A General Method for the Synthesis of 3,5-Cyclovitamin D_3 and Derivatives. A Stereoselective Synthesis of Vitamin D_3†

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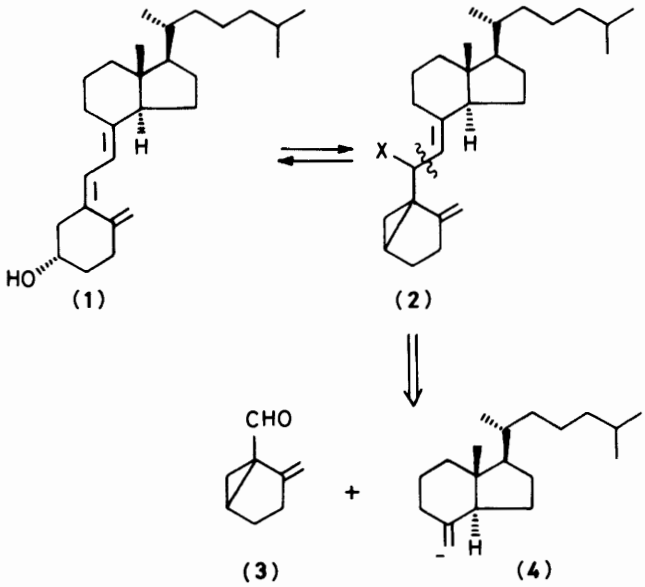
A stereoselective synthesis of vitamin D_3 (**1**) was achieved *via* 3,5-cyclovitamin D_3 (**33**) which was synthesized from the chiral aldehyde (**3**) and the vinyl bromide (**27**) derived from Grundmann's ketone (**25**). (±)-(*Z*)-5-(2-Cyclohexylidene-ethylidene)-4-methylenecyclohexane-*r*-1, *t*-3-diol (**24**) as a model compound of 1α-hydroxyvitamin D_3 was also stereoselectively synthesized *via* the solvolysis of (±)-α-cyclohexylidenemethyl-3β-methoxymethoxy-2-methylenebicyclo[3.1.0]hexane-1-methanol (**21**) which was prepared from the aldehyde(**12**) and the organostannane (**16**).

During our study directed toward a synthesis of vitamin D derivatives,[1] our attention has been focussed on the conversion of vitamin D_3 (**1**) into 3,5-cyclovitamin D_3 derivatives (**2**) and their stereoselective reconversion into the starting vitamin D_3 (**1**), which has been reported by Mazur.[2] On the basis of this observation, we were led to develop an efficient method for the synthesis of 3,5-cyclovitamin D_3 (**2**), and the condensation of the aldehyde (**3**) and the vinyl anion (**4**) was seen as one of the most effective routes for this purpose. Here, we report our results on the synthesis of 3,5-cyclovitamin D_3 and its derivatives by this route, and their stereoselective conversion into vitamin D_3 (Scheme 1).

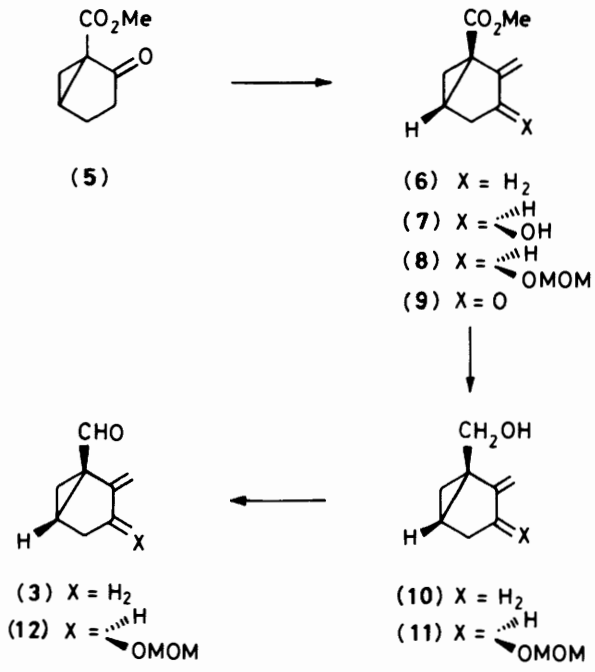


(1) (2) (3) (4)

Scheme 1.

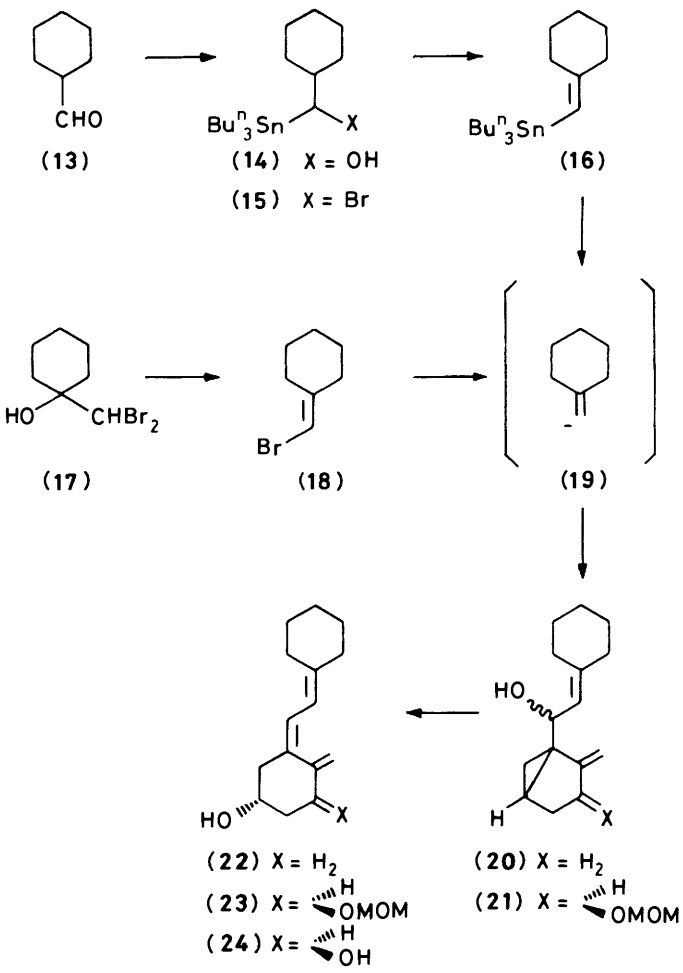
The synthesis of the bicyclo[3.1.0]hexanes (**3**) and (**12**), which were important components for generating the A-ring of the vitamin D series, was achieved as shown in Scheme 2.

