A Stereoselective Synthesis of 1α-Hydroxyvitamin D_3 [1]

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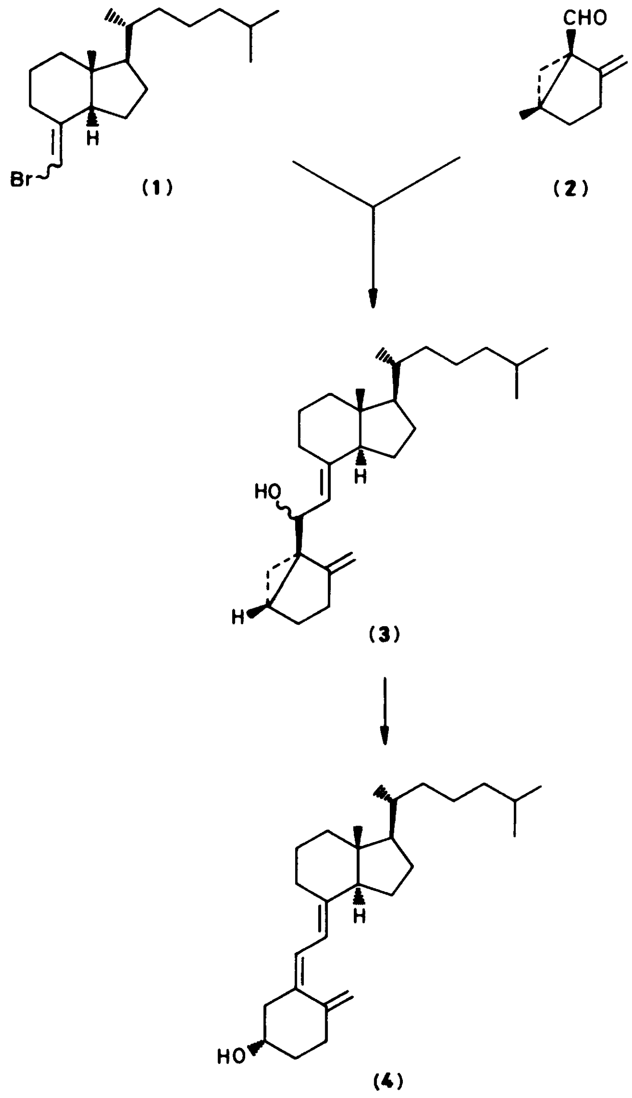
A stereoselective synthesis of 1α-hydroxyvitamin D_3 (**16**) was achieved through the solvolysis of the 3,5-cyclovitamin D_3 (**14**) which was prepared from (−)-(1*R*,3*S*,5*S*)-3-methoxymethoxy-2-methylene-bicyclo[3.1.0]hexanecarbaldehyde (**13**) and 8-bromomethylenedes-AB-cholestane (**1**).

It has become clear that the primary requirement for activity in vitamin D analogues is the presence of a 1α-hydroxy group,[2] and synthetic 1α-(1*S*) hydroxyvitamin D_3 (**16**) is now being used in the clinical treatment of nephritic bone disease in humans.[3] These facts and our recent interest in vitamin D chemistry prompted us to develop an efficient synthetic pathway to 1α-hydroxyvitamin D_3. In our previous paper on synthetic studies toward vitamin D_3,[4] we reported a stereoselective synthesis of vitamin D_3 (**4**) from the 3,5-cyclovitamin D_3 (**3**) which was prepared by a coupling reaction of the chiral aldehyde (**2**) and the vinyl bromide (**1**) (Scheme 1). By following this strategy, we generated a stereoselective synthesis of 1α-hydroxyvitamin D_3 (**16**), which we report here.



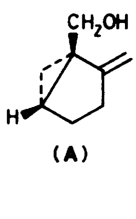
Scheme 1.

