec. (from CH_2Cl_2-EtOH) (Found: C, 70.96; H, 10.15; S, 5.54. $C_{34}H_{58}O_3SSi$ requires C, 71.02; H, 10.17; S, 5.58%); δ 0.06 (6 H, s), 0.67 (3 H, s), 0.88 (9 H, s), 1.03 (3 H, d, J 7), 3.64 (2 H, broad s), 4.0 (1 H, m), 4.4-4.8 (2 H, 2 broad d, J 10) and 5.2 (2 H, m); m/z 510 (M^+ - SO_2, 40), 495 (2), 453 (10), 385 (3), 378 (8), 253 (26), 251 (12), 193 (50), 119 (100), and 118 (46%), and the (6R) SO_2-adduct (7b), more polar isomer, as needles (7.7 g, 42%), m.p. 121-122°C dec. (from CH_2Cl_2-EtOH) (Found: C, 70.99; H, 10.20; S, 5.52. $C_{34}H_{58}O_3SSi$ requires C, 71.02; H, 10.17; S, 5.58%); δ 0.06 (6 H, s), 0.58 (3 H, s), 0.88 (9 H, s), 1.03 (3 H, d, J 7), 3.65 (2 H, broad s), 3.95 (1 H, m), 4.5-4.9 (2 H, 2 broad d, J 10), and 5.2 (2 H, m); m/z 510 (M^+ - SO_2) and 119.

1(S),3(R)-Bis(tert-butyldimethylsilyloxy)-9,10-seco-ergosta-5(E),7(E),10(19),22(E)-tetraene (11) and 1(R),3(R)-bis(tert-butyldimethylsilyloxy)-1,10-seco-ergosta-5(E),7(E),10(19),22(E)-tetraene (12). The (6S) (7a) or (6R) (7b) SO_2-adduct, or a mixture of these, (16.4 g, 28.5 mmol) was suspended in 96% ethanol (250 ml) and sodium hydrogen carbonate (20 g) was added. The stirred mixture was heated under reflux for 90 min, cooled, partially concentrated in vacuo, and partitioned between ethyl acetate and water. The organic layer was washed consecutively with water and brine, dried and concentrated to give the known[12] (5E)-vitamin D_2 TBDMS ether (8) as an oil. This was dissolved in a solution of N-methylmorpholine N-oxide in CH_2Cl_2, which had been prepared by drying (30 min over $MgSO_4$) a solution containing N-methylmorpholine N-oxide monohydrate (16 g, 119 mmol) in CH_2Cl_2 (160 ml) and filtering. The stirred solution was heated under reflux, and a solution of selenium dioxide (3.0 g, 27 mmol) in methanol (160 ml) was added rapidly. Heating under reflux was continued for 50 min before the reaction mixture was cooled, diluted with more dichloromethane, washed consecutively with water and brine, dried and concentrated to give a mixture of the known[12] (1S)- (9) and (1R)- (10) hydroxy-5(E)-vitamin D_2 TBDMS ethers as an orange foam of sufficient purity for use in the next stage. Analytical HPLC (1% EtOAc in hexane as eluant; detector wavelength 270 nm) showed the product to contain 9, T_R 9.5 min, and 10, T_R 7.2 min, in a 6:1 proportion. The product was dissolved in DMF (80 ml), and imidazole (4.3 g, 63 mmol) and TBDMS chloride (5.1 g, 34 mmol) were added. The mixture was stirred at 20°C for 90 min and then partitioned between EtOAc (450 ml) and water (200 ml). The EtOAc layer was washed twice with water and brine, dried and concentrated to give a crystalline solid which was purified by filtration through silica gel (200 g) (eluting with 1% ether in petroleum ether) followed by recrystallisation from Et_2O-EtOH to give the (1S)-bis-TBDMS ether (11), less polar isomer, as needles (5.7 g), m.p. 113-114°C (Found: C, 75.04; H, 11.33; $C_{40}H_{72}O_2Si_2$ requires C, 74.93; H, 11.32%); λ_{max} 270 nm (ε 25900); δ 0.07 (12 H, s), 0.57 (3 H, s), 0.88 (9 H, s), 0.91 (9 H, s), 1.03 (3 H, d, J 7), 4.22 (1 H, m), 4.54 (1 H, dd, J 5 and 9), 4.97 (2 H, m), 5.20 (2 H, m), 5.82 (1 H, d, J 11), and 6.47 (1 H, d, J 11); m/z 640 (M^+, 12), 625 (2), 583 (5), 515 (2), 508 (49), 451 (6), 383 (10), 379 (5), 355 (3), and 248 (100%). The mother liquor from the recrystallisation of 11 was concentrated and purified by chromatography (1% ether in petroleum ether as eluant) to give the (1R)-isomer (12) (1.2 g, 7%) as an oil/foam, λ_{max} 269 nm (ε 22000); δ 0.08 (12 H, s), 0.59 (3 H, s), 0.90 and 0.93 (each 9 H, s), 1.03 (3 H, d, J 7), 3.68 and 4.05 (each 1 H, m), 5.04 and 5.20 (each 2 H, m), 5.84 and 6.52 (each 1 H, d, J 11); m/z 640 (M^+) and 248, and an additional 1.2 g (after recrystallisation, as above) 11 (total yield 6.8 g, 37% from 7).

