Convergent Synthesis of 1α-Hydroxyvitamin D_5

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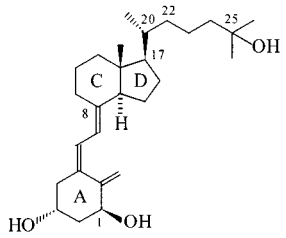
An eleven-step, high-yielding (46%) synthesis of 1α-hydroxyvitamin D_5 (**2**) starting from vitamin D_2 (**4**) is described, in which a Julia olefination sequence is used for the construction of the (24*R*)-ethyl-substituted side chain.

Introduction

The hormonally active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 [**1**, 1α,25$(OH)_2D_3$], produces its biological responses through the regulation of gene transcription.[1] The discovery of the presence of vitamin D receptors in a variety of tissues suggested possible functions of 1α,25$(OH)_2D_3$ (**1**) besides its classical role in calcium-bone homeostasis. In particular, the hormone was found to be capable of regulating cell proliferation and of inducing malignant cellular differentiation.[2] However, its therapeutic utility in the treatment of certain cancers remains limited as effective doses provoke hypercalcemia. In recent years, this has prompted a very active search for vitamin D analogues that can dissociate the cell-differentiating effects from the calcemic effects.[3] Among possible structural variations, numerous side-chain modifications have led to interesting analogues, such as 23-yne, 22-oxa, 20-*epi*, homo [e.g. 24-bis(homo)] derivatives, that show the above discriminatory potential.[3] In this context, it has recently been reported that the 1α-hydroxylated derivative of (24*R*)-ethylvitamin D_3, i.e. 1α-hydroxyvitamin D_5 [**2**; 1α(OH)D_5], is non-calcemic, yet inhibits growth and induces differentiation in human breast carcinoma cell lines.[4] Of particular interest is the absence of a polar functionality at the end of the side chain, the presence of which is usually considered important for effective binding to the receptor.



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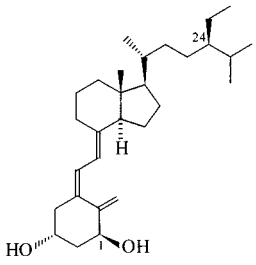

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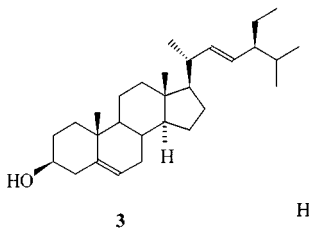
The previously reported 13-step semi-synthesis of 1α(OH)D_5 (**2**) proceeds from stigmasterol (**3**), in which the 24-ethylated side chain is already present.[5] With reference to a structure−reactivity study of similar side-chain alkylated analogues, a convergent strategy becomes mandatory. The present work describes such an approach, the potential of which is illustrated by the 11-step total synthesis of 1α(OH)D_5 (**2**) in high overall yield (46%) from commercially available vitamin D_2 (**4**).



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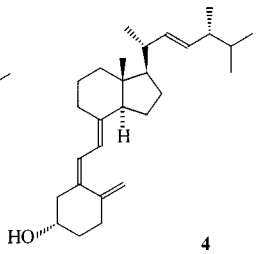

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Results and Discussion

The convergent approach is summarized in Scheme 1. The key steps are (i) a Julia olefination sequence for the construction of the side chain,[6] i.e. reaction of the anion derived from sulfone **5** and (*S*)-2-ethyl-3-methylbutanal (**6**) to yield **7**, and (ii) a classical Wittig−Horner coupling for the introduction of the *seco*-B,A-ring moiety,[7] i.e. reaction of ketone **8** with the anion derived from phosphane oxide **9**. This particular strategy was selected considering the future aim of generating libraries of vitamin D analogues using solid-phase combinatorial techniques. Indeed, the introduction of structural diversity within the side chain and the A-ring could, in principle, be realized using the above approach, where the central part, including the C20,C22 fragment is attached to the solid phase via the aromatic sulfone.