Methyl 2-oxobicyclo[3.1.0]hexane-1-carboxylate (**5**)[5] was first hydrolysed with potassium hydroxide to give the keto acid (**6**) [m.p. 58—59 °C; *m/z* 140 (M^+)] in 98% yield. Acid (**6**) was then condensed with (−)-menthol in the presence of dicyclohexylcarbodi-imide (DCC) to afford the menthyl ester (**7**) as a diastereoisomeric mixture which was easily separated by silica gel column chromatography into (**7a**) {*m/z* 278 (M^+); $[\alpha]_D^{20}$ −48.8°} and (**7b**) {*m/z* 278 (M^+); $[\alpha]_D^{20}$ −91.5°} in 44 and 50% isolated yield, respectively.† The methylene ester (**8**)‡ {*m/z* 276 (M^+); $[\alpha]_D^{20}$ −98.8°} obtained from keto ester (**7b**) in 73% yield by Wittig reaction with methyltriphenylphosphonium bromide and sodium t-amylate (sodium 2-methylbutan-2-olate) was then oxidized with t-butyl hydroperoxide and selenium dioxide to give, in 37% yield, the allylic alcohol§ (**10**) {*m/z* 292 (M^+); $[\alpha]_D^{20}$ −72.7°} together with the unsaturated ketone (**9**) {*m/z* 290 (M^+); $[\alpha]_D^{20}$ −107.0°}; the alcohol was then converted by methoxymethyl chloride in the presence of Hünig's base (*N*-ethyldi-isopropylamine) into the corresponding ether (**11**) {*m/z* 336 (M^+); $[\alpha]_D^{20}$ −80.6°} in 80% yield. The protected ester (**11**) was then reduced with lithium aluminium hydride to afford the alcohol (**12**) {*m/z* 184 (M^+); $[\alpha]_D^{20}$ +32.6°} in 92% yield, which was oxidized with pyridinium chlorochromate (PCC) to afford, in 76% yield, the key intermediate (**13**) {*m/z* 182 (M^+); $[\alpha]_D^{20}$ −39.7°}. The vinyl bromide (**1**)[4] was metallated with t-butyl-lithium and coupled

† These compounds had been synthesized previously but the specific rotations had not been presented; D. F. Taber, S. A. Saleh, and R. W. Korsmeyer, *J. Org. Chem.*, 1980, **45**, 4699.

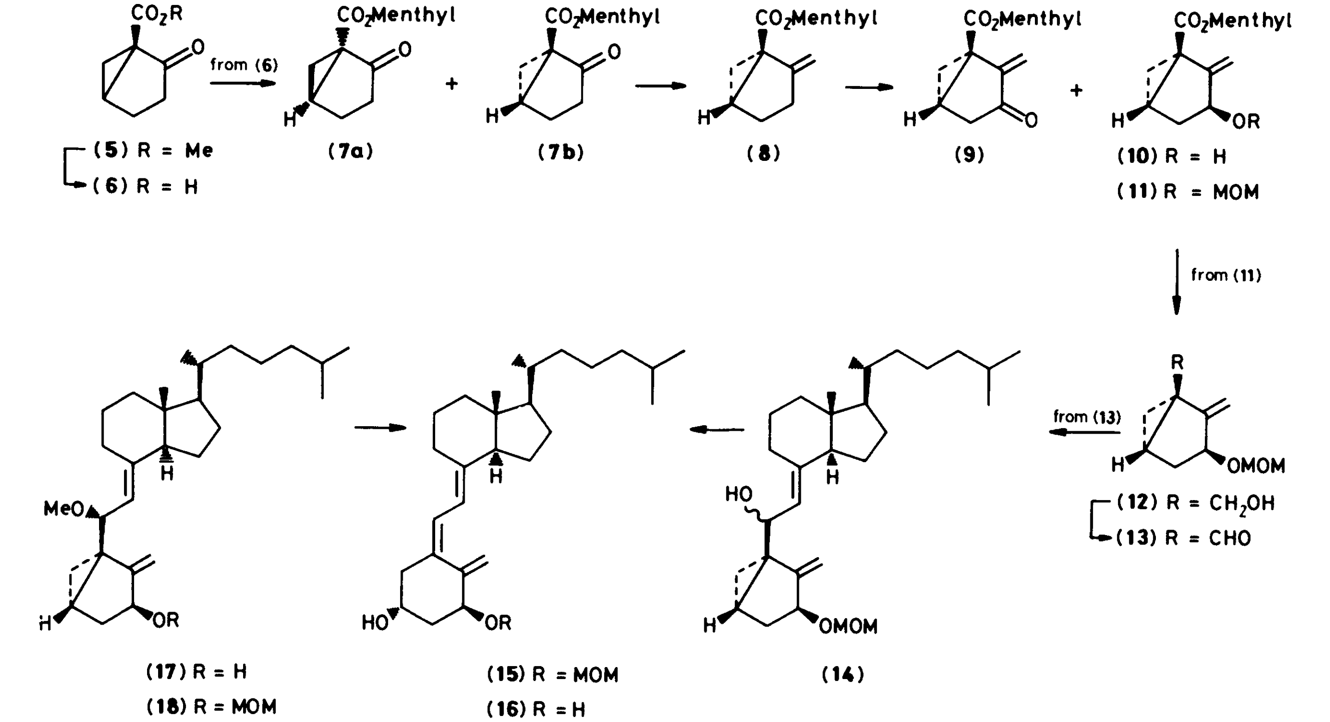
‡ This compound had been prepared previously by the same type of reaction as for the keto ester (**7b**), although none of its physical data had been given; S. R. Willson, M. S. Haque, A. M. Venkatesan, and P. A. Zucker, *Tetrahedron Lett.*, 1984, **25**, 3151.

