SIMONSEN LECTURE*

Synthetic Approaches to Vitamin D and its Relatives

By B. Lythgoe
DEPARTMENT OF ORGANIC CHEMISTRY, THE UNIVERSITY, LEEDS
LS2 9JT

1 Introduction

The natural vitamin D_3, required for normal bone calcification, is formed in man by the action of ultraviolet light on 7-dehydrocholesterol present in the skin (Scheme 1). Reversible photochemical cleavage of the 9,10-bond first gives precalciferol$_3$ (1); a reversible thermal hydride shift then gives the vitamin (2). A third 9,10-seco-sterol, tachysterol$_3$ (3), is formed by the photochemical *cis* → *trans* isomerization (also reversible) of the central double bond in precalciferol$_3$. The technical preparation of vitamin D_3 uses the route of Scheme 1; and of course, if combined with a synthesis of 7-dehydrocholesterol, this route also affords a total synthesis of the vitamin.

However, a more direct synthetic route can be imagined, in which a monocyclic fragment representing ring A and an appropriate hydrindane derivative representing rings C and D are united so as to generate the conjugated triene system of the vitamin. Experiments on this, the A → CD approach, were started in Manchester (Burkhardt[1]) and in Göttingen (Dimroth[2]) shortly after the gross structure of vitamin D_2 was elucidated, and before the stereochemical details became clear; these initiatives did not, however, reach a successful conclusion. I was at that time a research worker in Manchester and, no doubt, a latent interest in the problem was then implanted which eventually led me into active participation. The present lecture describes experiments on the total synthesis of the vitamins D_2 and D_3 and some important relatives.

2 Early Photochemical Routes to Vitamins D

It may be useful to summarize here developments in the field up to about 1960. The hydrindanes (4)[3] and (6),[4] obtained by the oxidation of vitamin D_2 (Scheme 2), and the corresponding compounds from vitamin D_3, offer readily available starting materials for experiments on partial synthesis. The pioneer workers[1,2] envisaged a synthesis of vitamin D_2 from the epimeric dienones (8), obtained by interaction of the $\alpha\beta$-unsaturated aldehyde (6) with 4-hydroxycyclohexanone.

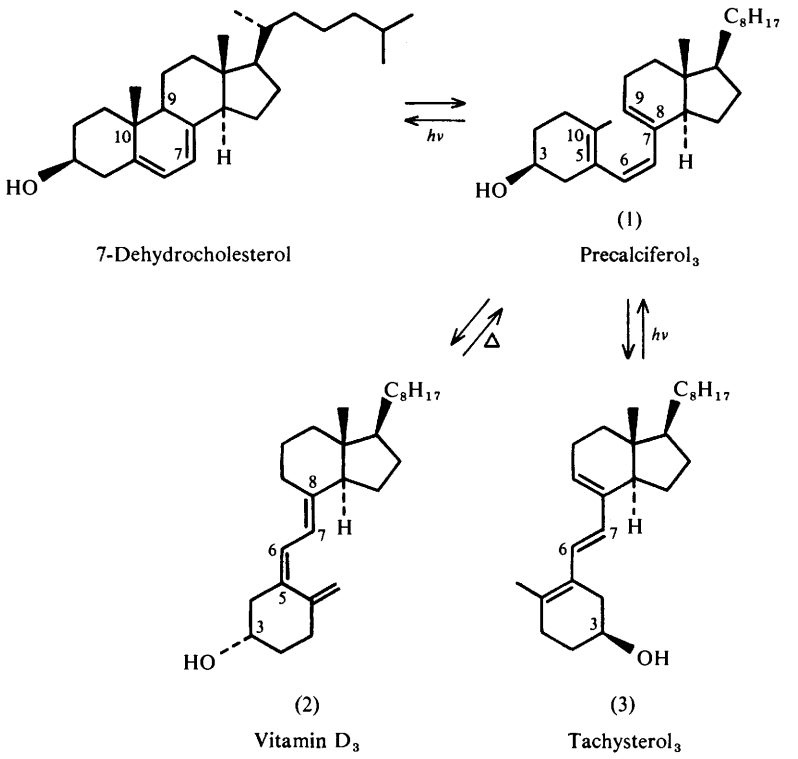
*First delivered at the Scientific Societies' Lecture Theatre, London W1, on 18th Jan 1979.