1(S),3(R)-Bis(tert-butyldimethylsilyloxy)-9,10-seco-ergosta-5,7(E),10(19),22(E)-tetraene (6S) (13a) and (6R) (13b) SO_2-adducts. The bis-TBDMS ether (11) (4.0 g, 6.2 mmol) was dissolved in Et_2O (10 ml) and liquid SO_2 (50 ml) and the mixture was stirred under reflux for 30 min. The SO_2 and ether were distilled off, and the residue was dried in vacuo to give white needles (4.4 g, 100%), showing two spots on TLC (10% Et_2O in petroleum ether as eluant) corresponding to 13a (R_f ca. 0.25) and 13b (R_f ca. 0.1) (Found: C, 67.97; H, 10.26; S, 4.37. $C_{40}H_{72}O_4S\,Si_2$ requires C, 68.12; H, 10.29; S, 4.55%); δ 0.57 and 0.66 (2 s; relative heights, 1:3.3). Separation by chromatography (eluting with 20% Et_2O in petroleum ether) gave the (6S) SO_2-adduct (13a) as needles, m.p. 107-109°C dec. (from Et_2O-MeOH) (Found: C, 67.89; H, 10.24 ; S, 4.35. $C_{40}H_{72}O_4S\,Si_2$ requires C, 68.12; H, 10.29; S, 4.55%); ν_{max} ($CHCl_3$) 1310 and 1160 cm^{-1}; δ 0.06 (12 H, br s), 0.66 (3 H, s), 0.87 (9 H, s), 0.89 (9 H, s), 1.02 (3 H, d, J 7), 3.45-4.1 (2 H, br ABq, J 16), 4.20 (1 H, m), 4.35 (1 H, m), 4.67 (2 H, m), and 5.19 (2 H, m), and the (6R) SO_2-adduct (13b) as an oil; ν_{max} ($CHCl_3$) 1310 and 1160 cm^{-1}; δ 0.06 (12 H, br s), 0.57 (3 H, s), 0.87 and 0.89 (each 9 H, s), 1.02 (3 H, d, J 7), 3.45-4.1 (2 H, br ABq, J 16), 4.15 (1 H, m), 4.4 (1 H, m), 4.5-4.95 (2 H, 2 br d, J 10).

1(S),3(R)-Bis(tert-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5,7(E),10(19)-triene (6S) SO_2-adduct (14a). The (6S) SO_2-adduct (13a) (4.4 g, 6.2 mmol) was dissolved in CH_2Cl_2 (120 ml) and MeOH (40 ml). The stirred solution was cooled to -65°C and treated with ozonised oxygen until TLC showed essentially complete consumption of starting material (ca. 40 min). The solution was then purged with N_2, and PPh_3 (2.5 g, 9.5 mmol) was added. After warming slowly to 0°C, the reaction mixture was diluted with more CH_2Cl_2, washed consecutively with 5% $NaHCO_3$ solution, water, and brine, and dried and concentrated. The residue was purified by chromatography (30% ether in petroleum ether as eluant) to give the aldehyde (14a) as needles (3.2 g, 81%), m.p.

122-124°C dec. (Found: C, 64.33; H, 9.59; S, 4.87. $C_{34}H_{60}O_5S\,Si_2$ requires C, 61.10; H, 9.49, S, 5.03%); ν_{max} ($CHCl_3$) 1720, 1310 and 1160 cm^{-1}; δ 0.06 (12 H, br s), 0.70 (3 H, s), 0.87 and 0.88 (18 H, 2 s), 1.13 (3 H, d, J 7), 3.45-4.1 (2 H, br AB q, J 16), 4.20 (1 H, m), 4.35 (1 H, m), 4.70 (2 H, m), and 9.58 (1 H, d, J 3). [N.B. The use of the (6R) SO_2-adduct (13b) as starting material in this preparation gives the aldehyde (14b), more polar isomer, in the same yield, as an oil: ν_{max} ($CHCl_3$) 1720, 1310 and 1160 cm^{-1}; δ 0.07 (12 H, br s), 0.61 (3 H, s), 0.88 and 0.89 (18 H, 2 s), 1.14 (3 H, d, J 7), 3.45-4.1 (2 H, br AB q, J 16), 4.15 (1 H, m), 4.4 (1 H, m), 4.5-4.95 (2 H, 2 br d, J 10), and 9.57 (1 H, d, J 3)]