† Preliminary communications: H. Nemoto, X.-M. Wu, H. Kurobe, M. Ihara, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1983, **24**, 4257; *ibid.*, 1984, **25**, 3095.

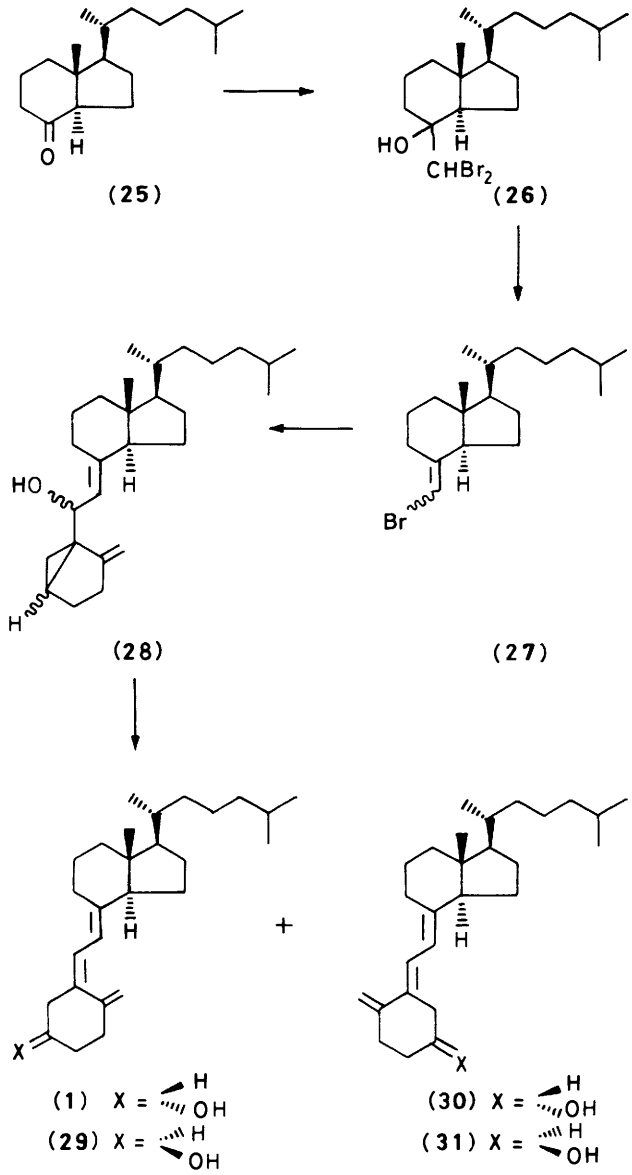


Scheme 2.

First, methyl 2-methylenebicyclo[3.1.0]hexane-1-carboxylate (**6**), prepared in 47% yield by the Wittig reaction of methyl 2-oxobicyclo[3.1.0]hexane-1-carboxylate (**5**)[3] with methyl (triphenyl)phosphonium bromide and n-butyl-lithium in tetrahydrofuran (THF), was converted into the aldehyde (**3**) in 85% overall yield *via* the alcohol (**10**) by successive treatment with lithium aluminium hydride in THF followed by pyridinium chlorochromate in dichloromethane. Secondly, the ester (**8**) possessing a protected hydroxy group at C-3, which was obtained in 39% overall yield together with the ketone (**9**) in 34% yield *via* the allylic oxidation of compound (**6**) with selenium dioxide (SeO_2) and t-butyl hydroperoxide[4,5] in dichloromethane followed by treatment of the resulting



Scheme 3.



Scheme 4.

hydroxy compound (7) with methoxymethyl chloride in dichloromethane in the presence of di-isopropylethylamine, was converted into the aldehyde (12) *via* the alcohol (11) in 59% overall yield by following the same procedures as for the preparation of the aldehyde (3), namely reduction with lithium aluminium hydride and oxidation with pyridinium chlorochromate. Next, our attention was turned to developing an efficient source for generating vinyl anions such as (4) and its coupling reaction with the aldehydes (3) and (12) obtained above.