General strategies for the synthesis of vitamin D have recently been reviewed.[8] With regard to the elaboration of the side chain, several of these involve the construction of the C22−C23 bond through single-bond (nucleophilic displacement at C22) or double-bond (Wittig or Julia olefination) formation. Specific strategies have also been developed for elaboration of the (24*R*)-methyl-22-enyl side chain typical of vitamin D_2 (**4**).[8] Julia olefinations have previously been reported involving the C22 aldehyde as an

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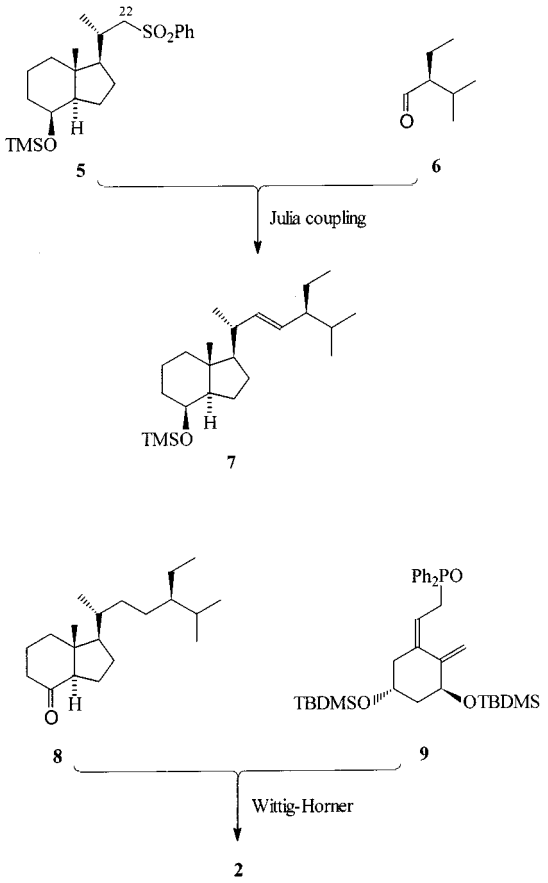
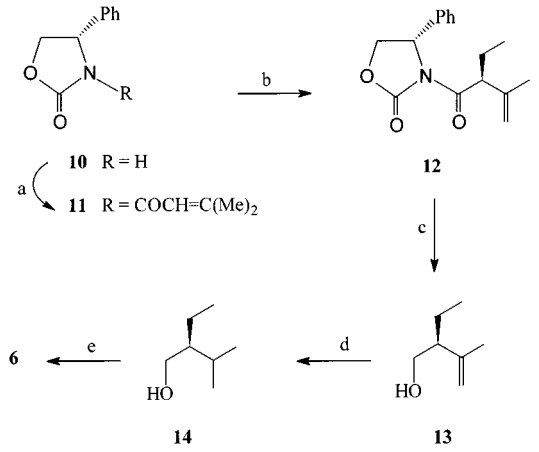


Scheme 1. Convergent strategy for the synthesis of **2**



Scheme 2. Enantioselective synthesis of aldehyde **6**; reagents: (a) *n*BuLi, THF, −78 °C, 0.5 h, 3,3-dimethylacryloyl chloride, −78 °C to 0 °C, 3 h, 99%; (b) KHMDS, THF, −78 °C; −30 °C, EtI, 4 h, 55%; (c) LAH, THF, −78 °C, 1 h, 90%; (d) H_2, PtO_2, EtOAc, 2 h, 96%; (e) TPAP, NMO DCM, 25 °C, 1 h, 98%

electrophilic component.[9] The alternative Julia approach with the nucleophilic component at C22 (cf. **5**) has been employed in the past in our laboratory for the elaboration of 24-hydroxy-substituted derivatives,[10] but has, to the best of our knowledge, not hitherto been used for the preparation of the sterically more congested 24-alkyl-substituted analogues.

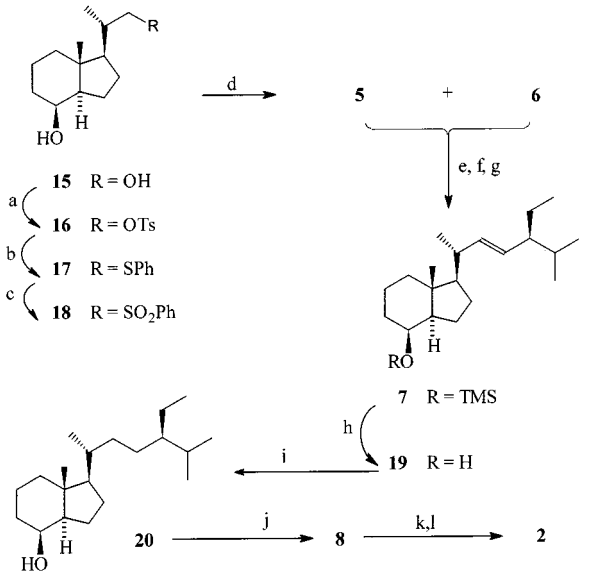
The synthesis of the required enantiomerically pure aldehyde **6** was based on Evans' oxazolidinone auxiliary methodology[11] as outlined in Scheme 2. After conversion of (*S*)-(+)-4-phenyl-2-oxazolidinone (**10**) into enone **11** (*n*BuLi, THF, −78 °C, followed by 3-methyl-2-butenoyl chloride, −78 °C to 0 °C; 99% yield), the latter was deprotonated with potassium hexamethyldisilazide (KHMDS) and the resulting enolate anion (THF, −30 °C) was alkylated with iodoethane (−30 °C to 0 °C) to yield the deconjugated derivative **12** in 54% overall yield. After reductive cleavage of the chiral auxiliary with lithium aluminum hydride (LAH, THF; 90% yield), alcohol **13** was hydrogenated (Adams' catalyst; 96% yield) and the resulting **14** was oxidized with tetrapropylammonium perruthenate (TPAP)[12] to give aldehyde **6** (98% yield).