1(S),3(R)-Bis-(tert-butyldimethylsilyloxy)-20(S)-formyl-9,10-secopregna-5(E),7(E),10(19)-triene (15). The aldehydes (14) (14.3 g, 22 mmol) were suspended in ethanol (300 ml) and $NaHCO_3$ (14 g) added. The stirred mixture was heated under reflux for 90 min, cooled, partially concentrated in vacuo, and partitioned between EtOAc (350 ml) and water (200 ml). The organic layer was washed with water and brine, dried, and concentrated to give a crystalline product (12.6 g) which was used as such in the next step. Analytical HPLC (1% EtOAc in hexanes as eluant; detector wavelength 270 nm) showed the product to contain the aldehyde (15) (90%), T_R 4.8 min, and its (20R) epimer (16) (5%), T_R 4.1 min, and these were separated from a sample by chromatography (5% Et_2O in petroleum ether as eluant): 15, needles, m.p. 113-115°C (from EtOH) (Found: C, 71.16; H, 10.54. $C_{34}H_{60}O_3\,Si_2$ requires C, 71.27; H, 10.55%); λ_{max} 270 nm (ϵ 26700); ν_{max} ($CHCl_3$) 1720 cm^{-1}; δ 0.08 (12 H, s), 0.61 (3 H, s), 0.88 and 0.92 (18 H, 2 s), 1.16 (3 H, d, J 7 Hz), 4.20 (1 H, m), 4.50 (1 H, m), 4.98 (2 H, m), 5.85 (1 H, d, J 11 Hz), 6.46 (1 H, d, J 11 Hz), and 9.60 (1 H, d, J 3 Hz); m/z 572 (M^+, 21), 558 (4), 515 (14), 440 (80), 383 (26), 379 (7), 355 (3), and 248 (100%). 16: δ 0.06 (12 H, s), 0.55 (3 H, s), 0.86 and 0.90 (each 9 H, s), 1.05 (3 H, d, J 7), 4.21 (1 H, m), 4.5 (1 H, m), 4.95 (2 H, m), 5.82 and 6.44 (each 1 H, d, J 11), and 9.55 (1 H, d, J 5); m/z 572 (M^+) and 248.

Cyclopropylcarbonylmethylenetriphenylphosphorane (I).

A. Bromoacetylcyclopropane. To a stirred, ice-cooled solution of cyclopropyl methyl ketone (21 g, 0.25 mol) in methanol (150 ml) was added bromine (40 g, 0.25 mol). The reaction was allowed to proceed (decolourisation) below 10°C. Stirring was then continued at room temperature for 30 min before water (75 ml) was added. After a further 15 min the mixture was diluted with water (225 ml) and extracted four times with Et_2O. The ether extracts were washed with 10% Na_2CO_3 solution, water, brine, and dried. After removing the solvent in vacuo, the residue was distilled to give bromoacetylcyclopropane (35.5 g, 87%), b.p. 71-73°C/13 mmHg; δ 0.9-1.3 (4 H, m), 2.05-2.35 (1 H, m), and 4.02 (2 H, s).

B. Cyclopropylcarbonylmethyltriphenylphosphonium bromide. Bromoacetylcyclopropane (27.1 g, 0.17 mol) and triphenylphosphine (43.5 g, 0.17 mol) were mixed and allowed to react spontaneously (exothermic reaction). The resulting solid cake was dissolved in CH_2Cl_2 (200 ml) (with warming) and treated with Et_2O (300 ml) to precipitate the phosphonium bromide as colourless needles (59.1 g, 84%), m.p. 214-215°C (Found: C, 64.81; H, 5.26. $C_{23}H_{22}OBrP$ requires C, 64.95; H, 5.21%); δ 1.02 (4 H, m), 2.75 (1 H, m), 5.89 (2 H, d, J 12), and 7.45-8.0 (15 H, m).

C. Cyclopropylcarbonylmethylenetriphenylphosphorane (I). The phosphonium bromide from B (67 g, 158 mmol) was dissolved in CH_2Cl_2 (900 ml), and the solution was extracted with sodium hydroxide solution (2 N, 900 ml). The organic layer was washed with brine, dried and concentrated in vacuo to give a product which was purified by recrystallisation from dichloromethane-acetone to give the phosphorane (I) as needles (46.6 g, 86%), m.p. 181-182°C (Found: C, 79.99; H, 6.24; $C_{23}H_{21}OP$ requires C, 80.22; H, 6.15%); δ 0.60 (2 H, m), 0.85 (2 H, m), 1.75 (1 H, m), 3.77 (1 H, br d, J 26) and 7.1-7.8 (15 H, m).

