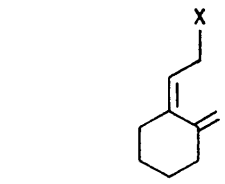
Calciferol and its Relatives. Part 22.[1] A Direct Total Synthesis of Vitamin D_2 and Vitamin D_3[2]

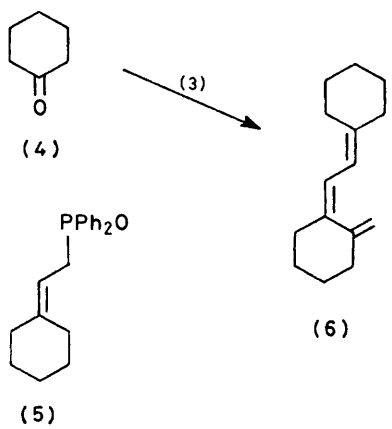
By **Basil Lythgoe,* Thomas A. Moran, Mayara E. N. Nambudiry, John Tideswell,** and **Paul W. Wright,**
Department of Organic Chemistry, The University, Leeds LS2 9JT

Direct total syntheses are described of 3-deoxyvitamin D_2, vitamin D_2, and vitamin D_3. For the first, the lithio-derivative of (*Z*)-2-(2-methylenecyclohexylidene)ethyl(diphenyl)phosphine oxide and the Windaus–Grundmann ketone $C_{19}H_{32}O$ were the reacting partners; for the second, the same ketone and the lithio-derivative of a protected form of (*S*)-(*Z*)-2-(5-hydroxy-2-methylenecyclohexylidene)ethyl(diphenyl)phosphine oxide; and for the third, the same lithio-derivative and des-AB-cholestan-8-one. In these reactions, the original *Z*-allyl geometry of the phosphine oxides was completely preserved in the 5,6-double bond of the products, and the new (7,8-) double bond was formed with exclusive *E*-geometry.

EACH of the three isomeric conjugated trienes 5-*trans*-vitamin D_3,[3] tachysterol$_3$,[4] and precalciferol$_3$[5] has been obtained by total synthesis; as each of them can be transformed into vitamin D_3, the first two photochemically,



(1) X = OH
(2) X = PPh_3^+ Br^-
(3) X = PPh_2O



(4) (5) (6)

the last thermally, three formal total syntheses of the vitamin are available. The present paper describes a further total synthesis in which the triene system of the vitamin is constructed directly, instead of by an isomerisation process. We also report the application of a similar approach to the total synthesis of vitamin D_2, for which previously only partial syntheses [3b,6] were available.

The plan of the present synthesis was to use the *Z*-dienediol (13) † as the source of ring A of the vitamin together with the attached C-10 methylene group and the bridging carbon atoms C-6 and C-7. At the outset we proposed to effect the synthesis by converting the dienediol (13) into a suitably protected Wittig reagent which could be brought into reaction with the C_{18} ketone [7] (17), so constructing the 7,8-double bond of the vitamin (19). This plan of synthesis could be expected to have advantages in efficiency, since in it the more complex of the two necessary fragments, that representing rings C and D, is used in its simplest form. An equally important consideration was that the plan appeared to offer a simple solution to the stereochemical problems. We had shown in earlier work [8] that allylic alcohols having a double bond with *Z*-geometry [such as is present in the dienediol (13)] can be transformed into phosphonium bromides and used in Wittig reactions to give olefins in which the original allyl geometry is preserved; thus the (natural) *Z*-geometry of the 5,6-double bond of the vitamin would be secured. Secondly, although in many reactions between allylic Wittig reagents and unsymmetrical carbonyl compounds mixtures of two products are obtained, with different geometries at the newly formed double bond, we observed that similar reaction using the C_{19} Windaus–Grundmann [9] ketone (8) appeared to give only one isomer, presumably that in which the newly formed double bond had *E*-geometry (see later). Thus our

† All the structures in this paper represent absolute configurations.

[1] Part 21, B. Lythgoe, R. Manwaring, J. R. Milner, T. A. Moran, M. E. N. Nambudiry, and J. Tideswell, *J.C.S. Perkin I*, 1978, 387.

[2] Preliminary communication, B. Lythgoe, M. E. N. Nambudiry, and J. Tideswell, *Tetrahedron Letters*, 1977, 3685.

[3] (*a*) H. H. Inhoffen, H. Burkhardt, and G. Quinkert, *Chem. Ber.*, 1959, **92**, 1564; (*b*) H. H. Inhoffen, K. Irmscher, H. Hirschfeld, U. Stache, and A. Kreutzer, *ibid.*, 1958, **91**, 2309.