Aldehyde **6** has been obtained previously in the context of the elucidation of the absolute configuration of the 24-stereocentre of stigmasterol (**3**);[13] the (+)-aldehyde **6** obtained here was further reduced with LAH to the corresponding (−)-alcohol **14**. The expected absolute configuration, as shown in **12**, **13**, **14**, and **6** (Scheme 2), was confirmed by comparison of the signs of the optical rotations of **14** and **6** with those of the corresponding derivatives described in the literature.[13] The enantiomeric excess was determined at the stage of alcohol **14** by analysis of the ^{1}H NMR spectrum of the corresponding Mosher ester (> 95% *ee*). It is interesting to note that when palladium was used instead of platinum as the catalyst in the hydrogenation of alcohol **13**, a much lower enantiomeric excess was observed for **14** (ca. 40% *ee*) due to migration of the double bond during the reduction process.[14] Although the above asymmetric synthesis of **6** is certainly not the shortest conceivable, this strategy was selected as it proceeds via unsaturated intermediates (i.e. **12** and **13**) that allow for future functionalization, in particular the introduction of hydroxy groups.

The synthesis of sulfone **5** has been reported previously without experimental details.[10] It involves a four-step sequence starting from Lythgoe−Inhoffen diol (**15**), which is readily available from vitamin D_2 (**4**) by ozonolysis followed by reductive workup.[15] After selective tosylation of **15** (*p*-toluenesulfonyl chloride, pyridine; 93% yield), **16** was treated with potassium thiophenolate (DMSO; 91% yield) and the resulting sulfide **17** was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA, DCM; 99% yield) to yield sulfone **18**. Protection of the hydroxy group as trimethylsilyl (TMS) ether (*N*-trimethylsilylimidazole, DCM; 96% yield) eventually led to **5**.

Coupling of the lithiated sulfone **5** (LDA, THF) with aldehyde **6** followed by in situ trapping with acetic anhydride (triethylamine, THF)[16] led to a mixture of acetylated derivatives (Scheme 3). These were further reductively (sodium amalgam, buffer) cleaved to give alkene **7**. After removal of the TMS protective group with tetrabutylammonium fluoride (TBAF), alcohol **19** was obtained in 67% overall yield based on **5**. As shown by the ^{1}H NMR resonances of the olefinic protons at C22 and C23, product **19** was obtained isomerically pure,[17] indicating that no detectable racemiz-

ation of the aldehyde **6** had occurred. Subsequent hydrogenation of the $\Delta^{22,23}$-double bond in **19**, using Adams' catalyst gave **20** (99% yield), which was further oxidized using Ley's procedure[12] to give the corresponding ketone **8** (99% yield). The eventual transformation of ketone **8** into 1α(OH)D_5 (**2**) was accomplished using the reliable Wittig−Horner coupling sequence, involving the anion derived from phosphane oxide **9** (89% yield),[18] followed by TBAF deprotection (99% yield).