We have independently converted ester (**8**) into the corresponding alcohol (**A**) by reduction with lithium aluminium hydride, and confirmed its absolute configuration to be correct by comparison with an authentic sample.[4]



(**A**)

§ Although the stereochemistry at C-3 of compound (**10**) could be deduced from the reaction mechanism, *i.e.* sterically favoured β-side attack of the oxidizing reagent, it remained to be confirmed unambiguously at that stage.



Scheme 2. MOM = $MeOCH_2$

with the chiral aldehyde (**13**) prepared above to give, in 34% yield, the alcohol (**14**) [*m/z* 444 (M^+)] as a mixture of stereoisomers. The alcohol (**14**) was then subjected to solvolysis with toluene-*p*-sulphonic acid (PTSA) in aqueous 1,4-dioxane to afford the protected 1α-hydroxyvitamin D_3 (**15**) {*m/z* 444 (M^+); $[\alpha]_D^{20}$ +25.5°} in 77% yield. The compound (**15**) thus obtained was identical in all respects (including optical rotation) with an authentic sample which was synthesized by solvolysis of compound (**18**) [*m/z* 458 (M^+)], prepared in turn by protection of the known alcohol[6] (**17**). Finally, compound (**15**) was deprotected with hydrochloric acid in methanol to furnish 1α-hydroxyvitamin D_3 (**16**) in 39% yield, which was identical in all respects (including optical rotation) with an authentic sample.

Thus, we have achieved an effective pathway to 1α-hydroxyvitamin D_3, as shown in Scheme 2.

Experimental

General Methods.—All m.p.s were determined on a Yanaco micromelting-point apparatus and uncorrected. I.r. spectra were recorded for $CHCl_3$ solutions on a Hitachi 260-10 spectrophotometer. N.m.r. spectra were measured for $CDCl_3$ solution on a JEOL-PMX-60 or a JEOL-PS-100 spectrometer. Chemical shifts are reported as δ-values relative to internal tetramethylsilane (Me_4Si). Mass spectra were taken on a Hitachi M-52G or a JEOL-JMS-OISG-2 spectrometer. All optical rotations were measured in chloroform solution on a JASCO DIP-4 polarimeter using a 1-dm cell.

2-Oxobicyclo[3.1.0]*hexane-1-carboxylic Acid* (**6**).—A mixture of methyl 2-oxobicyclo[3.1.0]hexane-1-carboxylate (**5**) (35.4 g, 230 mmol), potassium hydroxide (25.8 g, 453 mmol), water (45 ml), and methanol (500 ml) was stirred at room temperature for 20 min. After evaporation of the solvent, the residue was acidified with 10% aqueous hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride, and dried (sodium sulphate). After removal of the solvent, the residue was chromatographed on silica gel (300 g) with hexane–ethyl acetate (1 : 1 v/v) as eluant to give the *carboxylic acid* (**6**) (31.6 g, 98%) as needles (Found: C, 59.9; H, 5.7. $C_7H_8O_3$ requires C, 60.0; H, 5.75%); m.p. 58—59 °C (from Et_2O); $\nu_{max.}$ 3 200, 1 760, and 1 700 cm^{-1}; δ_H 1.76 (1 H, t, *J* 4 Hz) and 11.15 (1 H, br s); *m/z* 140 (M^+).