[20(R) (17) and 20(S) (18)] 1(S),3(R)-Bis(tert-butyldimethylsilyloxy)-20-(3'-cyclopropyl-3'-oxyprop-1'(E)-enyl)-9,10-secopregna-5(E),7(E),10(19)-triene. A stirred solution of the aldehyde mixture 15/16 (10.5 g) from the SO_2-extrusion step and the phosphorane I (15 g, 44 mmol) in dimethyl sulphoxide (60 ml) was heated at 105°C for 4 h. After cooling, the reaction solution was partitioned between EtOAc (250 ml) and water (200 ml). The ethyl acetate layer was washed twice with water and brine, dried, and concentrated in vacuo to give a residue which was purified by chromatography (10% ether in petroleum ether as eluant) and recrystallisation to give the 20(R) enone (17), more polar isomer, as needles, m.p. 123-124°C (from Et_2O-MeOH) (7.51 g, 63% from 14) (Found: C, 73.24; H, 10.48. $C_{39}H_{66}O_3Si_2$ requires C, 73.29; H, 10.41%); λ_{max} 230 and 270 (ϵ 21200 and 26800); ν_{max} 1687, 1668 and 1626 cm^{-1}; δ 0.06 (12 H, s), 0.59 (3 H, s), 0.87 and 0.90 (each 9 H, s), 1.13 (3 H, d, J 7), 4.2 (1 H, m), 4.5 (1 H, m), 4.96 (2 H, m), 5.8 (1 H, d, J 11 Hz), 6.14 (1 H, d, J 16 Hz), 6.45 (1 H, d, J 11 Hz), and 6.78 (1 H, dd, J 9 and 16 Hz); m/z 638 (M^+, 10), 623 (2), 581 (7), 506 (54), 449 (8), 383 (6), 379 (10), 355 (2), and 248 (100%). The mother liquor was concentrated and rechromatographed and the fractions containing the less polar isomer combined with those from the first column to give the 20(S) enone (18) (0.45 g, 4% from 14), needles, m.p. 97-99°C (from Et_2O-MeOH) (Found: C, 73.26, H, 10.38. $C_{39}H_{66}O_3Si_2$ requires C, 73.29; H, 10.41%); λ_{max} 230 and 269 nm (ϵ 20500 and 26400); ν_{max} 1686, 1667 and 1625 cm^{-1}; δ 0.06 (12 H, s), 0.52 (3 H, s), 0.87 and 0.90 (each 9 H, s), 1.03 (3 H, d, J 7), 4.2 (1 H, m), 4.5 (1 H, m), 4.96 (2 H, m), 5.80 (1 H, d, J 11), 6.14 (1 H, d,J 16), 6.45 (1 H, d, J 11) and 6.81 (1 H, dd, J 9 and 16); m/z 638 (M^+) and 248.

1(S),3(R)-Bis(tert-butyldimethylsilyloxy)-20(R)-(3'-cyclopropyl-3'-oxopropyl)-9,10-secopregna-5(E),7(E),10(19)-triene (19). A mixture of the enone (17) (200 mg, 0.3 mmol), $NaHCO_3$ (0.5 g), sodium dithionite ($Na_2S_2O_4$) (0.5 g), and methyltridecylammonium chloride (0.05 g) in benzene (10 ml) and water (10 ml) was stirred vigorously under reflux for 90 min. After cooling, the reaction mixture was partitioned between Et_2O and water, and the organic layer was washed with water, dried and concentrated in vacuo. The residue was purified by chromatography (silica gel, 30 g ; 5% Et_2O in petroleum ether) to give the ketone (19) (144 mg, 72%) as colourless plates, m.p. 93-94°C (from ether-methanol) (Found: C, 73.07; H, 10.70, $C_{39}H_{68}O_3\,Si_2$ requires C, 73.06; H, 10.69%); ν_{max} (KBr) 1700 cm^{-1}; δ 0.06 (12 H, s), 0.55 (3 H, s), 0.87 and 0.90 (each 9 H, s), 4.2 (1 H, m), 4.5 (1 H, m), 4.96 (2 H, m), 5.82 (1 H, d, J 11) and 6.45 (1 H, d, J 11); m/z 640 (M^+, 7), 625 (2), 583 (3), 508 (36), 451 (6), 383 (3), 379 (5), 355 (3), and 248 (100%); λ_{max} 270 nm (ϵ 24900).