Scheme 3. Synthesis of 1α-hydroxyvitamin D_5 (**2**); reagents: (a) TsCl, pyridine, 0 °C, 18 h, 93%; (b) PhSH, K_2CO_3, DCM, 3 h, 91%; (c) *m*-CPBA, DCM, 25 °C, 4 h, 99%; (d) *N*-(TMS)imidazole, DCM, 96%; (e) LDA, THF, −78 °C, **6**; (f) Ac_2O, Et_3N, THF, −78 °C to 25 °C; (g) 3.0% Na(Hg), Na_2HPO_4, MeOH/THF, −78 °C to 0 °C; (h) TBAF, 25 °C, 12 h, 67% (from **5**); (i) H_2, PtO_2, 25 °C, 2 h, 99%; (j) TPAP, NMO, DCM, 25 °C, 40 min, 99%; (k) *n*BuLi, THF, −78 °C, **9**, 2 h, then to 25 °C, 89%; (l) TBAF, THF, 12 h, 99%

Experimental Section

General: Thin-layer chromatography was performed on Merck silica gel 60F-254 TLC plates. All products were purified by flash chromatography (Merck silica gel 60F-254) or high-performance liquid chromatography (HPLC): Waters 4000, Kontron 420/422. − Optical rotations, $[\alpha]_D^{20}$ ($CHCl_3$): Perkin−Elmer polarimeter 241. − IR (NaBr): Perkin−Elmer 1600 series spectrometer. − ^{1}H NMR ($CDCl_3$): 500 MHz; Bruker AN-500 (internal TMS as reference). − ^{13}C NMR ($CDCl_3$): 50 MHz; Varian Gemini 200 (with DEPT program). − MS: Finnigan 4000 or Hewlett−Packard 5988A.

Oxazolidinone 11: To a solution of (*S*)-(+)-4-phenyl-2-oxazolidinone (4.9 g, 30 mmol) in dry tetrahydrofuran (150 mL) at −78 °C was added a 2.5 M solution of *n*-butyllithium in hexane (12.0 mL, 30 mmol). After 30 min, 3-methyl-2-butenoyl chloride (3.8 mL, 33 mmol) was added dropwise and the resulting mixture was stirred for 30 min at −78 °C. During warming to 0 °C over a period of 3 h, the reaction mixture was quenched with a neutral buffer solution (25 mL). After concentration of the resulting suspension in vacuo, the residue was extracted with ethyl acetate and the organic phase was washed with saturated $NaHCO_3$ solution and brine, and dried ($MgSO_4$). After removal of the solvent in vacuo, recrystallization of the residue from isooctane/acetone afforded **11** (7.3 g, 99%) as colorless crystals; m.p. 99−100 °C. − $[\alpha]_D^{20}$ = +117 (*c* = 0.88, $CHCl_3$). − R_f = 0.50 (isooctane/ethyl acetate, 3:1). − UV (methanol): λ_{max} = 209, 234 nm. − IR (KBr): $\tilde{\nu}$ = 3036, 2923, 1752, 1678, 1617, 1460, 1393, 1324, 1248, 1221, 1182, 844, 714, 694 cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.97 (d, *J* = 1.0 Hz, 3 H), 2.10 (d, *J* = 1.0 Hz, 3 H), 4.23 (dd, *J* = 8.8, 4.2 Hz, 1 H), 4.67 (t, *J* = 8.8 Hz, 1 H), 5.49 (dd, *J* = 8.8, 4.1 Hz, 1 H), 6.96 (t, *J* = 1 Hz, 1 H), 7.32 (m, 3 H), 7.38 (m, 2 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.4, 28.2, 57.7, 69.8, 115.7, 125.8, 128.5, 129.2, 139.4, 153.8, 160.0, 164.5. − MS; *m*/*z* (%): 245 (27) $[M]^+$, 217 (3), 201 (13), 186 (18), 164 (16), 162 (26), 145 (20), 120 (22), 104 (29), 91 (14), 83 (100), 82 (58), 77 (15), 55 (27). − $C_{14}H_{15}NO_3$ (245.28): calcd. C 68.56, H 6.16, N 5.71; found C 68.54, H 6.07, N 5.65.