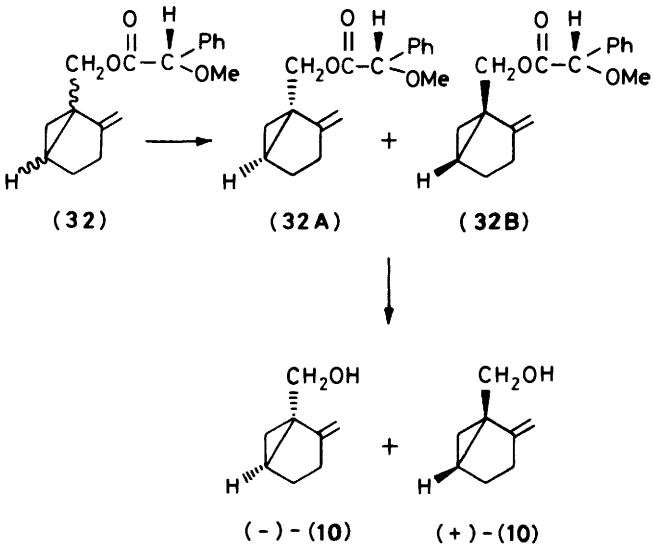
In preliminary experiments, the synthesis of the cyclohexylidene analogues (20) and (21) and their solvolysis were attempted. Thus, treatment of cyclohexanecarbaldehyde (13) with tributylstannyl-lithium, prepared by the reaction of tributylstannyl chloride and lithium in THF, gave the stannyl carbinol (14), which was converted into the bromide (15) on reaction with triphenylphosphine and tetrabromomethane in CH_2Cl_2 in 36% overall yield.[6,7] Dehydrobromination of compound (15) with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in a mixture of dimethylformamide (DMF) and toluene afforded the vinylstannane (16) in 64% yield. The coupling reaction was first examined using the aldehyde (3). Thus, lithiation[8] of compound (16) with n-butyl-lithium in THF, followed by addition of the aldehyde (3) afforded, in 76% yield, the condensation product (20) which was subjected to solvolysis in the presence of a catalytic amount of toluene-*p*-sulphonic acid in aqueous dioxane to give the (*Z*)-triene (22) in 66% yield. The spectral data of the product (22) thus obtained were consistent with those reported.[9] The alcohol (21), prepared in 76.8% yield by a coupling reaction between the aldehyde (12) and the vinyl anion (19) derived from the vinylstannane (16) under the same reaction conditions as above, was also subjected to solvolysis to give the (*Z*)-triene (23) in 65.3% yield, which was deprotected by heating in the presence of a small amount of conc. hydrochloric acid in methanol to furnish the diol (24) in 69.5% yield (Scheme 3).

As the coupling reaction and the solvolysis of the resultant alcohols (20) and (21) were found to proceed smoothly to give the (*Z*)-trienes (22) and (23), we investigated an alternative preparation of the vinyl anion (19). The dibromide (17)[10] was reduced with zinc and acetic acid in dichloromethane[11] to give the cyclohexylidene bromide (18) in 83.5% yield. The metallation[11] of the bromide (18) with two equivalents of t-butyl-lithium in THF, followed by condensation with the aldehyde (3) afforded, in 79.2% yield, an epimeric mixture of the alcohols (20), which was identical with the authentic sample obtained above. Since it was clear that the synthetic route to the

cyclohexylidene anion (**19**) *via* the vinyl bromide (**18**) was more effective than that *via* the vinylstannane (**16**), the vinyl bromide was used as a source of the vinyl anion (**4**) for the attempted synthesis of vitamin D_3.

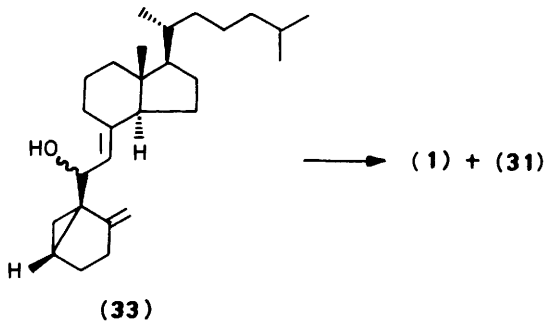
Thus, Grundmann's ketone (**25**)[12] was treated with dibromomethane in the presence of lithium dicyclohexylamide[10] in THF to give, in 43.3% yield, the dibromide (**26**) which was subjected to reduction with zinc and acetic acid.[11] The vinyl bromide (**27**) thus obtained in 89% yield as a mixture of two isomers in the ratio 1:0.9 was metallated and coupled with the racemic aldehyde (**3**) under the same reaction conditions as above to produce the alcohols (**28**) in 55% yield as a mixture of stereoisomers. Solvolysis[13] of the stereoisomeric mixture of alcohols (**28**) in the presence of toluene-*p*-sulphonic acid in aqueous dioxane, followed by silica gel column chromatography, gave two products (Scheme 4). The spectral data of the less polar product (13% yield) were superposable on those of *trans*-vitamin D_3[1] (**31**) while those of the polar product (35.3% yield) were very similar to those of vitamin D_3 (**1**). However, high-pressure liquid chromatography (h.p.l.c.) of the latter revealed that the product was a 1:1 mixture of two epimers, (**1**) and (**29**). Therefore the former product might also be a mixture of the two epimers, (**30**) and (**31**). On the basis of the above result, we then investigated a stereoselective synthesis of vitamin D_3 (**1**) starting from the chiral aldehyde (**3**).

First, (±)-2-methylenebicyclo[3.1.0]hexane-1-methanol (**10**) was treated with (+)-(*S*)-*O*-methylmandelic acid [methoxy(phenyl)acetic acid] in the presence of dicyclohexylcarbodiimide (DCC) and 4-(*NN*-dimethylamino)pyridine[14] to give, in 95.5% yield, a diastereoisomeric mixture of the esters (**32**), the separation of which was accomplished by h.p.l.c. The two ester fractions were respectively hydrolysed with potassium hydroxide in methanol to afford quantitatively the alcohols (+)-(**10**) and (−)-(**10**) (Scheme 5). The alcohol (+)-(**10**), the absolute



Scheme 5.