[4] R. S. Davidson, S. M. Waddington-Feather, D. H. Williams, and B. Lythgoe, *J. Chem. Soc.* (*C*), 1967, 2534.

[5] T. M. Dawson, J. Dixon, P. S. Littlewood, B. Lythgoe, and A. K. Saksena, *J. Chem. Soc.* (*C*), 1971, 2960.

[6] I. T. Harrison and B. Lythgoe, *J. Chem. Soc.*, 1958, 837.

[7] H. Brockmann and A. Busse, *Z. physiol. Chem.*, 1938, **256**, 252. The ketone is readily obtained by oxidation of the corresponding 8β-ol: H. H. Inhoffen, G. Quinkert, S. Schütz, D. Kampe, and G. F. Domagk, *Chem. Ber.*, 1957, **90**, 664. Total synthesis: ref. 3*a*; P. S. Littlewood, B. Lythgoe, and A. K. Saksena, *J. Chem. Soc.* (*C*), 1971, 2955; and papers cited therein.

[8] I. T. Harrison and B. Lythgoe, *J. Chem. Soc.*, 1958, 843.

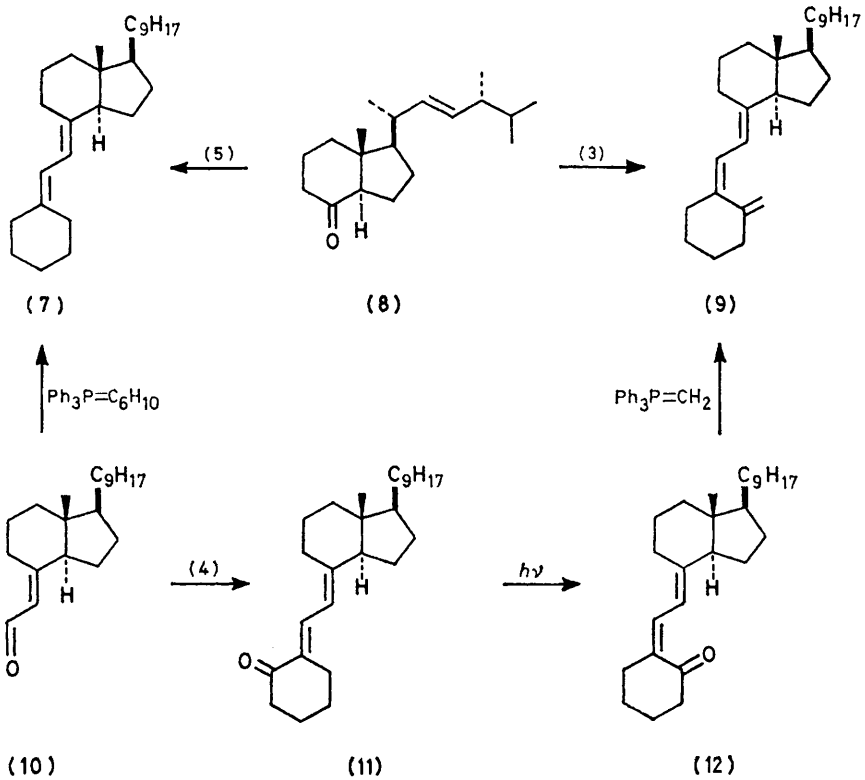
[9] A. Windaus and W. Grundmann, *Annalen*, 1936, **524**, 295.

intended synthesis was expected to secure the (natural) *E*-geometry of the 7,8-double bond of the vitamins.

The *Z*-dienediol (13) was first obtained [10] as a product of degradation of vitamin D_2; it has more recently [1] been obtained in the proper optically active form by synthesis from (+)-cyclohex-4-ene-1,*trans*-2-dicarboxylic acid. In exploratory work [10] a convenient synthesis of the model *Z*-dienol (1) was found which made it comparatively easily available, and as the absence of a secondary hydroxy group removed a source of complication, it was used instead of the dienediol (13) in our early experiments on the preparation of the necessary Wittig reagents.

Reaction of the dienol (1) with the complex [11] from *N*-bromosuccinimide and dimethyl sulphide in the presence of triphenylphosphine gave in low yield a crystalline solid with the composition and spectral properties expected for the phosphonium compound (2). Better yields were obtained when the dienol (1) was converted into the allylic chloride, which was then treated without purification with triphenylphosphine in acetone containing an excess of sodium iodide; this gave the iodide corresponding to (2) in *ca.* 70% yield. Both the bromide (2) and the corresponding iodide were found to give the expected red solutions when treated in tetrahydrofuran with n-butyl-lithium. However, the red colour faded even in the absence of any apparent reagent, and the red solutions failed to show the expected reaction with cyclohexanone.