(−)-*Menthyl* (1S,5S)-*2-Oxobicyclo*[3.1.0]*hexane-1-carboxylate* (**7a**) *and* (−)-*Menthyl* (1R,5R)-*2-Oxobicyclo*[3.1.0]*hexane-1-carboxylate* (**7b**).—To a stirred solution of the acid (**6**) (13 g, 93 mmol), l-menthol (14.3 g, 92 mmol), and 4-(dimethylamino)pyridine (DMAP) (2.2 g, 18 mmol) in dichloromethane (300 ml) was added portionwise DCC (22.7 g, 110 mmol) at 0 °C. After the mixture had been stirred for 2.5 h at room temperature, it was filtered through Celite. The filtrate was evaporated to give a residue which was chromatographed on silica gel (200 g) with hexane–ethyl acetate (93 : 7 v/v) as eluant. Evaporation of the first and second fractions afforded the *menthyl esters*. (**7a**) (11.3 g, 44%) and (**7b**) (12.8 g, 50%) as oil.

The menthyl ester (**7a**) (Found: C, 73.3; H, 9.5. $C_{17}H_{26}O_3$ requires C, 73.35; H, 9.4%) had $\nu_{max.}$ 1 740 and 1 700 cm^{-1}; δ_H 0.76 (3 H, d, *J* 6 Hz), 0.90 (6 H, d, *J* 6 Hz), and 4.75 (1 H, dt, *J* 4 and 11 Hz); *m/z* 278 (M^+); $[\alpha]_D^{20}$ −48.8° (*c* 1.06).

The *menthyl ester* (**7b**) (Found: C, 72.95; H, 9.45%) $\nu_{max.}$ 1 740 and 1 700 cm^{-1}; δ_H 0.74 (3 H, d, *J* 6 Hz), 0.88 (6 H, d, *J* 6 Hz), and 4.78 (1 H, dt, *J* 4 and 11 Hz); *m/z* 278 (M^+); $[\alpha]_D^{20}$ − 91.5° (*c* 0.77).

(−)-*Menthyl* (1R,5R)-*2-Methylenebicyclo*[3.1.0]*hexane-1-carboxylate* (**8**).—To a stirred suspension of methyltriphenylphosphonium bromide (7.7 g, 22 mmol) in toluene (80 ml) was added portionwise sodium 2-methylbutan-2-olate (1.9 g, 17.4 mmol) at 0 °C and the mixture was stirred for 2 h at room temperature. To this solution was added dropwise a solution of the keto ester (**7b**) (2.7 g, 9.7 mmol) in toluene (10 ml). After the mixture had been stirred for a further 2 h at room temperature, it was treated with saturated aqueous ammonium chloride and extracted with benzene. The extract was washed with saturated aqueous sodium chloride, and dried (sodium sulphate). The residue resulting from evaporation of the solvent was chromatographed on silica gel (50 g) with hexane–ethyl acetate (97:3 v/v) as eluant to give the *olefin* (**8**) (2.0 g, 73%) as an oil, $\nu_{max.}$ 1 710 and 1 655 cm^{-1}; δ_H 0.70 (3 H, d, *J* 6 Hz), 0.81 (6 H, d, *J* 6 Hz), 4.70 (1 H, dt, *J* 4 and 11 Hz), and 5.00 and 5.56 (2 H, each d, *J* 2 Hz); *m/z* 276 (M^+) (Found: M^+, 276.2076. $C_{18}H_{28}O_2$ requires *M*, 276.2088); $[\alpha]_D^{20}$ −98.8° (*c* 0.80).

(+)-(1R,5R)-2-*Methylenebicyclo*[3.1.0]*hexan*-1-*ylmethanol* (**A**).—To a stirred suspension of lithium aluminium hydride (22.9 mg, 0.6 mmol) in tetrahydrofuran (THF) (2 ml) was added portionwise a solution of ester (**8**) (169 mg, 0.6 mmol) at 0 °C, and the mixture was stirred for 1 h at room temperature, then treated successively with wet ether (0.02 ml), 15% aqueous sodium hydroxide (0.02 ml), and water (0.06 ml), and filtered through Celite. The filtrate was washed with saturated aqueous sodium chloride, and dried (sodium sulphate). Evaporation of the solvent afforded a residue which was chromatographed on silica gel (2 g) with hexane–ethyl acetate (85:15 v/v) as eluant to give the alcohol (**A**) (55.5 mg, 73%) as an oil. This was identical with an authentic sample[4] in all aspects.