configuration of which was determined by its conversion into vitamin D_3 (**1**), was oxidised with pyridinium chlorochromate to the corresponding aldehyde (+)-(**3**) in 77.9% yield, which was coupled with the vinyl anion (**4**) generated from the bromide (**27**) as before. 3,5-Cyclovitamin D_3 (**33**) obtained in 46.5% yield was separated into two components by silica gel column chromatography. Solvolysis of the polar compound (26% yield) as above gave vitamin D_3 (**1**) in 54.8% yield, which was identical



with an authentic sample in all respects; formation of the *trans*-isomer (**31**) was not detected by t.l.c. analysis. On the other hand, the less polar compound furnished, in the same reaction, vitamin D_3 (**1**) in 23.9% yield and *trans*-vitamin D_3 (**31**) in 19.2% yield. Thus, a stereoselective synthesis of vitamin D_3 has been accomplished. Since it was made clear from previous studies[5] that the cleavage of the cyclopropane ring proceeded with inversion of stereochemistry, the absolute configuration of the alcohol (+)-(**10**) was determined to be as shown.*

Experimental

General Methods.—All m.p.s were taken with a Yanagimoto micromelting-point apparatus (MP-S2). I.r. spectra were measured with a Hitachi 260-10 recording spectrophotometer, n.m.r. spectra with JEOL-PMS-60 and JEOL-PS-100 instruments using tetramethylsilane as internal standard, and mass spectra with Hitachi M-52-G and JEOL-JMS-01SG-2 spectrometers. Optical rotations were obtained on a JASCO-PIP-SL polarimeter using a 1-dm cell. H.p.l.c. was carried out with a Hitachi 635 instrument. After extraction, the organic solutions were dried over anhydrous sodium sulphate.

(±)-*Methyl* 2-*Methylenebicyclo*[3.1.0]*hexane*-1-*carboxylate* (**6**).—To a stirred solution of triphenylphosphonium methylide [prepared from methyl(triphenyl)phosphonium bromide (35.4 g) and 1.5M-butyl-lithium solution in n-hexane (63.5 ml)] in anhydrous THF (250 ml) was added a solution of methyl 2-oxobicyclo[3.1.0]hexane-1-carboxylate (**5**)[3] (10.2 g) in anhydrous THF (10 ml) at −20 °C and the mixture was stirred for 1 h at the same temperature and for 2 h at room temperature. The reaction mixture was treated with aqueous ammonium chloride and extracted with benzene. The extract was washed with water, dried, and evaporated to give a residue which was chromatographed on silica gel (100 g) using n-hexane–ethyl acetate (20:1 v/v) as eluant to afford the *ester* (**6**) (4.7 g, 47%) as an oil (Found: C, 70.95; H, 8.15. $C_9H_{12}O_2$ requires C, 71.05; H, 7.95%); $\nu_{max.}(CHCl_3)$ 1 710 cm^{-1} (CO_2CH_3); $\delta_H(CCl_4)$ *inter alia* 1.10 (1 H, t, *J* 4 Hz, 6-H), 3.70 (3 H, s, CO_2Me), 5.05 and 5.65 (together 2 H, each d, *J* 2 Hz, $C{=}CH_2$).

(±)-2-*Methylenebicyclo*[3.1.0]*hexane*-1-*methanol* (**10**).—To a stirred slurry of lithium aluminium hydride (730 mg) in anhydrous THF (100 ml) was added the ester (**6**) (3 g) at 0 °C. After being stirred for 1 h, the reaction mixture was treated with 10% aqueous sodium hydroxide and extracted with ether. The extract was washed with aqueous sodium chloride, dried, and evaporated to give a residue which was chromatographed on

* Recently, Wilson and his co-workers synthesized vitamin D_3 *via* 3,5-cyclovitamin D_3: S. R. Wilson and M. S. Haque, *Tetrahedron Lett.*, 1984, **25**, 3147; S. R. Wilson, M. S. Haque, A. M. Venkatesan, and P. A. Zucker, *ibid.*, p. 3151.

silica gel (60 g) using n-hexane–ethyl acetate (20:1 v/v) as eluant to afford the *alcohol* (**10**) (2.45 g, 100%) (Found: C, 77.05; H, 9.55. $C_8H_{12}O$ requires C, 77.4; H, 9.75%); *m/z* 124 (M^+); $\nu_{max.}$($CHCl_3$) 3 500 cm^{-1} (OH); δ_H(CCl_4) *inter alia* 4.77 (2 H, br s, C=CH_2) and 3.62 (2 H, br s, CH_2OH).

(±)-1-*Formyl*-2-*methylenebicyclo*[3.1.0]*hexane*(2-*Methylenebicyclo*[3.1.0]*hexane*-1-*carbaldehyde*) (**3**).—To a slurry of pyridinium chlorochromate (620 mg) in dichloromethane (30 ml) was added a solution of the alcohol (**10**) (220 mg) in dichloromethane (20 ml) and the mixture was stirred for 1 h at room temperature. The reaction mixture was then treated with Florisil, and filtered through Celite. After the filtrate was evaporated the residue was chromatographed on silica gel (5 g) using dichloromethane as eluant to give the aldehyde (**3**) (156 mg, 71%) as an oil, *m/z* 122 (M^+); $\nu_{max.}$($CHCl_3$) 1 690 cm^{-1} (C=O); δ_H(CCl_4) *inter alia* 5.01 (1 H, s, C=C*H*H), 5.34 (1 H, s, C=CH*H*), and 9.52 (1 H, s, CHO).