Work with phosphonium compounds was then discontinued, since we had already made some successful experiments on the preparation of allylic diphenylphosphine oxides and their use in Horner [12] olefination reactions. In continuation, we observed [13] that the allylic chloride derived from the dienol (1) reacted with lithium diphenylphosphide to give, after oxidation of the product, samples of the phosphine oxide (3) which, although not completely pure, reacted with cyclohexanone to give substantial yields of the (impure) *Z*-triene [6] (6). Thus in this case the Horner variant succeeded where the Wittig olefination method did not.

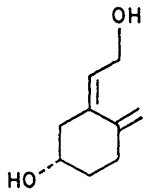


General methods were then worked out [14] for the preparation of geometrically homogeneous allylic diphenylphosphine oxides, and it was shown that the use of these compounds in Horner reactions provided a convenient one-step synthesis of conjugated dienes in which the original allyl geometry is preserved.

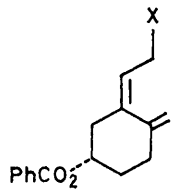
As in the corresponding Wittig reactions, the Horner reactions of allylic diphenylphosphine oxides with the Windaus–Grundmann ketone (8) appeared to give only

[10] J. V. Frosch, I. T. Harrison, B. Lythgoe, and A. K. Saksena, *J.C.S. Perkin I*, 1974, 2005.
[11] E. J. Corey, C. V. Kim, and M. Takeda, *Tetrahedron Letters*, 1972, 4339.
[12] L. Horner, W. Klink, and H. Hoffmann, *Chem. Ber.*, 1963, **96**, 3133; and earlier papers cited therein.
[13] P. W. Wright, Ph.D. Thesis, Leeds, 1974.
[14] B. Lythgoe, T. A. Moran, M. E. N. Nambudiry, S. Ruston, J. Tideswell, and P. W. Wright, *Tetrahedron Letters*, 1975, 3863; B. Lythgoe, T. A. Moran, M. E. N. Nambudiry, and S. Ruston, *J.C.S. Perkin I*, 1976, 2386.

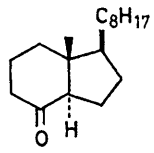
one geometric isomer. For example, (2-cyclohexylideneethyl)diphenylphosphine oxide [14] (5) formed a lithio-derivative which reacted with the ketone (8) to give only one conjugated diene (7). Its *E*-configuration was apparent from its formation by a second method, namely



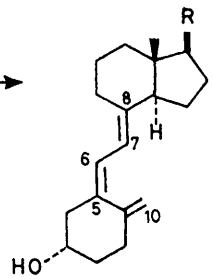
(13)

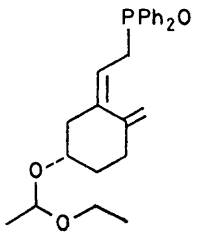


(14) X = $OCO_2 \cdot CH_2 \cdot CCl_3$
(15) X = OH
(16) X = PPh_2O



(17)





(18)

(19) R = C_8H_{17}
(20) R = C_9H_{17}

by interaction of the C_{21} αβ-unsaturated aldehyde (10), first obtained from degradation of vitamin D_2 by Heilbron and his co-workers,[15] with cyclohexylidenetriphenylphosphorane. It was therefore expected that the use of the Horner method in a synthesis of vitamin D_2 or one of its relatives would favour the formation of a product with the natural *E*-geometry of the 7,8-double bond.

Conversion [14] of the *Z*-dienol (1) into its 2,6-dichlorobenzoate, and treatment with lithium diphenylphosphide, followed by oxidation of the product with hydrogen peroxide, gave the crystalline phosphine oxide (3) in a yield of *ca.* 44% from the alcohol (1). Its lithio-derivative reacted with the Windaus–Grundmann ketone (8) to give (*ca.* 70%) a crystalline product, the spectral data for which indicated the 3-deoxyvitamin D_2 structure (9). For confirmation, this compound was prepared by a second method, in which the 5*Z*-geometry was secured photochemically.[6] The αβ-unsaturated aldehyde (10) and cyclohexanone reacted in the presence of sodium ethoxide to give the *E,E*-dienone (11), irradiation of which provided the 5*Z*,7*E*-isomer (12). Treatment with methylenetriphenylphosphorane completed the preparation of 3-deoxyvitamin D_2 (9), identical with the product from the phosphine oxide route.