Oxidation of (−)-*Menthyl* (1R,5R)-2-*Methylenebicyclo*-[3.1.0]*hexane*-1-*carboxylate* (**8**).—To a stirred mixture of selenium dioxide (310 mg, 2.8 mmol) and t-butyl hydroperoxide (1.05 g, 11.7 mmol) in dichloromethane (25 ml) was added dropwise a solution of compound (**8**) (1.48 g, 5.4 mmol) in dichloromethane (7 ml) at room temperature. After the mixture had been stirred for 1 h at the same temperature, it was treated with 10% aqueous sodium hydroxide (100 ml) and extracted with ether. The extract was washed with saturated aqueous sodium chloride, and dried (sodium sulphate). Removal of the solvent gave a residue which was chromatographed on silica gel (5 g). From the fraction obtained with hexane–ethyl acetate (92:8 v/v) as eluant, the *ketone* (**9**) (455 mg, 29%) was obtained as an oil. The *alcohol* (**10**) (572 mg, 37%) was obtained as an oil from the fraction with hexane–ethyl acetate (85:15 v/v) as eluant.

The ketone (**9**) had $\nu_{max.}$ 1 720 and 1 715 cm^{-1}; δ_H 0.70 (3 H, d, *J* 6 Hz), 0.82 (6 H, d, *J* 6 Hz), 4.43—5.00 (1 H, m), and 5.96 and 6.20 (2 H, each d, *J* 2 Hz); *m/z* 290 (M^+) (Found: M^+, 290.1879. $C_{18}H_{26}O_3$ requires *M*, 290.1881); $[\alpha]_D^{20}$ −107.0° (*c* 0.19).

The alcohol (**10**) had $\nu_{max.}$ 3 600 and 1 720 cm^{-1}; δ_H 0.76 (3 H, d, *J* 6 Hz), 0.88 (6 H, d, *J* 6 Hz), 3.85—4.50 (1 H, m), 4.70 (1 H, dt, *J* 4 and 11 Hz), and 5.31 and 5.80 (2 H, each d, *J* 2 Hz); *m/z* 292 (M^+) (Found: M^+, 292.2028. $C_{18}H_{28}O_3$ requires *M*, 292.2027); $[\alpha]_D^{20}$ −72.7° (*c* 2.96).

(−)-*Menthyl* (1R,3S,5S)-3-*Methoxymethoxy*-2-*methylenebicyclo*[3.1.0]*hexane*-1-*carboxylate* (**11**).—To a stirred solution of the alcohol (**10**) (542 mg, 1.9 mmol) and *N*-ethyl diisopropylamine (Hünig's base) (432 mg, 3.3 mmol) in dichloromethane (18 ml) was added dropwise methoxymethyl chloride (MOMCl) (224 mg, 2.8 mmol) at 0 °C. After the mixture had been stirred for 10 h at room temperature, it was treated with saturated aqueous sodium chloride (70 ml) and extracted with ether. The extract was washed with saturated aqueous sodium chloride, and dried (sodium sulphate). The residue obtained on evaporation of the solvent was chromatographed on silica gel (10 g) with hexane–ethyl acetate (97:3 v/v) as eluant to give the *ether* (**11**) (520 mg, 80%) as an oil (Found: C, 71.1; H, 9.65. $C_{20}H_{32}O_4$ requires C, 71.4; H, 9.6%); $\nu_{max.}$ 1 710 cm^{-1}; δ_H 0.75 (3 H, d, *J* 6 Hz), 0.86 (6 H, d, *J* 6 Hz), 3.38 (3 H, s), 4.13 (1 H, dt, *J* 4 and 11 Hz), 4.66 (2 H, s), 4.33—5.00 (1 H, m), and 5.26—5.50 and 5.76—5.93 (2 H, each m); *m/z* 336 (M^+); $[\alpha]_D^{20}$ −80.6° (*c* 0.96).