(±)-*Methyl* 3β-*Hydroxy*-2-*methylenebicyclo*[3.1.0]*hexane*-1-*carboxylate* (**7**) *and* (±)-*Methyl* 2-*Methylene*-3-*oxobicyclo*[3.1.0]*hexane*-1-*carboxylate* (**9**).—To a mixture of selenium dioxide (0.264 g), t-butyl hydroperoxide (1.275 g), and dichloromethane (200 ml) was added a solution of compound (**6**) (0.693 g) in dichloromethane (3 ml) at room temperature and the mixture was stirred for 1 h at the same temperature. The resulting mixture was treated with 10% aqueous sodium hydroxide (60 ml) and extracted with ether. The extract was washed successively with 10% aqueous sodium hydroxide and water, and dried. The residue resulting from the evaporation of the solvent was chromatographed on silica gel (3 g) using n-hexane–ethyl acetate (9:1 v/v) as eluant to give the keto ester (**9**) (260 mg, 34%) as an oil from the first fraction, *m/z* 166 (M^+); $\nu_{max.}$($CHCl_3$) 1 710 cm^{-1} (C=O); δ_H($CDCl_3$) *inter alia* 0.85 (1 H, t, *J* 4 Hz, 6-H), 3.73 (3 H, s, CO_2Me), 5.90 (1 H, s, C=CH*H*), and 6.17 (1 H, s, C=C*H*H).

From the second fraction, the *hydroxy ester* (**7**) (316 mg, 41%) was obtained as an oil (Found: C, 64.1; H, 7.3. $C_9H_{12}O_3$ requires C, 64.3; H, 7.15%); *m/z* 168; $\nu_{max.}$($CHCl_3$) 3 580 and 1 715 cm^{-1} (ester); δ_H($CDCl_3$) *inter alia* 0.98 (1 H, t, *J* 5 Hz, 6-H), 3.69 (3 H, s, CO_2Me), 4.20 (1 H, m, C*H*OH), 5.33 (1 H, d, *J* 2 Hz, C=C*H*H), and 5.81 (1 H, d, *J* 2 Hz, C=CH*H*).

(±)-*Methyl* 3β-*Methoxymethoxy*-2-*methylenebicyclo*[3.1.0]*hexane*-1-*carboxylate* (**8**).—To a stirred solution of the hydroxy ester (**7**) (120 mg) and di-isopropylethylamine (138 mg) in dichloromethane (4 ml) was added methoxymethyl chloride (69 mg) dropwise at room temperature. After the mixture had been stirred for 5 h at room temperature, the resulting mixture was diluted with water (15 ml) and extracted with ether. The extract was washed with water, dried, and evaporated. The residue was chromatographed on silica gel (1 g) using n-hexane–ethyl acetate (100:3 v/v) as eluant to give the *methoxymethoxy ester* (**8**) (147 mg, 97%) as an oil (Found: C, 62.15; H, 7.4. $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.55%); *m/z* 212 (M^+); $\nu_{max.}$($CHCl_3$) 1 715 cm^{-1} (ester); δ_H(CCl_4) *inter alia* 0.98 (1 H, t, *J* 5 Hz, 6-H), 3.36 (3 H, s, OCH$_2$O*Me*), 3.68 (3 H, s, CO_2Me), 4.10 (1 H, m, 3-H), 4.64 (2 H, s, OCH_2OMe), 5.32 (1 H, br s, C=C*H*H), and 5.79 (1 H, br s, C=CH*H*).

(±)-3β-*Methoxymethoxy*-2-*methylenebicyclo*[3.1.0]*hexane*-1-*methanol* (**11**).—According to the same procedure as described for the synthesis of the alcohol (**10**) from the ester (**6**), the *hydroxy derivative* (**11**) was obtained from compound (**8**) in 84% yield as an oil (Found: C, 65.45; H, 8.55. $C_{10}H_{16}O_3$ requires C, 65.2; H, 8.7%); *m/z* 184 (M^+); $\nu_{max.}$($CHCl_3$) 3 500 cm^{-1} (OH); δ_H(CCl_4) *inter alia* 3.35 (2 H, s, OCH$_2$O*Me*), 3.80 (2 H, m, CH_2OH), 4.10 (1 H, m, 3-H), 4.65 (2 H, s, OCH_2OMe), 5.10 (1 H, br s, C=C*H*H), and 5.16 (1 H, br s, C=CH*H*).

(±)-*Formyl*-3β-*methoxymethoxy*-2-*methylenebicyclo*[3.1.0]*hexane* (3β-*Methoxymethoxy*-2-*methylenebicyclo*[3.1.0]*hexane*-1-*carbaldehyde*) (**12**).—According to the same procedure as described for the preparation of the aldehyde (**3**) from the alcohol (**10**), the *aldehyde* (**12**) was obtained from the alcohol (**11**) in 77% yield as an oil (Found: M^+, 182.0936. $C_{10}H_{14}O_3$ requires *M*, 182.0941); $\nu_{max.}$($CHCl_3$) 1 695 cm^{-1} (C=O); δ_H(CCl_4) *inter alia* 1.07 (1 H, m, 6-H), 3.33 (3 H, s, OCH$_2$O*Me*), 4.10 (1 H, m, 3-H), 4.60 (2 H, s, OCH_2OMe), 5.24 (1 H, d, *J* 3 Hz, C=C*H*H), 5.59 (1 H, d, *J* 3 Hz, C=CH*H*), and 9.63 (1 H, s, CHO).

[*Bromo*(*cyclohexyl*)*methyl*]*tributylstannane* (**15**).—To a stirred solution of lithium-di-isopropylamide [prepared by addition of a 1.5M-solution of n-butyl-lithium in hexane (17.16 ml) to a solution of di-isopropylamine (4.29 ml) in anhydrous THF (20 ml) at −78 °C] was added dropwise tributyltin hydride (2.6 g) at −78 °C and the mixture was stirred for 30 min. After the addition of a solution of cyclohexanecarbaldehyde (**13**) (1 g) in anhydrous THF (2 ml), the resulting reaction mixture was stirred for 25 min at the same temperature, diluted with aqueous ammonium chloride, and extracted with n-hexane. The extract was washed with water, dried, and evaporated to give the hydroxy stannane (**14**) as an oil which was used for the next reaction without further purification because of its instability.