1(S),3(R)-Bis(tert-butyldimethylsilyloxy)-20(R)-(3'ξ-cyclopropyl-3'-hydroxypropyl)-9,10-secopregna-5(E),7(E),-10(19)-triene (20). An ice-cooled, stirred solution of the ketone (19) (225 mg, 0.35 mmol) in tetrahydrofuran (3 ml) was diluted with methanol (8 ml) and treated with $NaBH_4$ (140 mg) portionwise over 5 min. After a further 10 min, the reaction mixture was partitioned between ethyl acetate (30 ml) and water (30 ml), and the organic layer was washed with water, dried, and concentrated in vacuo to give the side chain saturated alcohols (20) as a gum (0.22 g, 99%); λ_{max} 270 nm; δ 0.06 (12 H, s), 0.15-0.65 (4 H, m), 0.55 (3 H, s), 0.86 and 0.90 (each 9 H, s), 4.2 (1 H, m), 4.55 (1 H, m), 4.96 (2 H, m), 5.81 (1 H, d, J 11.5) and 6.46 (1 H, d, J 11.5); δ_C (75.5 MHz) -5.1 and -4.9 ($SiCH_3$'s); 2.0, 2.3, 2.5 and 2.7 (C-26,27); 11.9 (C-18); 17.8, 17.9 and 18.1 (C-25 and $SiC(CH_3)_3$'s); 18.6 and 18.7 (C-21); 22.1 (C-11); 23.4 (C-15); 25.7 ($CH(CH_3)_3$'s); 27.5 (C-16), 28.8 (C-9); 31.5 and 31.6 (C-23); 33.5 and 33.7 (C-22); 35.8 and 36.0 (C-20); 36.4 (C-4), 40.4 (C-12), 43.8 (C-2), 45.7 (C-13), 56.3 (C-17), 56.3 (C-14), 67.1 (C-3), 70.1 (C-1), 77.0 and 77.2 (C-24), 106.4 (C-19), 116.3 (C-7), 121.6 (C-6), 135.2 (C-5), 143.1 (C-8) and 153.5 (C-10). (See Note 19.)

3'(R) (21) and 3'(S) (22) 1(S),3(R)-Bis(tert-butyldimethylsilyloxy)-20(R)-(3'-cyclopropyl-3'-hydroxyprop-1'(E)-enyl)-9,10-secopregna-5(E),7(E),10(19)-triene. An ice-cooled, stirred solution of the enone (17) (4.31 g, 6.74 mmol) in tetrahydrofuran (8 ml) was diluted with 0.4 M $CeCl_3.6H_2O$ in methanol (18 ml) and further with methanol (9 ml), and treated with sodium borohydride (0.50 g), portionwise over 5 min. After a further 10 min, the reaction mixture was partitioned between EtOAc (250 ml) and water (200 ml) and the organic layer was washed with water (100 ml), dried, and concentrated in vacuo. HPLC analysis (using 4% EtOAc in hexanes as eluant; detector wavelength 270 nm) showed the product to be a mixture of the allylic alcohols (21) and (22) and the side chain saturated alcohols (20) described above (T_R ca. 10, 12, and 8 min, respectively) in the proportions 61:38:1 . Purification by chromatography (10% ethyl acetate in petroleum ether as eluant) gave the 3'(R) allylic alcohol (21), less polar isomer, (2.37 g, 55%) as needles, m.p. 117-118°C (from petroleum ether-MeOH) (Found: C,72.73; H,10.74. $C_{39}H_{68}O_3Si_2$ requires: C, 73.06; H,10.69%); λ_{max} 270 (ε 25000); δ 0.06 (12 H, s), 0.15-0.65 (4 H, m), 0.57 (3 H, s), 0.87 and 0.90 (18 H, 2 s), 1.05 (3 H, d, J 7 Hz), 3.45 (1 H, m), 4.2 (1 H, m), 4.55 (1 H, m), 4.96 (2 H, m), 5.51 (2 H, m), 5.82 (1 H, d, J 11 Hz) and 6.47 (1 H, d, J 11 Hz); m/z 640 (M^+, 6), 625 (1), 623 (1), 583 (2), 508 (29), 493 (1), 490 (2), 451 (3), 383 (6), 379 (5), 355 (2), and 248 (100%), and the 3'(S) allylic alcohol (22) (1.42 g, 33 %) as needles, m.p. 122-123°C (from petroleum ether-MeOH) (Found: C,72.22; H,10.65. $C_{39}H_{68}O_3Si_2$ requires: C,73.06; H,10.69%); λ_{max} 270 (ε 24100); δ 0.06 (12 H, s), 0.15-0.65 (4 H, m), 0.57 (3 H, s), 0.87 and 0.90 (18 H, 2 s), 1.05 (3 H, d, J 7 Hz), 3.45 (1 H, m), 4.2 (1 H, m), 4.55 (1 H, m), 4.96 (2 H, m), 5.47 (2 H, m), 5.82 (1 H, d, J 11 Hz) and 6.47 (1 H, d, J 11 Hz); m/z 640 (M^+) and 248.