Oxazolidinone 12: To a solution of enone **11** (2.453 g, 10 mmol) in dry tetrahydrofuran (120 mL) at −78 °C was added a 0.5 M solution of potassium hexamethyldisilazide in toluene (21 mL, 10.5 mmol). After 1 h, iodoethane (2.4 mL, 30 mmol) was added dropwise at −30 °C and the resulting mixture slowly allowed to warm to 0 °C. After stirring for a further 3 h at 0 °C, the mixture was quenched with a neutral buffer solution (80 mL). After extraction with diethyl ether, the organic phase was washed with brine and dried ($MgSO_4$). Removal of the solvent in vacuo, followed by flash chromatography of the residue eluting with ethyl acetate/isooctane (1:20 to 1:5) afforded **12** (1.514 g, 55%) as colorless crystals, m.p. 89−90 °C, along with some starting material (0.260 g, 11%). − R_f = 0.36 (isooctane/ethyl acetate, 8:3). − $[\alpha]_D^{20}$ = +153 (*c* = 1.085, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 2967, 1779, 1710, 1458, 1388, 1327, 1232, 894, 704 cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77 (t, *J* = 7.4 Hz, 3 H), 1.58 (m, 1 H), 1.74 (m, 1 H), 1.80 (s, 3 H), 4.24 (dd, *J* = 8.6, 3.5 Hz, 1 H), 4.34 (dd, *J* = 8.0, 6.5 Hz, 1 H), 4.65 (t, *J* = 8.6 Hz, 1 H), 4.90 (br. s, 2 H), 5.41 (dd, *J* = 8.6, 3.4 Hz, 1 H), 7.42−7.28 (m, 5 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.08, 20.98, 24.11, 51.85, 58.01, 69.62, 113.82, 125.75, 128.65, 129.18, 139.44, 142.83, 153.46, 173.17. − MS; *m*/*z* (%): 273 (0.2) $[M]^+$, 244 (17), 230 (2), 200 (5), 110 (100). − $C_{16}H_{19}NO_3$ (273.34): calcd. C 70.31, H 7.01, N 5.12; found C 70.38, H 7.02, N 5.17.

(*S*)-2-Ethyl-3-methyl-3-buten-1-ol (13): To a solution of derivative **12** (0.79 g, 2.89 mmol) in dry diethyl ether (30 mL) at 0 °C was added a 1 M solution of lithium aluminum hydride in diethyl ether (8.7 mL, 8.7 mmol). After stirring for 1 h at 0 °C, the suspension was quenched with sodium sulfate decahydrate (1.3 g). The resulting mixture was filtered through Celite and washed with diethyl ether. After careful concentration of the filtrate to a volume of ca. 2 mL, *n*-pentane (20 mL) was added, which led to the precipitation of oxazolidinone **10**. After filtration and concentration by careful distillation, purification by HPLC (acetone/pentane, 1:20) afforded **13** (0.298 g, 90%). − R_f = 0.40 (isooctane/ethyl acetate, 3:2). − $[\alpha]_D^{20}$ = +10 (*c* = 1.006, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3358, 2963, 2930, 2875, 1646, 1455, 1377, 1047, 890 cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.4 Hz, 3 H), 1.37 (m, 2 H), 1.67 (s, 3 H), 2.17 (m, 2 H), 3.53 (m, 2 H), 4.82 (br. s, 1 H), 4.94 (br. s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.89, 18.78, 22.24, 51.89, 63.88, 113.87, 144.94. − MS: *m*/*z* (%) = 114 (2) $[M]^+$, 99 (100), 96 (30), 91 (25), 8 (35), 83 (40), 69 (35), 57 (65), 55 (85), 43 (80).

(*S*)-2-Ethyl-3-methyl-1-butanol (14): A suspension of alkene **13** (0.228 g, 2 mmol) and Adams' catalyst (0.150 g) in ethyl acetate (100 mL) was hydrogenated at room temperature for 2 h. After filtration and concentration of the filtrate in vacuo by careful distillation, HPLC of the residue (acetone/pentane, 1:20) afforded **14** as a colorless liquid (0.223 g, 96%). − R_f = 0.42 (isooctane/ethyl acetate, 3:2). − $[\alpha]_D^{20}$ = −4 (*c* = 1.075, $CHCl_3$); [ref.[13] $[\alpha]_D^{20}$ = −9.47 (*c* = 2.126, $CHCl_3$)]. − IR (film): $\tilde{\nu}$ = 3442, 2959, 2875, 1465, 1386, 1035 cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (br., 9 H),

1.28 (m, 2 H), 1.40 (m, 1 H), 1.80 (m, 1 H), 3.61 (m, 2 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.31, 19.50, 19.92, 20.45, 27.70, 48.42, 63.45. − MS: *m*/*z* (%): 116 (3), 98 (14) [M^+ − 18], 85 (38), 69 (25), 57 (32), 43 (100).