To a solution of the hydroxy stannane (**14**) in dichloromethane (15 ml) was added tetrabromomethane (4.44 g) and a solution of triphenylphosphine (2.72 g) in dichloromethane (5 ml) at 0 °C. After being stirred for 2 h at room temperature, the reaction mixture was diluted with water and extracted with n-hexane. The extract was washed with water, dried, and evaporated to give a residue, which was chromatographed on silica gel (20 g) using n-hexane as eluant to afford the bromide (**15**) [1.5 g, 36% from the aldehyde (**13**)] as an oil, δ_H(CCl_4) *inter alia* 3.50 (1 H, d, *J* 6 Hz, $Bu_3^nSnCHBr$).

The Cyclohexylidene Stannane (**16**).—A mixture of the bromide (**15**) (4 g), DBU (3.92 g), DMF (80 ml), and toluene (20 ml) was stirred and refluxed for 4 h and the resulting reaction mixture was diluted with water and extracted with benzene. The extract was washed successively with 10% hydrochloric acid and water, and dried. The residue resulting from the evaporation of the solvent was chromatographed on neutral alumina (100 g) using n-hexane as eluant to give the *vinylstannane* (**16**) (2.1 g, 64%) as an oil (Found: C, 59.45; H, 9.7. $C_{19}H_{38}Sn$ requires C, 59.25; H, 9.95%); $\nu_{max.}$($CHCl_3$) 1 596 cm^{-1} (C=C); δ_H(CCl_4) *inter alia* 5.24 (1 H, s, Bu_3^nSnCH=C).

(±)-α-*Cyclohexylidenemethyl*-2-*methylenebicyclo*[3.1.0]*hexane*-1-*methanol* (**20**).—To a stirred solution of the vinylstannane (**16**) (600 mg) in anhydrous THF (4 ml) was added a solution of 1.56M-butyl-lithium in n-hexane (1.1 ml) at −78 °C. After the mixture had been stirred for 2 h at −35 °C, a solution of the (±)-aldehyde (**3**) (190 mg) in anhydrous THF (1 ml) was added at −78 °C. The resulting reaction mixture was stirred for 30 min at the same temperature, then quenched with aqueous ammonium chloride, and extracted with ether. The extract was washed with water, dried, and evaporated to give the residue which was chromatographed on silica gel (20 g) using n-hexane–ethyl acetate (100:3 v/v) as eluant to give the *coupled compound* (**20**) (258 mg, 76%) as an oil (Found: M^+, 218.1664. $C_{15}H_{22}O$ requires *M*, 218.1669); $\nu_{max.}$($CHCl_3$) 3 580 (OH) and 1 640 cm^{-1} (C=C); δ_H(CCl_4) *inter alia* 4.99 (4 H, m, C*H*OH and olefinic hydrogens).

(±)-(*Z*)-3-(2-*Cyclohexylidene-ethylidene*)-4-*methylenecyclo-*

hexanol (**22**).—A mixture of compound (**20**) (80 mg), toluene-*p*-sulphonic acid (21 mg), dioxane (1.5 ml), and water (0.5 ml) was stirred for 10 min at 55 °C and the reaction mixture was then treated with aqueous sodium hydrogen carbonate and extracted with ether. The extract was washed with aqueous ammonium chloride and dried. The residue resulting from the evaporation of the solvent was chromatographed on silica gel (2 g) using n-hexane–ethyl acetate (20:1 v/v) as eluant to give the (*Z*)-triene (**22**) (53 mg, 66%) as an oil, the spectral data of which were identical with those reported.[9]

(±)-α-*Cyclohexylidenemethyl*-3-*methoxymethoxy*-2-*methylenebicyclo*[3.1.0]*hexane*-1-*methanol* (**21**).—According to the same procedure as described for the synthesis of the alcohol (**20**) by the coupling reaction between the aldehyde (**3**) and the vinyl anion (**19**) generated from the vinylstannane (**16**), the *coupled compound* (**21**) was obtained in 76.8% yield as an oil by the reaction between the aldehyde (**12**) and the vinyl anion (**19**) (Found: M^+, 278.1879. $C_{17}H_{26}O_3$ requires *M*, 278.1880); $\nu_{max.}$($CHCl_3$) 3 570 (OH) and 1 655 cm^{-1} (C=C); δ_H(CCl_4) *inter alia* 0.56 (1 H, t, *J* 4 Hz, 6-H), 3.38 (3 H, s, OCH_2OMe), 4.14 (1 H, m, $CHOCH_2OMe$), 4.68 (2 H, s, OCH_2OMe), 4.84 (2 H, m, *CH*OH and olefinic hydrogen), and 5.18 (2 H, m, olefinic hydrogens).

(±)-(*Z*)-3-(2-*Cyclohexylidene-ethylidene*)-t-5-*methoxymethoxy*-4-*methylenecyclohexan*-r-1-*ol* (**23**).—By the same procedure as described for the synthesis of the (*Z*)-triene (**22**) by the solvolysis of compound (**20**), the (Z)-*triene* (**23**) was obtained in 65.3% yield as an oil by the solvolysis of the alcohol (**21**) (Found: M^+, 278.1876. $C_{17}H_{26}O_3$ requires *M*, 278.1880); $\lambda_{max.}$(MeOH) 265 nm (ε 13 200); δ_H(CCl_4) *inter alia* 3.36 (3 H, s, OCH_2OMe), 4.16 (1 H, m, *CH*OH), 4.28 (1 H, m, $CHOCH_2OMe$), 4.58 (2 H, s, OCH_2OMe), 5.20 (2 H, br s, $C=CH_2$), 6.00 (1 H, br s, olefinic hydrogen), and 6.30 (1 H, br s, olefinic hydrogen).