Epoxidation of 21 and 22 under Sharpless' kinetic resolution conditions: [1'(R),2'(R),3'(R) (23), 1'(S), 2'(S) ,3'(R) (24), 1'(S),2'(S),3'(S) (25), and 1'(R), 2'(R) ,3'(S) (26)] 1(S),3(R)-(3'-cyclopropyl-1',2'-epoxy-3'-hydroxypropyl)-9,10-secopregna-5(E),7(E),10(19)-triene. Four parallel experiments were performed as follows:- $Ti(OPr^i)_4$ (0.28 g, 1 mmol, 1.2 eq.) was weighed into a dry flask which was then sealed with a septum cap. After establishing an N_2 atmosphere, the following liquids were injected sequentially at -20°C:(i) optically active diethyl tartrate (DET) (0.25 g, 1.2 mmol, 1.5 eq.) in CH_2Cl_2 (7 ml); (ii) a mixture (see t=0 HPLC analysis below) of 21 and 22 (0.52 g, 0.81 mmol, 1 eq.) in CH_2Cl_2 (3 ml); (iii) azeotropically dried[22] t-BuOOH (1.6 ml, 0.45 M, 0.72 mmol, 0.9 eq.) in $(CH_2Cl)_2$, the latter being added after a 15 min interval. The reaction solution was then maintained at ca. -20°C (in a freezer, between examinations). At intervals, an aliquot (20 μl) was withdrawn and quenched by partitioning between water (2 ml) and hexane (1ml) at 20°C, and the hexane phase analysed directly by HPLC (4% EtOAc in hexanes as eluant; detector 270 nm). The results were as follows: [Normalised ratios (± 1%) of components 21-26 (the components being given in that order); T_R: 21, 10; 22, 12; 23, 25; 24, 31; 25, 23; 26, 34 min (reaction time in hours)] : Expt 1 [(+)-DET] 48:52:0:0:0:0 (0; starting mixture); 27:0: [7] :14: [53] :1 (96); Expt 2 [(+)-DET] 97:3:0:0:0:0 (0); 90:2:2:5:1:0 (4) ; 66:0:9:22:3:0 (36); 35:0:20: [42] :3:0 (120). Expt 3 [(-)-DET] 97:3:0:0:0:0 (0); 49:3:46:2:0:0 (4); 16:3:78:3:0:0 (36); 10:3: [84] : 3:0:0 (120). Expt 4 [(-)-DET] 6:94:0:0:0:0 (0); 0:31:6:0:32: [31] (72). Thus, 21 is removed selectively from either a 97:3 (Expt 3) or a 6:94 (Expt 4) mixture of 21 and 22, showing that (-)-DET reagent reacts faster with 21 than with 22. Similarly, 22 is removed selectively from a ca. 1:1 (Expt 1) [or a 97:3 (Expt2)] mixture of 21 and 22, showing the (+)-DET reagent reacts faster with 22 than with 21. After the last examination the reaction mixture was quenched by partitioning between 5% $NaHCO_3$ solution (20 ml) and EtOAc (50 ml) at 20°C. The mixture was filtered and the organic layer was washed with brine, dried and concentrated to give a residue which was purified by chromatography (silica gel, 100 g, 20% EtOAc in petroleum ether as eluant) to give an oily product [23+25, 137 mg / 24, 147 mg / 23, 276 mg / 26, 85 mg, respectively from Expts 1-4] corresponding to the HPLC peak(s) indicated above in a box in the final HPLC analysis. Thus, the four expts gave each a different isomer, except for Expt 1 which gave a ca. 1:1 mixture of 23 and 25, since these were not separable preparatively. The NMR data obtained (except for Expt 1) did not show any cross-contamination. 23/24/25/26; λ_{max} 270 nm; δ_C (75.5 MHz; common values ± 0.1 p.p.m.; values outside this range are given in the order 23-26 unless otherwise stated) -5.1 and -5.0 ($SiCH_3$'s); 1.5/1.5/1.3/2.0 (C-26); 2.4/2.3/2.0/2.3 (C-27); 12.0 (C-18); 13.4 (23, 25)/14.4 (24, 26) (C-25); 17.0 (23, 26)/15.8 (24, 25) (C-21); 17.9 and 18.0 ($CH(CH_3)_3$'s); 22.2 (C-11); 23.2 (C-15); 25.7 ($CH(CH_3)_3$'s); 26.7 (23, 26)/26.1 (24, 25) (C-16); 28.8 (C-9); 36.4 (C-4); 39.1 (23, 26)/38.0 (24, 25) (C-20); 40.2 (C-12); 43.8 (C-2); 46.0 (C-13); 54.0 (23, 26)/56.2 (24, 25) (C-17); 55.8 (C-14); 59.9/59.2/58.1/61.4 (C-23); 62.1/61.4/59.4/63.0 (C-22); 67.0 (C-3); 70.1 (C-1); 73.6/75.4/72.8/74.7 (C-24); 106.4 ± 0.2 (C-19); 116.5 (C-7); 121.4 (C-6); 135.5 (C-5); 142.5 (C-8); 153.4 (C-10). δ_H (300 MHz) 23: 0.06 and 0.07 (12 H, 2 s, $SiCH_3$'s), 0.30 - 0.45 (4 H, 2 m, 26-H_2 and 27-H_2), 0.55 (3 H, s, 18-H_3), 0.61 (1 H, m, 25-H), 0.87 and 0.90 (each 9 H, s, $CH(CH_3)_3$), 1.14 (3 H, d, J 6.4, 21-H_3), 2.32 (1 H, br d, J 13.9, 4β-H), 2.55 (1 H, dd, J 5.2 and 13.9, 4α-H), 2.81 (1 H, dd, J 2.0 and 8.4,22-H), 2.90 (1 H, br d, J 11.9, 9β-H), 3.04-3.13 (2 H, m, 23-H, 24-H), 4.22 (1 H, m, 3-H), 4.54 (1 H, dd, J 4.3 and 9.0, 1-H), 4.95 and 4.99 (each 1 H, m, 19-H_2), 5.83 (1 H, d, J 11.3, 7-H), and 6.46 (1 H, d, J 11.3, 6-H). The corresponding signals for the other isomers are as follows (only non-identical patterns and/or J values given):- 24: 0.05 and 0.06, 0.20 - 0.35, 0.53 (18-H_3), 0.55, 0.85 and 0.89, 1.00 (d, J 6.6, 21-H_3), 2.27, 2.57, 2.71-2.91 [4 H, including 2.74 (dd, J 1.9