These model experiments having had a satisfactory outcome, work was commenced with the optically active *Z*-dienediol (13). It reacted with a restricted amount of trichloroethyl chloroformate [16] mainly at the primary hydroxy group; benzoylation of the product gave the diester (14), and removal of the trichloroethyl carbonate group gave the secondary monobenzoate (15). This was treated with chloromethylenedimethylammonium chloride [17] to convert it into the primary allylic chloride; reaction with lithium diphenylphosphide, followed by oxidation with hydrogen peroxide, gave the crystalline benzoate-phosphine oxide (16). Alkaline hydrolysis of the benzoate group, and reaction of the secondary hydroxy group with ethyl vinyl ether then gave the protected phosphine oxide (18) in *ca.* 46% yield from the dienediol (13).

The lithio-derivative of the phosphine oxide (18) was generated at −75 °C and was treated with the ketone (8) between −40 and 20 °C, and the product was hydrolysed with aqueous acetic acid to remove the protecting acetal group. After chromatography, crystalline vitamin D_2 (20) with satisfactory spectral characteristics was obtained in *ca.* 60% yield from the phosphine oxide (18). It was further characterised by conversion into the 3,5-dinitrobenzoate. Since the ketone (8) has recently [18] been obtained by total synthesis, the present work constitutes the first total synthesis of vitamin D_2.

Reaction in a similar manner between the phosphine oxide (18) and des-AB-cholestan-8-one [7] (17) gave vitamin D_3 (19) in a yield (u.v.) of over 59%. The known crystalline 3,5-dinitrobenzoate which was prepared from it was obtained in 53% overall yield from the ketone (17).

EXPERIMENTAL

Unless otherwise specified, optical rotations refer to solutions in chloroform, u.v. data to solutions in ethanol, and n.m.r. data to solutions in deuteriochloroform. T.l.c. and p.l.c. were carried out with Kieselgel GF_{254}. Light petroleum refers to the fraction b.p. 60—80 °C unless otherwise specified.

(Z)-2-(2-*Methylenecyclohexylidene*)*ethyl*(*triphenyl*)*phosphonium Bromide* (2).—Dimethyl sulphide (1 cm^3) was added to a stirred suspension of *N*-bromosuccinimide (2.0 g) in dry methylene chloride (100 cm^3) at 0 °C under nitrogen; the mixture was cooled to −20 °C and the dienol (1) (930 mg) was added in methylene chloride (10 cm^3). The mixture was then allowed to warm to 0 °C during 30 min, and kept at this temperature during the addition of triphenylphosphine (4.7 g) in methylene chloride (15 cm^3). Stirring

[15] I. M. Heilbron, R. N. Jones, K. M. Samant, and F. S. Spring, *J. Chem. Soc.*, 1936, 905; A. Windaus and U. Riemann, *Z. physiol. Chem.*, 1942, **274**, 206.

[16] T. B. Windholz and D. B. R. Johnston, *Tetrahedron Letters*, 1967, 2555.

[17] D. R. Hepburn and H. R. Hudson, *J.C.S. Perkin I*, 1976, 754.

[18] B. Lythgoe, D. A. Roberts, and I. Waterhouse, *J.C.S. Perkin I*, 1977, 2608.

was continued for 4 h, and then for a further 16 h with the mixture at 20 °C. The solution was then washed with water, dried, and evaporated. Crystallisation of the residue from acetone–ether, and repeated recrystallisation from the same solvent, gave the *phosphonium bromide* (2) (550 mg) as needles, m.p. 170—172°, $\nu_{max.}$ (Nujol) 690s, 721s, and 750s cm^{-1}, τ 4.7—5.1 (1 H, m, $=CH-CH_2$), 5.07br (1 H, s, $=CH_2$), 5.21 and 5.45 (2 H, dd, J 7 and 14 Hz, CH_2–P), and 5.40 (1 H, obscured s, $=CH_2$) (Found: C, 69.65; H, 5.85; Br, 17.35; P, 6.65. $C_{27}H_{28}BrP$ requires C, 70.0; H, 6.05; Br, 17.3; P, 6.7%).