(±)-(*Z*)-5-(2-*Cyclohexylidene-ethylidene*)-4-*methylenecyclohexane*-r-1, t-3-*diol* (**24**).—A mixture of the (*Z*)-triene (**23**) (65 mg), conc. hydrochloric acid (4 drops), and methanol (4 ml) was stirred for 1.5 h at 60 °C and the reaction mixture was then treated with aqueous sodium hydrogen carbonate and extracted with ether. The extract was washed with aqueous sodium chloride, dried, and evaporated to give a residue which was chromatographed on silica gel (1 g) using ether as eluant to afford the *dihydroxy triene* (**24**) (38 mg, 69.5%) as a glass (Found: M^+, 234.1622. $C_{15}H_{22}O_2$ requires *M*, 234.1620); $\lambda_{max.}$(MeOH) 261 nm (ε 18 400); δ_H(CCl_4) *inter alia* 4.20 (1 H, m, 1-H), 4.41 (1 H, m, 3-H), 5.00 (1 H, br s, C=C*H*H), 5.31 (1 H, br s, C=CH*H*), 6.02 (1 H, br s, olefinic hydrogen), and 6.32 (1 H, br s, olefinic hydrogen).

The Cyclohexylidene Bromide (**18**).—A mixture of the dibromide (**17**) (3.2 g), zinc (1.54 g), acetic acid (3 g), and dichloromethane (50 ml) was stirred and refluxed for 20 h and then filtered through Celite. The filtrate was washed successively with water, aqueous sodium hydrogen carbonate, and water, and dried. The residue resulting from evaporation of the solvent was distilled to give the vinyl bromide (**18**) (1.72 g, 83.5%) as an oil, b.p. 75—79 °C (35 mmHg); *m/z* 174, 176 (M^+); $\nu_{max.}$($CHCl_3$) 1 630 cm^{-1} (C=C); δ_H(CCl_4) *inter alia* 5.71 (1 H, s, C=CBrH).

Alternative Preparation of Compound (**20**).—To a solution of the vinyl bromide (**18**) (300 mg) in anhydrous THF (4 ml) was added a solution of 1.7M-t-butyl-lithium in n-hexane (1.6 ml) at 78 °C. After the mixture had been stirred for 1 h at the same temperature, a solution of the (±)-aldehyde (**3**) (146 mg) in anhydrous THF (1 ml) was added. The resulting reaction mixture was stirred for 30 min at −78 °C, quenched with aqueous ammonium chloride, and extracted with ether. The extract was washed with aqueous sodium chloride, dried, and evaporated to give a residue which was chromatographed on silica gel (10 g) using n-hexane–ethyl acetate (100:3 v/v) as eluant to afford compound (**20**) (206 mg, 79.2%) as an oil. The product (**20**) thus obtained was identical with that previously prepared on the basis of its spectral comparison.

Hydroxy Dibromide Adduct (**26**) *of Grundmann's Ketone* (**25**).—A solution of lithium dicyclohexylamide [prepared by addition of a 1.5M solution of n-butyl-lithium (14.55 ml) to a solution of dicyclohexylamine (4.12 g) in anhydrous THF (100 ml) at −78 °C] was added to a stirred solution of dibromomethane (3.95 g) in anhydrous THF (80 ml) at −96 °C. After addition of a solution of Grundmann's ketone (**25**) (3 g) in anhydrous THF (5 ml), the resulting reaction mixture was stirred for 20 min at the same temperature, quenched with aqueous ammonium chloride, and extracted with benzene. The extract was washed with water, dried, and evaporated to give a residue which was chromatographed on silica gel (100 g) using n-hexane–ethyl acetate (20:1 v/v) as eluant to afford the *adduct* (**26**) (2.2 g, 43.3%) as an oil (Found: C, 52.45; H, 7.65; Br, 36.8. $C_{19}H_{34}Br_2O$ requires C, 52.05; H, 7.8; Br, 36.45%); $\nu_{max.}$($CHCl_3$) 3 550 cm^{-1} (OH); δ_H(CCl_4) *inter alia* 5.61 (1 H, s, $CHBr_2$).

4-*Deoxo*-4-*bromomethylene Derivative* (**27**) *of Grundmann's Ketone*.—A mixture of the hydroxy dibromide (**26**) (350 mg), zinc (180 mg), acetic acid (144 mg), and dichloromethane (10 ml) was stirred and refluxed for 13 h and then filtered through Celite. The filtrate was washed successively with water, aqueous sodium hydrogen carbonate, and water, and dried. The residue resulting from evaporation of the solvent was chromatographed on silica gel (1 g) using n-hexane as eluant to give the *vinyl bromide* (**27**) (242 mg, 89%) as an oil (Found: M^+, 342.1773. $C_{19}H_{33}Br$ requires *M*, 340.1781); $\nu_{max.}$($CHCl_3$) 1 620 cm^{-1} (C=C); δ_H(CCl_4) *inter alia* 5.56 and 5.86 (1 H, each s, C=CBrH).

Cyclovitamin D_3 (**28**).—To a solution of the vinyl bromide (**27**) (240 mg) in anhydrous THF (3 ml) was added a solution of 2.2M-t-butyl-lithium in n-hexane (0.65 ml) at −78 °C. After the mixture had been stirred for 1 h at the same temperature, a solution of the (±)-aldehyde (**3**) (86 mg) in anhydrous THF (0.5 ml) was added. The resulting reaction mixture was stirred for 30 min at −78 °C, quenched with aqueous ammonium chloride, and extracted with ether. The extract was washed with aqueous sodium chloride, dried, and evaporated to give a residue which was chromatographed on silica gel (1 g) using n-hexane–ethyl acetate (100:3 v/v) as eluant to afford cyclovitamin D_3 (**28**) (150 mg, 55%) as a diastereoisomeric mixture, *m/z* 384 (M^+); δ_H ($CDCl_3$) *inter alia* 0.58 and 0.53 (3 H, each s, 13-Me).