(*S*)-2-Ethyl-3-methylbutanal (6): To a stirred suspension of alcohol **14** (0.116 g, 1.0 mmol), 4-methylmorpholine *N*-oxide (0.235 g, 2.0 mmol), and 4 Å molecular sieves (powdered, 0.500 g) in dichloromethane (2 mL), tetrapropylammonium perruthenate (0.020 g, 0.05 mmol) was added in a single portion at room temperature. After stirring for 1 h, the mixture was passed through a short column of silica gel eluting with dichloromethane. After concentration by careful distillation, HPLC (2% acetone in pentane) afforded **6** (0.108 g, 95%) as a colorless liquid. − R_f = 0.42 (isooctane/ethyl acetate, 3:2). − $[\alpha]_D^{20}$ = +32 (*c* = 0.322, $CHCl_3$); ref.[13] $[\alpha]_D^{20}$ = +37.0. − IR (film): $\tilde{\nu}$ = 2964, 2877, 2706, 1728, 1463, 1388, 1371, 1179 cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.9 (br., 9 H), 1.28 (m, 2 H), 1.64 (s, 1 H), 1.97 (m, 1 H), 9.62 (d, *J* = 3.4 Hz, 1 H). − MS: *m*/*z* (%) = 114 (5) $[M]^+$, 85 (15), 72 (34), 57 (44), 43 (100).

Sulfide 17: A suspension of tosylate **16** (1.0 g, 2.73 mmol), thiophenol (560 μL, 5.46 mmol), and anhydrous potassium carbonate (1.13 g, 8.19 mmol) in dry dimethyl sulfoxide (25 mL) was stirred under argon at 30 °C for 3 h. After quenching by pouring into water, the mixture was extracted with diethyl ether and the organic phase was washed with brine and dried over magnesium sulfate. After filtration and concentration, the residue was purified by flash chromatography on silica gel (isooctane/acetone, 4:1) to afford the sulfide **17** (0.755 g, 91%) as a colorless oil. R_f = 0.56 (isooctane/acetone, 3:2). − IR (film): $\tilde{\nu}$ = 3431, 3057, 1584, 1480 cm^{-1}. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97 (s, 3 H), 1.15 (d, *J* = 6.5 Hz, 3 H), 2.70 (dd, *J* = 12.3, 8.6 Hz, 1 H), 3.18 (dd, *J* = 12.3, 2.8 Hz, 1 H), 4.13 (br. s, 1 H), 7.10−7.40 (m, 5 H). − MS; *m*/*z* (%): 304 (75) $[M]^+$, 286 (1), 177 (10), 152 (28), 123 (100).

Sulfone 18: To a solution of sulfide **17** (0.690 g, 2.27 mmol) in dry dichloromethane (100 mL), a solution of *m*-chloroperbenzoic acid (1.350 g, 5.50 mmol) in dry dichloromethane (10 mL) was added dropwise at room temperature. After stirring for 3 h under argon, the mixture was quenched with saturated sodium hydrogen carbonate solution. After extraction with diethyl ether, the organic phase was washed with 10% aqueous sodium sulfite solution and brine, and dried with magnesium sulfate. After filtration and concentration of the filtrate in vacuo, the residue was purified by flash chromatography (isooctane/acetone, 7:3) to afford sulfone **18** (0.752 g, 99%) as a white solid. R_f = 0.35 (isooctane/acetone, 3:2). − IR (KBr): $\tilde{\nu}$ = 3536, 3063, 1303, 1145 cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (s, 3 H), 1.17 (d, *J* = 6.5 Hz, 3 H), 2.84 (dd, *J* = 14.2, 5.6 Hz, 1 H), 3.14 (dd, *J* = 14.2, 1.3 Hz, 1 H), 4.05 (br. s, 1 H), 7.93−7.54 (m, 5 H). − MS; *m*/*z* (%): 321 (5), 177 (9), 135 (24), 77 (100). − $C_{19}H_{28}O_3S$ (336.44): calcd. C 67.83, H 8.39; found C 67.67, H 8.59.

Hydroxy-Protected Sulfone 5: A solution of sulfone **18** (0.703 g, 2.09 mmol) and *N*-trimethylsilylimidazole (766 μL, 5.23 mmol) in dry dichloromethane (5 mL) was stirred at room temperature under argon for 2 h. Subsequent flash chromatography on silica gel (diethyl ether/pentane, 3:7) afforded sulfone **5** (0.821 g, 96% yield) as white crystals; m.p. 65−66 °C. − $[\alpha]_D^{20}$ = +59 (*c* = 0.696, $CHCl_3$). − R_f = 0.40 (diethyl ether/pentane, 3:7). − IR (KBr): $\tilde{\nu}$ = 2957, 2928, 2864, 1449, 1304, 1250, 1150, 1086, 1033, 840, 743, 723, 688 cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.03 (s, 9 H), 0.83 (s, 3 H), 1.16 (d, *J* = 6.5 Hz, 3 H), 1.90 (m, 1 H), 2.03 (m, 1 H), 2.82 (dd, *J* = 14.2, 9.8 Hz, 1 H), 3.15 (d, *J* = 14.2 Hz, 1 H), 3.95 (br. s, 1 H), 7.57 (t, *J* = 7.6 Hz, 2 H), 7.65 (t, *J* = 7.4 Hz, 1 H), 7.91 (d, *J* = 7.7 Hz, 2 H). − MS; *m*/*z* (%): 408 (2), $[M]^+$, 383 (5), 365 (8), 283 (4), 267 (8), 183 (42), 135 (40), 108 (36), 73 (100). − $C_{22}H_{36}O_3SSi$ (408.67): calcd. C 64.66, H 8.88; found C 64.58, H 8.96.