and 7.4, 22-H), 2.86 (9β-H), and 23-H, 24-H], 4.21, 4.53, 4.94 and 4.97, 5.83 and 6.46. 25: 0.06 and 0.07, 0.28 - 0.46, 0.55 (18-H_3), 0.58, 0.86 and 0.90, 1.02 (d, J 6.7, 21-H_3), 2.29, 2.58, 2.84 - 2.94 (3 H, m), 3.14 (1 H, m), 4.22, 4.54, 4.95 and 4.99, 5.85, and 6.46. 26: 0.06 and 0.07, 0.25 - 0.45, 0.55, 0.58, 0.87 and 0.90, 1.13 (d, J 6.4, 21-H_3), 2.32, 2.55,2.68 (22-H), 2.84 - 2.94 (2 H, m, 9-βH and 23-H), 3.02 (1 H, dd, J 2.3 and 4.4, 24-H), 4.22, 4.54, 4.95 and 4.99, 5.83, and 6.46.

1(S),3(R)-Bis(tert-butyldimethylsilyloxy)-20(R)-(3'(R)-cyclopropyl-3'-hydroxyprop-1'(E)-enyl)-9,10-secopregna--5(Z),7(E), 10(19)-triene (27). A solution of the alcohol (21) (1.00 g, 1.56 mmol), anthracene (170 mg), and triethylamine (1 drop) in toluene (75 ml) in a pyrex flask was irradiated with light from a high pressure ultraviolet lamp, type TQ 718Z2 (Hanau) at 20°C for 60 min. The solution was filtered, concentrated in vacuo and the residue purified by chromatography (15% ethyl acetate in petroleum ether as eluant) to give the (5Z)-vitamin derivative (27) as an oil/foam (886 mg, 89 %); λ_{max} 264 nm; δ 0.06 (12 H, s), 0.15-0.65 (4 H, m), 0.55 (3 H, s), 0.88 (18 H, s), 1.05 (3 H, d, J 7), 3.5 (1 H, m), 4.2 (1 H, m), 4.35 (1 H, m), 4.85 (1 H, m), 5.17 (1 H, m), 5.50 (2 H, m), 5.99 (1 H, d, J 12) and 6.24 (1 H, d, J 12), m/z 640 (M^+, 7), 625 (1), 623 (2), 583 (1), 508 (34), 493 (2), 490 (7), 451 (3), 383 (4), 379 (5), 355 (5), and 248 (100%).

1(S),3(R)-Bis(tert-butyldimethylsilyloxy)-20(R)-(3'(S)-cyclopropyl-3'-hydroxyprop-1'(E)-enyl)-9,10-secopregna--5(Z),7(E),10(19)-triene (28). The use of the alcohol (22) (1.13 g, 1.76 mmol) as starting material instead of 21 in the preceding preparation gave the (5Z)-vitamin derivative (28) as an oil/foam (1.04 g, 92 %); λ_{max} 264 nm; δ 0.06 (12 H, s), 0.15-0.65 (4 H, m), 0.55 (3 H, s), 0.88 (18 H, s), 1.05 (3 H, d, J 7), 3.45 (1 H, m), 4.2 (1 H, m), 4.35 (1 H, m), 4.85 (1 H, m), 5.17 (1 H, m), 5.46 (2 H, m), 5.99 and 6.24 (each 1 H, d, J 12); m/z 640.462 (M^+, 7; $C_{39}H_{68}O_3Si_2$ requires 640.471), 248 (100%).