The Solvolysis of Cyclovitamin D_3 (**28**).—A mixture of cyclovitamin D_3 (**28**) (300 mg), toluene-*p*-sulphonic acid (45 mg), dioxane (15 ml), and water (5 ml) was stirred for 10 min at 55 °C and the reaction mixture was then treated with aqueous sodium hydrogen carbonate and extracted with ether. The extract was washed with aqueous sodium chloride and dried. The residue resulting from evaporation of the solvent was chromatographed on silica gel (1 g). Elution with n-hexane–ethyl acetate (100:8 v/v) afforded *trans*-vitamin D_3 (39 mg, 13%) as an epimeric mixture whose spectra data were consistent with those of an authentic sample.[1] Elution with n-hexane–ethyl acetate (10:1 v/v) gave a mixture of vitamin D_3 and 3-epivitamin D_3 (106 mg, 35.3%) as an oil which was separated into two components on h.p.l.c. with Hitachi gel 3011 using methanol–chloroform (8:2 v/v) as eluant. The spectral data of both products were consistent with those of authentic samples.[15]

(2-*Methylenebicyclo*[3.1.0]*hexan*-1-*yl*)*methyl Methoxy*(*phenyl*)*acetate* (**32**).—To a solution of 2-methylenebicyclo[3.1.0]hexane-1-methanol (**10**) (4.448 g), (+)-(*S*)-*O*-methylmandelic acid [methoxy(phenyl)acetic acid] (6.55 g), and 4-(*NN*-dimethylamino)pyridine (0.825 g) in dichloromethane (100 ml) was added a solution of DCC (8.512 g) in dichloromethane (10 ml) at 0 °C. The mixture was stirred for 30 min at the same temperature, then for 2.5 h at room temperature, and was then evaporated and the resulting residue was extracted with benzene. The extract was washed successively with aqueous sodium hydrogen sulphate and water, and then dried. The residue resulting from evaporation of the solvent was chromatographed on silica gel (100 g) using n-hexane–ethyl acetate (20:1 v/v) as eluant to give the *mandelates* (**32**) (9.315 g, 95.5%) as an oil. Separation of the mandelates (**32**) thus obtained was performed by h.p.l.c. with LiChrosorb SI-60 using n-hexane–ethyl acetate (50:1 v/v) as eluant to give the *cis*-isomers (**32A**) and (**32B**), in the ratio 1:1, both as oils. For the α-*isomer* (**32A**) (Found: C, 74.9; H, 7.45. $C_{17}H_{20}O_3$ requires C, 74.95; H, 7.4%); $\nu_{max.}$($CHCl_3$) 1 710 cm^{-1} (C=O); δ_H($CDCl_3$) *inter alia* 3.40 (3 H, s, OMe), 4.22 and 4.36 (each 1 H, each d, *J* 12 Hz, OCH_2), and 4.72—4.76 (3 H, m, C*H*(OMe)Ph and C=CH_2). For the β-*isomer* (**32B**) (Found: C, 74.65; H, 7.3%); $\nu_{max.}$($CHCl_3$) 1 710 cm^{-1} (C=O); δ_H($CDCl_3$) *inter alia* 3.39 (3 H, s, OMe), 4.19 and 4.34 (each 1 H, each d, *J* 12 Hz, OCH_2), and 4.64—4.76 (3 H, m, C*H*(OMe)Ph and C=CH_2).

(+)-2-*Methylenebicyclo*[3.1.0]*hexane*-1-*methanol* (**10**).—A mixture of the mandelate (**32B**) (2.18 g), potassium hydroxide (0.9 g), water (2 ml), and methanol (30 ml) was stirred for 20 min at room temperature and then the resulting reaction mixture was extracted with ether. The extract was washed with aqueous sodium chloride, dried, and evaporated to give a residue which was chromatographed on silica gel (50 g) using n-hexane–ethyl acetate (20:1 v/v) as eluant to afford the title compound (+)-(**10**) (985 mg, 99%) as an oil, $[\alpha]_D^{20}$ +45.0° (*c* 0.44 in n-hexane), whose spectral data in solution were identical with those of the racemate (**10**) obtained previously.

(−)-2-*Methylenebicyclo*[3.1.0]*hexane*-1-*methanol* (**10**).—By the same procedure as described above for the synthesis of compound (+)-(**10**), the isomer (−)-(**10**) was obtained in 99% yield as an oil, $[\alpha]_D^{20}$ −46.5° (*c* 0.46 in n-hexane).

(+)-2-*Methylenebicyclo*[3.1.0]*hexane*-1-*carbaldehyde* (**3**).—By the same procedure as described for the synthesis of the racemic aldehyde (±)-(**3**) from (±)-2-methylenebicyclo[3.1.0]-hexane-1-methanol (**10**), the optically active aldehyde (+)-(**3**) was obtained in 77.9% yield as an oil.

Cyclovitamin D_3 (**33**) *and its Solvolysis*.—According to the same procedure as described for the synthesis of compound (**28**), cyclovitamin D_3 (**33**) was obtained, by using (+)-2-methylenebicyclo[3.1.0]hexane-1-carbaldehyde (**3**) instead of (±)-(**3**), as an epimeric mixture at C-6 in 46.5% yield and this was separated into two components by silica gel column chromatography. The solvolysis of the polar compound, obtained in 26% yield, following the same procedure as for compound (**28**), afforded vitamin D_3 (**1**) in 54.8% yield, while from the solvolysis of the less polar compound, obtained in 20.5% yield, a mixture of vitamin D_3 (**1**) (23.8%) and *trans*-vitamin D_3 (**31**) (19.2%) was obtained.

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