Alkene 19: To a solution of sulfone **5** (0.204 g, 0.5 mmol) in dry tetrahydrofuran (5 mL) at −78 °C was added a 2 M solution of lithium diisopropylamide (300 μL, 0.6 mmol) in tetrahydrofuran/hexane. After stirring for 1 h at −78 °C, aldehyde **6** (0.090 g, 0.8 mmol) was added and the resulting mixture was stirred at this temperature for a further 2 h. After the addition of 4-(dimethylamino)pyridine (50 mg), triethylamine (1.5 mL), and acetic anhydride (500 μL), the mixture was stirred for a further 1 h at −78 °C for 1 h and then slowly allowed to warm to room temperature. The reaction was then quenched with saturated ammonium chloride solution (5 mL) and the suspension obtained was extracted with diethyl ether. The organic phase was washed with brine and dried with magnesium sulfate. After filtration and concentration of the filtrate in vacuo, the yellow oily residue was passed through a short column of silica gel (ethyl acetate/isooctane, 1:4) to afford a crude solid (0.290 g). This was immediately dissolved in methanol (5 mL) and the resulting solution was added to a stirred mixture of 3% sodium amalgam (4.0 g, 5.2 mmol) and disodium phosphate (1.0 g) in dry tetrahydrofuran (10 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and then slowly allowed to warm to room temperature. After the addition of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (5 mL, 5 mmol), the resulting mixture was stirred at room temperature for 12 h. After quenching with water (20 mL), the suspension obtained was extracted with diethyl ether. The organic phase was washed with brine and dried with magnesium sulfate. After filtration and concentration of the filtrate in vacuo, the residue was purified by flash chromatography (isooctane/acetone, 20:1) and HPLC (pentane/acetone, 20:1) to afford alkene **19** (0.098 g, 67% yield) as a colorless oil. − $[\alpha]_D^{20}$ = +27 (*c* = 0.437, $CHCl_3$). − R_f = 0.42 (isooctane/ethyl acetate, 5:1). − IR (film): $\tilde{\nu}$ = 3420, 2954, 2869, 1458, 1367, 1167, 1065, 990, 972, 943 cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86−0.78 (m, 9 H), 0.948 (s, 3 H), 0.996 (d, *J* = 6.6 Hz, 3 H), 4.08 (br. s, 1 H), 5.02 (A*B*d, *J* = 15.2, 8.6 Hz, 1 H), 5.14 (*A*Bd, *J* = 15.2, 8.7 Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.4, 13.8, 17.5, 19.1, 21.2, 21.2, 22.7, 25.5, 28.1, 32.0, 33.7, 40.2, 40.4, 41.8, 51.4, 52.8, 56.5, 69.6, 129.5, 138.2. − MS; *m*/*z* (%): 292 (3) $[M^+]$, 274 (2), 231 (12), 188 (5), 162 (12), 135 (44), 93 (37), 81 (62), 55 (100).

Alcohol 21: A mixture of alkene **19** (0.065 g, 0.22 mmol) and platinum(IV) oxide hydrate (0.050 g) in ethyl acetate (25 mL) was hydrogenated at room temperature for 3 h. After filtration through a short column of silica gel, HPLC (acetone/pentane, 1:40) afforded alcohol **20** (0.065 g, 99% yield) as a colorless oil. R_f = 0.42 (isooctane/ethyl acetate, 5:1). − $[\alpha]_D^{20}$ = +45 (*c* = 0.663, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3422, 2956, 2871, 1458, 1366, 990 cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87−0.80 (m, 9 H), 0.898 (d, *J* = 6.5 Hz, 3 H), 0.93 (s, 3 H), 4.07 (d, *J* = 2.2 Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.2, 13.7, 17.6, 18.8, 19.2, 20.0, 22.7, 23.2, 26.2, 27.3, 29.2, 33.7, 33.9, 35.8, 40.5, 42.0, 45.9, 52.7, 56.7, 69.6. − MS; *m*/*z* (%): 294 (3) $[M^+]$, 278 (1), 233 (1), 180 (2), 163 (4), 135 (10), 125 (12), 111 (100), 97 (20), 69 (19), 55 (36), 43 (36). − $C_{20}H_{38}O$ (294.52): calcd. C 81.56, H 13.00; found C 81.53, H 13.07.