For the preparation of the corresponding phosphonium iodide, the dienol (1) (460 mg) was converted into the chloride by reaction in methylene chloride with the complex from dimethyl sulphide and *N*-chlorosuccinimide; the product formed an oil (460 mg), homogeneous to t.l.c. (benzene), $\nu_{max.}$ (film) 655s, and 910s cm^{-1}, τ 4.59 (1 H, t, J 7 Hz, $=CH-CH_2$), 5.03br (1 H, s, $=CH_2$), 5.20 (1 H, d, J 2 Hz, $=CH_2$), and 5.92 (2 H, d, J 7 Hz, $-CH_2Cl$). To a solution of the chloride (460 mg) in dry acetone containing triphenylphosphine (1.1 g), sodium iodide (500 mg) was added in portions with stirring, and the solution was kept in the dark at 22 °C for 24 h and then filtered from sodium chloride. Ether was added slowly to the filtrate, and the precipitate was recrystallised from acetone–ether to give the *phosphonium iodide* as pale yellow needles (910 mg), m.p. 148—149°, $\nu_{max.}$ (Nujol) 690s, 720s, 750s, and 908m cm^{-1}, τ 4.7—5.1 (1 H, m, $=CH$), 5.07br (1 H, s, $=CH_2$), 5.34 and 5.56 (2 H, dd, J 7 and 14 Hz, CH_2–P), and 5.52 (1 H, obscured s, $=CH_2$) (Found: C, 63.5; H, 5.3; I, 25.2; P, 6.15. $C_{27}H_{28}PI$ requires C, 63.5; H, 5.5; I, 24.9; P, 6.1%).

Synthesis of the Conjugated Diene (7) *from the Ketone* (8).—A suspension of (2-cyclohexylidene-ethyl)diphenylphosphine oxide (310 mg) in tetrahydrofuran (10 cm^3) at 0 °C under nitrogen was metallated with n-butyl-lithium (1 equiv.), and after ½ h the mixture was cooled to −78 °C. A solution of the ketone (8) (300 mg) in tetrahydrofuran (2 cm^3) was then added dropwise, discharging the red colour; the solution was kept overnight at room temperature. It was then diluted with ether and washed successively with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and was dried and evaporated. The product was purified by p.l.c., giving the *diene* (7) (153 mg), $[\alpha]_D^{20}$ +62.2°, $\lambda_{max.}$ 243, 251.5, and 261 nm (ε 31 300, 37 000, and 24 900), $\nu_{max.}$ (film) 851w, 862w, 970m, 1 344w, 1 372m, 1 448m, 1 615w, 2 865s, 2 922s, and 2 960s cm^{-1}, τ 4.05 (2 H, dd, J 12.5 Hz, $=CH-CH=$), 4.80 (2 H, m, $-CH=CH-$), and 9.42 (3 H, s, $C-CH_3$) (Found: M^+, 368.344 6. $C_{27}H_{44}$ requires M, 368.344 285).

Synthesis of the Conjugated Diene (7) *from the Aldehyde* (10).—A stirred solution of cyclohexylidenetriphenylphosphorane [from the phosphonium bromide (0.425 g)] in tetrahydrofuran (10 cm^3) under nitrogen at −78 °C was treated with the aldehyde (10) (302 mg) in tetrahydrofuran (2 cm^3); the mixture was then allowed to warm to room temperature, at which it was stirred overnight. It was diluted with ether and washed successively with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and then dried and evaporated. P.l.c. gave the diene (7) (128 mg), $[\alpha]_D^{22}$ +63.8°, with spectral characteristics identical with those of the material obtained from the ketone (8).

The Phosphine Oxide (3).—The alcohol (1) (1.38 g), 2,6-dichlorobenzoic acid (2.1 g), and dimethylformamide dineopentyl acetal (3.0 g) were heated under reflux in benzene (50 cm^3) for 1 h. The cooled solution was diluted with ether, washed with aqueous sodium hydrogen carbonate and with water, and then dried and evaporated. Crystallisation from light petroleum at −40 °C gave (Z)-2-(2-*methylenecyclohexylidene*)*ethyl* 2,6-*dichlorobenzoate* (2.0 g), m.p. 54—55°, $\nu_{max.}$ (film) 1 140, 1 272, 1 432, and 1 740 (all s) cm^{-1}, τ 2.71 (3 H, s, ArH), 4.49 (1 H, t, =CH), *ca.* 5.02 (overlap of 2 H, d, J 6.5 Hz, OCH_2 and 1 H, m, $=CH_2$), 5.25 (1 H, d, $W_{\frac{1}{2}}$ 4.5 Hz, $=CH_2$), 7.73 (4 H, m, allylic CH_2), and 8.30 (4 H, m, $W_{\frac{1}{2}}$ 11 Hz, CH_2) (Found: C, 62.05; H, 5.2; Cl, 23.35. $C_{16}H_{16}Cl_2O_2$ requires C, 61.7; H, 5.2; Cl, 22.8%).