(+)-(1R,3S,5S)-3-*Methoxymethoxy*-2-*methylenebicyclo*-[3.1.0]*hexan*-1-*ylmethanol* (**12**).—To a stirred suspension of lithium aluminium hydride (64.7 mg, 1.7 mmol) in THF (16 ml) was added dropwise a solution of the ether (**11**) (478 mg, 1.4 mmol) in THF (4 ml) at 0 °C, and the mixture was stirred for a further 1 h at room temperature. The reaction mixture was treated successively with wet ether (0.06 ml), 15% aqueous sodium hydroxide (0.06 ml), and water (0.18 ml), and then filtered through Celite. The filtrate was extracted with ether. The extract was washed with saturated aqueous sodium chloride and dried (sodium sulphate). Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (10 g) with hexane–ethyl acetate (7:3 v/v) as eluant to give the *alcohol* (**12**) (241 mg, 92%) as an oil (Found: C, 65.45; H, 8.55. $C_{10}H_{16}O_3$ requires, C, 65.2; H, 8.75%; $\nu_{max.}$ 3 600 and 1 650 cm^{-1}; δ_H 3.36 (3 H, s), 3.80 (2 H, d, *J* 2 Hz), 4.00—4.43 (1 H, m), 4.66 (2 H, s), and 5.16 (2 H, d, *J* 2 Hz); *m/z* 184 (M^+); $[\alpha]_D^{20}$ +32.6° (*c* 0.64).

(−)-(1R,3S,5S)-3-*Methoxymethoxy*-2-*methylenebicyclo*-[3.1.0]*hexanecarbaldehyde* (**13**).—A mixture of the alcohol (**12**) (209 mg, 1.1 mmol), PCC (366 mg, 1.7 mmol), Florisil (200 mg), and dichloromethane (10 ml) was stirred for 2 h at room temperature, and then filtered through Celite. The filtrate was washed successively with saturated aqueous sodium chloride, aqueous sodium hydrogen carbonate, and aqueous sodium chloride solution, and dried (magnesium sulphate). Removal of the solvent left a residue, which was chromatographed on silica gel (5 g) with hexane–ethyl acetate (95:5 v/v) as eluant to give the *aldehyde* (**13**) (156 mg, 76%) as an oil, $\nu_{max.}$ 1 700 and 1 650 cm^{-1}; δ_H 1.16 (1 H, t, *J* 4 Hz), 3.36 (3 H, s), 4.06—4.50 (1 H, m), 4.66 (2 H, s), 5.31 and 5.66 (2 H, each d, *J* 2 Hz), and 9.51 (1 H, s); *m/z* 182 (M^+) (Found: M^+, 182.0929. $C_{10}H_{14}O_3$ requires *M*, 182.0941); $[\alpha]_D^{20}$ −39.7° (*c* 0.68).

(1S)-3-*Deoxy*-6-*hydroxy*-1-*methoxymethoxy*-3,5-*cyclo*-5,6-*dihydrovitamin* D_3 (**14**) *and its Conversion into* (1S)-1 *Methoxymethoxyvitamin* D_3 (**15**).—To a stirred solution of the vinyl bromide (**1**)[4] (190 mg, 0.56 mmol) in THF (5 ml) was added dropwise a solution of t-butyl-lithium (1.7M in n-pentane; 0.5 ml) at −78 °C, and the mixture was stirred for 1 h at the same temperature. To this solution was added dropwise a solution of the aldehyde (**13**) (101.4 mg, 0.56 mmol) in THF (1 ml). The mixture was stirred for a further 20 min at the same temperature, then was quenched with saturated aqueous ammonium chloride (2 ml) and extracted with ether. The extract was washed with saturated aqueous sodium chloride and dried (sodium sulphate). Removal of the solvent afforded a crude product, which was chromatographed on silica gel (5 g) with hexane–ethyl acetate (9:1 v/v) as eluant to give the *cyclovitamin* D_3 (**14**) (83.6 mg, 34%) as an oil, $\nu_{max.}$ 3 600 cm^{-1}; δ_H 0.53 (3 H, s), 0.84 (6 H, d, *J* 6 Hz), 0.86 (3 H, d, *J* 6 Hz), 3.36 (3 H, s), 3.92—4.28 (2 H, m), 4.66 (2 H, s), 4.91 (1 H, br s), and 5.16 (2 H, br s); *m/z* 444 (M^+) (Found: M^+, 444.3583. $C_{19}H_{48}O_3$ requires *M*, 444.3603).