Ketone 8: To a suspension of alcohol **20** (0.060 g, 0.2 mmol), 4-methylmorpholine *N*-oxide (0.050 g, 0.4 mmol), and 4 Å molecular sieves (powdered, 0.1 g) in dichloromethane (2 mL) at room temperature, tetrapropylammonium perruthenate (5 mg) was added in

a single portion. The resulting mixture was stirred at room temperature for 40 min, passed through a short column of silica gel, and eluted with dry dichloromethane. After concentration of the eluate, HPLC (acetone/pentane, 1:40) yielded ketone **8** (0.059 g, 99% yield) as a colorless oil. $R_f = 0.55$ (isooctane/ethyl acetate, 5:1). − $[\alpha]_D^{20} = +12$ ($c = 0.762$, $CHCl_3$). − IR (film): $\tilde{\nu} = 2958, 2872, 1716, 1465, 1378, 1236, 1056\ cm^{-1}$. − ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.64$ (s, 3 H), 0.86−0.80 (m, 9 H), 0.95 (d, $J = 6.4$ Hz, 3 H), 2.45 (dd, $J = 11.8, 7.6$ Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 12.0, 12.5, 18.9, 19.0, 19.2, 19.9, 23.1, 24.2, 26.0, 27.6, 29.1, 33.8, 35.9, 39.0, 41.1, 45.8, 50.0, 56.6, 62.1, 212.4$. − MS; *m/z* (%): 292 (8) [M^+], 277 (6), 249 (15), 179 (4), 168 (12), 152 (22), 125 (66), 111 (76), 96 (48), 81 (57), 55 (100).

1α-Hydroxyvitamin D_5 (2): To a solution of phosphane oxide **9** (0.045 g, 0.077 mmol) in dry tetrahydrofuran (1 mL) at −78 °C was added a 2.5 M solution of *n*-butyllithium in hexane (35 μL, 0.875 mmol). To the deep-orange solution, a solution of ketone **8** (0.015 g, 0.051 mmol) in pentane (1 mL) was then added at −78 °C. After stirring for 2 h at −78 °C, the mixture was slowly allowed to warm to room temperature. It was then passed through a pad of silica gel, eluting with pentane. After concentration of the eluate, HPLC (0.2% acetone in pentane) afforded an oil (30 mg), which was immediately taken up in dry THF (1 mL) and treated with a 1 M solution of tetrabutylammonium fluoride (500 μL, 0.5 mmol). After stirring at room temperature for 12 h, the mixture was passed through a short column of silica gel (dichloromethane/methanol, 95:5). After concentration of the eluate, HPLC (acetone/pentane, 1:4) afforded 1α(OH)vit D_5 (19.4 mg, 99% yield) as a white solid. $R_f = 0.12$ (acetone/pentane, 6:1). − $[\alpha]_D^{20} = +26$ ($c = 0.810$, $CHCl_3$). − UV (MeOH): $\lambda_{max} = 262$ nm. − IR (KBr): $\tilde{\nu} = 3361, 2956, 2872, 1458, 1054\ cm^{-1}$. − ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.54$ (s, 3 H), 0.9−0.8 (m, 9 H), 0.921 (d, $J = 6.2$ Hz, 3 H), 2.31 (dd, $J = 13.4, 6.5$ Hz, 1 H), 2.60 (m, 1 H), 2.83 (m, 1 H), 4.23 (m, 1 H), 4.43 (m, 1 H), 5.00 (s, 1 H), 5.33 (s, 1 H), 6.02 (d, $J = 11.2$ Hz, 1 H), 6.38 (d, $J = 11.2$ Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 12.2, 19.1, 19.2, 20.0, 22.4, 23.2, 23.8, 26.2, 27.8, 29.2, 34.0, 36.6, 40.6, 42.9, 45.4, 45.9, 46.1, 56.5, 56.6, 66.9, 70.9, 111.8, 116.9, 125.1, 132.7, 147.4, 147.6$. − MS; *m/z* (%): 428 (2) [M^+], 410 (3), 287 (3), 251 (2), 152 (28), 134 (100), 81 (20), 43 (62).

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