To a stirred solution of the above 2,6-dichlorobenzoate (1.98 g) in tetrahydrofuran (20 cm^3) at −25 °C under nitrogen a solution of lithium diphenylphosphide [from diphenylphosphine (1.16 g)] in tetrahydrofuran (10 cm^3) and light petroleum (5 cm^3) was added dropwise. Stirring was continued at the same temperature for 1 h; the solution was then kept overnight at room temperature. Water (2 cm^3) was added, solvents were removed under reduced pressure, and the residue, dissolved in chloroform, was shaken successively with aqueous 5% hydrogen peroxide, aqueous 2N-sodium sulphite, aqueous sodium hydrogen carbonate, and water, and then dried and evaporated. Chromatography on silica gel and elution with chloroform gave (Z)-2-(2-*methylenecyclohexylidene*)*ethyl*(*diphenyl*)*phosphine oxide* (3), which separated from benzene–light petroleum as crystals (1.4 g), m.p. 96—97°, τ 2.1—2.7 (10 H, m, ArH), 4.65 (1 H, distorted q, =CH), 5.11 (1 H, m, $=CH_2$), 5.34 (1 H, m, $=CH_2$), and 6.71 (2 H, dd, J_{vic} 7.5, $J_{H.P}$ 14 Hz, CH_2P) (Found: C, 78.1; H, 7.05; P, 9.8. $C_{21}H_{23}OP$ requires C, 78.2; H, 7.2; P, 9.6%).

3-*Deoxyvitamin* D_2 (9) *from the Ketone* (8).—To a stirred solution of the phosphine oxide (3) (644 mg) in tetrahydrofuran (10 cm^3) at −78 °C, 1.37M-n-butyl-lithium in light petroleum (1.46 cm^3) was added, and stirring was continued for ½ h; the lithio-derivative precipitated. The mixture was stirred vigorously at the same temperature during the dropwise addition of a solution of the ketone (8) (600 mg) in tetrahydrofuran (5 cm^3). The mixture was then stirred at −40 °C for ½ h, after which it had become pale yellow; tetrahydrofuran (25 cm^3) was added, and stirring was continued at 25 °C for 1 h. The mixture was diluted with ether, washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and then dried and evaporated. P.l.c. (benzene–light petroleum, 1 : 1) gave 3-*deoxyvitamin* D_2 (9) (540 mg), which separated from ethyl acetate at −40 °C giving crystals, m.p. 40—41°, $\lambda_{max.}$ (EtOH with a little hexane) 263.5 nm (ε 17 600), $[\alpha]_D^{22}$ +13.0°, $\nu_{max.}$ (film) 892s, 1 605w, 1 630m, and 1 645m cm^{-1}, τ 3.88 (2 H, dd, J 12 Hz, H-6 and -7), 4.79 (2 H, m, $W_{\frac{1}{2}}$ 9.5 Hz, H-22 and -23), 5.01 (1 H, d, J 1.5 Hz, H-19), 5.23 (1 H, d, J 2.5 Hz, H-19), and 9.42 (3 H, s, CH_3–13) (Found: C, 88.2; H, 11.6; M^+, 380.343 2. $C_{28}H_{44}$ requires C, 88.3; H, 11.65%; M, 380.344 3), *m/e* 380 (28.8%, M^+), 255 (32.7%, $M - C_9H_{17}$), 121 (100%), and 120 (65.4%, $M - C_{19}H_{32}$).

Conversion of the Aldehyde (10) *into* 3-*Deoxyvitamin* D_2 (9).—The aldehyde (10) (1.2 g), cyclohexanone (11 cm^3), and sodium ethoxide [from sodium (0.22 g)] were kept together in dry ethanol (40 cm^3) at −20 °C under nitrogen for 1 h, and then at 0 °C for 25 min, after which acetic acid (1 cm^3) was added, and the solution was evaporated under reduced pressure. Aqueous sodium hydrogen carbonate was added, and the product was isolated with ether and freed from cyclohexanone by evaporation at 40 °C and 1 mmHg. Chromatography on silica gel (benzene; then 3% ethyl

acetate in benzene) gave crude material (1.0 g) which was rechromatographed on Kieselgel with the same eluants; this provided the (E,E)-*dienone* (11) (370 mg), m.p. 63—64° (from acetone at −40 °C), $\lambda_{max.}$ 313 nm (ε 23 600) (Found: C, 84.65; H, 11.35. $C_{27}H_{42}O$ requires C, 84.75; H, 11.1%).

The (*E,E*)-dienone (11) (0.45 g of material of 80% purity), dissolved in methanol (1 l) was irradiated at −50 °C with a G.E.C. mercury MBW/U lamp, the light from which was filtered through 3 cm thickness of aqueous 15% copper sulphate. After 1 h, ε 310 nm had fallen to 64% of its original value; the solution was diluted with water (1 l) and extracted with light petroleum (500 cm³)–ether (500 cm³). The extract was evaporated and the residue was subjected to p.l.c. to give the (*Z,E*)-dienone (12) as an oil (167 mg), $\lambda_{max.}$ 310 nm (ε 16 400), τ 3.43 (2 H, dd, *J* 13 Hz, =CH–CH=), 4.80 (2 H, m, –CH=CH), and 9.42 (3 H, s, C–CH_3).