A mixture of the cyclovitamin D_3 (**14**) (50.0 mg, 0.11 mmol), PTSA (6.4 mg), water (1.5 ml), and 1,4-dioxane (4.5 ml) was stirred for 5 min at 55 °C. The reaction mixture was then treated with saturated aqueous sodium hydrogen carbonate (5 ml) and extracted with ether. The extract was washed with saturated aqueous sodium chloride and dried (sodium sulphate). The residue obtained on evaporation of the solvent was chromatographed on silica gel (1 g) with hexane–ethyl acetate (85:15 v/v) as eluant to give (1S)-1-*methoxymethoxyvitamin* D_3 (**15**) (38.3 mg, 77%) as an oil, $\nu_{max.}$ 3 590 cm^{-1}; δ_H 0.50 (3 H, s), 0.83 (6 H, d, *J* 6 Hz), 0.86 (3 H, d, *J* 6 Hz), 3.30 (3 H, s), 3.92—4.35 (2 H, m), 4.45 (1 H, d, *J* 6 Hz), 4.65 (1 H, d, *J* 6 Hz), 5.05 (1 H, d, *J* 2Hz), 5.26 (1 H, d, *J* 2 Hz), 5.93 (1 H, d, *J* 10 Hz), and 6.35 (1 H, d, *J* 10 Hz); *m/z* 444 (M^+) (Found: M^+, 444.3568. $C_{19}H_{48}O_3$ requires ***M***, 444.3603); $[\alpha]_D^{20}$ +25.5° (*c* 1.37).

(1S,6R)-3-*Deoxy*-6-*methoxy*-1-*methoxymethoxy*-3,5-*cyclo*-5,6-*dihydrovitamin* D_3 (**18**).—To a stirred solution of (1*S*,6*R*)-3-deoxy-1-hydroxy-6-methoxy-3,5-cyclo-5,6-dihydrovitamin D_3 (**17**) (226 mg, 0.55 mmol) and Hünig's base (140 mg, 1.1 mmol) in dichloromethane (7 ml) was added dropwise MOMCl (49 mg, 0.6 mmol) at 0 °C. After having been stirred for 5 h at room temperature, the reaction mixture was diluted with saturated aqueous sodium chloride (30 ml) and extracted with ether. The extract was washed with saturated aqueous sodium chloride solution and dried (sodium sulphate). The residue obtained on evaporation of the solvent was chromatographed on silica gel (5 g) with hexane–ethyl acetate (10:1 v/v) as eluant to give the *methoxymethoxycyclovitamin* D_3 (**18**) (207 mg, 83%) as an oil, δ_H 0.55 (3 H, s), 0.87 (6 H, d, *J* 6 Hz), 0.91 (3 H, d, *J* 6 Hz), 3.26 (3 H, s), 3.38 (3 H, s), 4.10 (1 H, d, *J* 9 Hz), 4.22 (1 H, m), 4.65 (2 H, s), and 4.95—5.35 (3 H, m); *m/z* 458 (M^+) (Found: M^+, 458.3719. $C_{30}H_{50}O_3$ requires ***M***, 458.3681).

Solvolysis of Compound—(**18**).—A solution of compound (**18**) (207 mg, 0.45 mmol) and PTSA (32 mg) in a mixture of 1,4-dioxane (30 ml) and water (10 ml) was stirred for 5 min at 55 °C. After the same work-up as for the solvolysis of compound (**14**) described above, compound (**15**) (103 mg, 51%) was obtained as an oil. This compound was identical in all aspects with the sample prepared by the solvolysis of the allyl alcohol (**14**).

(1S)-1-*Hydroxyvitamin* D_3 (**16**).—A mixture of compound (**15**) (74 mg, 0.16 mmol), conc. hydrochloric acid (3 drops), and methanol (20 ml) was stirred for 3.5 h at 60 °C. The reaction mixture was then treated with saturated aqueous sodium hydrogen carbonate (10 ml) and extracted with ether. The extract was washed with saturated aqueous sodium chloride and dried (sodium sulphate). Evaporation of the solvent afforded a crude product, which was chromatographed on silica gel (2 g) with hexane–ethyl acetate (3:2 v/v) as eluant to give (1*S*)-1-hydroxyvitamin D_3 (26 mg, 39%) as needles, m.p. 137—139 °C [from ether—light petroleum (b.p. 35—60 °C)]; $[\alpha]_D^{20}$ +28.9° (*c* 0.28). This was identical with an authentic sample in all respects.

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