20(R)-(3'(R)-Cyclopropyl-3'-hydroxyprop-1'(E)-enyl)-1(S),3(R)-dihydroxy-9,10-secopregna-5(Z),7(E),10(19)-triene (29). A solution of 27 (886 mg,1.38 mmol) and tetrabutylammonium fluoride (2.1 g, 6.7 mmol) in tetrahydrofuran (40 ml) was heated at 60°C for 50 min. After cooling, the reaction solution was partitioned between EtOAc (150 ml) and 2% $NaHCO_3$ solution (100 ml), and the organic layer was washed with water and brine, dried and concentrated. The residue was purified by chromatography (silica gel, 50 g; EtOAc as eluant) to give the vitamin D analogue (29) (408 mg, 72 %) as needles, m.p. 143-145°C (from Et_2O-hexanes) (Found: C, 78.22; H, 9.86. $C_{27}H_{40}O_3$ requires C, 78.60; H, 9.77%); λ_{max} 264 nm (ε 17000); δ 0.15-0.65 (4 H, m), 0.56 (3 H, s), 0.75-1.1 (1 H, m), 1.05 (3 H, d, J 7 Hz), 3.47, (1 H, m), 4.2 (1 H, m), 4.4 (1 H, m), 4.99 (1 H, m), 5.31 (1 H, m), 5.50 (2 H, m), 5.99 and 6.36 (each 1 H, d, J 11); m/z 412 (M^+, 5), 394 (8), 379 (1), 376 (5), 287 (5), 285 (6), 283 (7), 269 (10), 267 (5), 265 (4), 251 (10), 152 (27) and 134 (100%).

20(R)-(3'-(S)-Cyclopropyl-3'-hydroxyprop-1'(E)-enyl)-1(S),3(R)-dihydroxy-9,10-secopregna-5(Z),7(E),10(19)-triene (MC 903, 4). The use of 28 (1.03 g, 1.61 mmol) as starting material instead of 27 in the preceding preparation gave MC 903 (4) (483 mg, 73 %), m.p. 166-168°C (from methyl formate) (Found: C, 78.30; H, 9.85. $C_{27}H_{40}O_3$ requires C, 78.60; H, 9.77%); λ_{max} 264 (ε 17200); δ 0.15-0.65 (4 H, m), 0.56 (3 H, s), 0.75-1.1 (1 H, m), 1.05 (3 H, d, J 7 Hz), 3.45 (1 H, m), 4.2 (1 H, m), 4.4 (1 H, m), 4.99 (1 H, m), 5.31 (1 H, m), 5.47 (2 H, m), 5.99 (1 H, d, J 11 Hz), and 6.36 (1 H, d, J 11 Hz); m/z 412 (M^+, 6), 394 (8), 379 (2), 376 (5), 287 (5), 285 (7), 283 (8), 269 (11), 267 (6), 265 (4), 251 (12), 152 (26), and 134 (100%).

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14. In the absence of base, no **15** or **16** is isolated. (Cf. the discussion of corresponding reactions in the 1-desoxy series in ref. 10.)
15. The presence of detectable amounts of "unnatural" (20R) epimer already in the samples of **14a** or **14b** was excluded by comparison with the mixture of (20R) SO_2-adducts prepared from an isolated sample of **16**, the corresponding (20R) epimers being slightly more polar on TLC than **14a** and **14b** respectively and having characteristically different ^{1}H-NMR spectra. (In particular, the C-21 H_3 doublet is consistently shifted ca. 0.1 p.p.m. to high field in all the 20-"unnatural" compounds described in this paper relative to the corresponding 20-"natural" compounds.)
16. The use of the configurationally-pure aldehydes **14** directly for the elaboration of the side chain (cf. our seleno-acetal route[11]) was precluded in the present work because of their instability to the thermal Wittig reaction. However, low temperature reactions with non-stabilised ylides can be efficiently performed on these substrates (unpublished work).
17. In an alternative synthesis of **17**, the 1α-hydroxyl group has been introduced and silylated after the incorporation of the new side chain via the sequence of ozonolysis of **7a** or **7b**, extrusion of SO_2, and Wittig reaction. This route gives comparable yields and obviates the need to convert the triene to the SO_2-adducts a second time, but in practise makes the synthesis less convenient for the generation of other target compounds: as indicated earlier, the primary objective was to couple a late key intermediate (**15**) with a variety of side chain fragments en route to target compounds having various side chain ring sizes. Thus, reaction with the corresponding cyclobutyl-containing phosphorane gave the cyclobutyl analogue of **17**, m.p. 114-115 °C. Structure-activity relationships for a series of homologues and other compounds related to **4** will be discussed elsewhere.
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21. This novel use of Sharpless oxidation in the kinetic resolution mode (ref. 22) to assign configurations in each of two diastereoisomers cannot be claimed as providing absolute proof, though it is considered highly unlikely that the hydrocarbyl nature of the proximal additional chirality would invert the expected selectivities. It may be noted in this connection that the proportion of **22** in the mixture **21/22** was dramatically increased when the reduction of **17** was performed with the (S)-BINAL-H reagent (R. Noyori, I. Tomino, Y. Tanimoto and M. Nishizawa, J. Amer. Chem. Soc., 1984, **106**, 6709), and this selectivity is also consistent with the assignment of the (24S) configuration in **22**. Final proof of the structure of MC 903 (**4**) awaits the results of X-ray crystallographic studies.
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