A solution of methylenetriphenylphosphorane [from methyltriphenylphosphonium bromide (0.93 g)] in tetrahydrofuran (12 cm³) and ether (6 cm³) was stirred under nitrogen during dropwise addition of the (*Z,E*)-dienone (12) (299 mg) in tetrahydrofuran (9 cm³), and stirring was continued for 35 min, after which a little acetone was added to destroy the excess of the reagent. After a further 4 h water (1 cm³) was added, solvents were removed under reduced pressure, and the residue was partitioned between light petroleum (b.p. 40—60°; 120 cm³) and 50% aqueous methanol (30 cm³); the petroleum phase was washed with more 50% methanol (30 cm³), and with water, and was dried and evaporated. The residual oil (340 mg) was subjected to p.l.c. (benzene–light petroleum, 1 : 1) to give 3-deoxyvitamin D_2 (9) (186 mg), $\lambda_{max.}$ 265 nm (ε 17 500); crystallisation from ethyl acetate at −40 °C gave material, m.p. 40—41°, $\lambda_{max.}$ 265 nm (ε 17 600), $[\alpha]_D^{22}$ +13.0°; its ^{1}H n.m.r. spectrum was identical with that of material obtained by the diphenylphosphine oxide method.

(S)-(Z)-2-(5-*Benzoyloxy*-2-*methylenecyclohexylidene*)-*ethanol* (15).—To a stirred solution of the dienediol (13) (2.335 g) in chloroform (35 cm³) and pyridine (7 cm³) at 0 °C, 2,2,2-trichloroethyl chloroformate (2.1 cm³) in chloroform (5 cm³) was added dropwise, after which the solution was stirred for 16 h at room temperature and then worked up in the usual manner to give the crude allyl carbonate, which was converted with benzoyl chloride in pyridine into the crude benzoate (14) (6.74 g), $\nu_{max.}$ (film) 1 720s and 1 762s cm^{-1}. A solution of the benzoate in glacial acetic acid (80 cm³) and ether (32 cm³) was stirred for 4 h at room temperature with freshly activated zinc dust (7 g); the mixture was then filtered and the residue was washed with chloroform. To the filtrate and washings more chloroform (500 cm³) was added, and the solution was washed with water, saturated aqueous sodium hydrogen carbonate, and brine, and then dried and evaporated. Chromatography of the residue on neutral alumina (chloroform) gave the *benzoate* (15) as an oil (3.066 g), $\nu_{max.}$ (film) 713, 1 117, 1 280, 1 720, and 3 400 (all s) cm^{-1}, τ 1.8—2.6 (5 H, m, ArH), 4.42 (1 H, t, *J* 7 Hz, =C*H*–CH_2), 4.75 (1 H, m, CH·OBz), 4.92 and 5.20 (each 1 H, poorly resolved d, $=CH_2$), and 5.72 (2 H, d, *J* 7 Hz, CH_2–OH) (Found: M^+, 258.124 99. $C_{16}H_{18}O_3$ requires *M*, 258.125 59).

(S)-(Z)-2-(5-*Benzoyloxy*-2-*methylenecyclohexylidene*)*ethyl*-(*diphenyl*)*phosphine Oxide* (16).—The benzoate (15) (3.0 g) in dimethylformamide (10 cm³) was added dropwise to a stirred solution of freshly prepared chloromethylenedimethylammonium chloride (2.648 g) in dimethylformamide (10 cm³) at 0 °C under nitrogen. Stirring and cooling were continued for 1 h, after which the mixture was poured into water and the product was isolated in the usual way with ether–pentane. The allylic chloride formed an oil (2.88 g), $\nu_{max.}$ (film) 712s, 1 029m, 1 072m, 1 116s, 1 180m, 1 256m, 1 278s, 1 319m, 1 455m, and 1 720s cm^{-1}, τ 1.8—2.7 (5 H, m, ArH), 4.40 (1 H, t, *J* 7.5 Hz, =C*H*–CH_2), 4.72 (1 H, m, CH–OBz), 4.86 and 5.03 (each 1 H, unresolved d, $=CH_2$), and 5.77 (2 H, d, *J* 7.5 Hz, $-CH_2Cl$). An 0.28M-solution of lithium diphenylphosphide in tetrahydrofuran was prepared from diphenylphosphine and n-butyl-lithium, and a portion (4.8 cm³) was added dropwise to a stirred solution of the above allylic chloride (289 mg) in tetrahydrofuran (10 cm³) at −60 to −50 °C under nitrogen; at the end of the addition a red colour persisted, and was destroyed by addition of a little water. The solvent was removed under reduced pressure, and the residue, dissolved in chloroform, was shaken successively with aqueous 5% hydrogen peroxide, aqueous sodium sulphite, dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and brine, and was then dried and evaporated. After purification by p.l.c. (ethyl acetate), the *phosphine oxide* (16) separated from benzene–light petroleum as needles (308 mg), m.p. 184—186°, $[\alpha]_D^{16}$ +43.9°, $\nu_{max.}$ (Nujol) 691, 710, 1 118, 1 176, 1 277, and 1 718 (all s) cm^{-1}, τ 1.9—2.7 (m, ArH), 4.60 (1 H, distorted q, =CH), 4.97 (1 H, m, $=CH_2$), 5.12 (1 H, m, $=CH_2$), and 6.65 (2 H, dd, J_{vic}, 7.5, $J_{H,P}$ 14 Hz, CH_2–P) (Found: C, 76.05; H, 6.5; P, 6.9. $C_{28}H_{27}O_3P$ requires C, 76.0; H, 6.1; P, 7.0%).

The Acetal (18).—The benzoate (16) (442 mg) and methanolic 1.4N-sodium hydroxide (70 cm³) were stirred together at room temperature for 16 h; normal work-up then afforded the hydroxy-phosphine oxide, $\nu_{max.}$ (film) 3 350 cm^{-1}. This was stirred with ethyl vinyl ether (1 cm³) in tetrahydrofuran (25 cm³) containing toluene-*p*-sulphonic acid (15 mg) at 0 °C for 1½ h. The mixture was then stirred with sodium carbonate powder (0.5 g) for 15 min, after which the tetrahydrofuran was removed under reduced pressure. The residue was extracted with chloroform, and the solution was washed with aqueous sodium hydrogen carbonate and brine, and then dried and evaporated to give the acetal (18) (402 mg) as a gum, homogeneous to t.l.c., $\nu_{max.}$ (film) 696s, 750s, 1 050s, 1 100s, 1 122s, 1 185s, and 1 440s cm^{-1}.

Vitamin D_2 (20).—The acetal (18) (294 mg) and 1.15M-n-butyl-lithium (0.6 cm³) were stirred together in tetrahydrofuran (5 cm³) at −75 °C under nitrogen for 30 min. To the deep red solution a solution of des-AB-ergost-22-en-8-one (8) (227 mg) in tetrahydrofuran (3 cm³) was added slowly; after ½ h at −75 °C stirring was continued for ½ h at −40 °C, then the mixture was warmed to room temperature, tetrahydrofuran (10 cm³) was added, and stirring was continued for 1½ h. The tetrahydrofuran was removed under reduced pressure and the residue was dissolved in ether (100 cm³) and washed with aqueous sodium hydrogen carbonate and brine; the solution was dried and evaporated. The residue was stirred with acetic acid (7.5 cm³) and water (1.2 cm³) for 2½ h, after which the mixture was diluted with water and neutralised with sodium hydrogen carbonate. The product was isolated with ether and purified by p.l.c. ($CHCl_3$) giving vitamin D_2 (20) (169 mg), m.p. 110—112° (from acetone at −40 °C), $\lambda_{max.}$ 266 nm (ε 17 500); the i.r. and ^{1}H n.m.r. spectra were identical with those of authentic material. The 3,5-dinitrobenzoate, obtained in 86% yield from the synthetic material, had m.p. 147—148° (from acetone–methanol) alone or mixed with authentic material,

and $[\alpha]_D^{20}$ +90.3°; authentic material had $[\alpha]_D^{20}$ +91.7°. The i.r. and ^{1}H n.m.r. spectra of the two samples were identical.

Vitamin D_3 (19).—The acetal (18) (370 mg) was metallated and brought into reaction with des-AB-cholestan-8-one (17) (238 mg) in the manner used for the synthesis of vitamin D_2, and the work-up was conducted similarly, to give vitamin D_3 (19) as a gum (229 mg), $\lambda_{max.}$ 265 nm (ε 16 500); the i.r. and ^{1}H n.m.r. spectra were identical with those of authentic material. Reaction with 3,5-dinitrobenzoyl chloride gave (80.5% yield) the 3,5-dinitrobenzoate, m.p. 129.5—131° (from acetone–methanol), alone or mixed with authentic material; $[\alpha]_D^{20}$ +96.6°. The i.r. and ^{1}H n.m.r. spectra were identical with those of an authentic specimen.

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