[1] J. B. Aldersley and G. N. Burkhardt, *J. Chem. Soc.*, 1938, 545; J. B. Aldersley, G. N. Burkhardt, A. E. Gillam, and N. C. Hindley, *ibid.*, 1940, 10.

[2] K. Dimroth, *Ber.*, 1938, **71**, 1333, 1346.

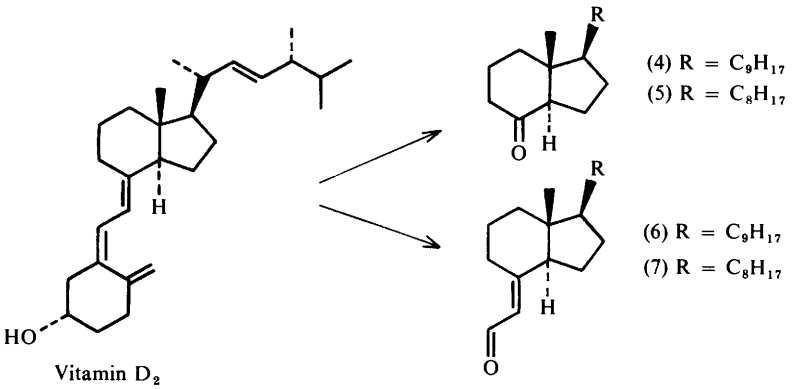
[3] A. Windaus and W Grundmann, *Annalen*, 1936, **524**, 295.

[4] I. M. Heilbron, R. N. Jones, K. M. Samant, and F. S. Spring, *J. Chem. Soc.*, 1936, 905.



Scheme 1

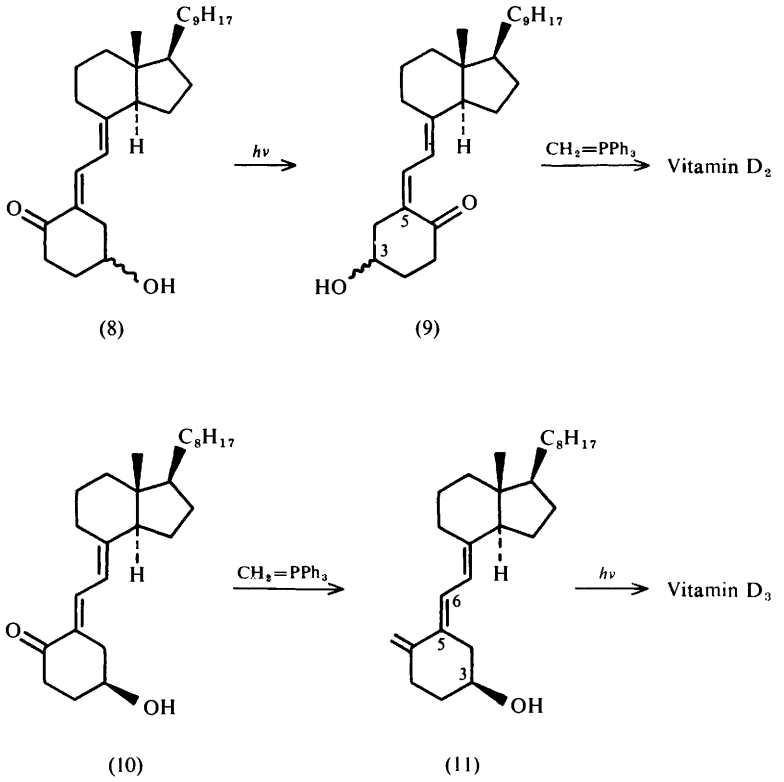
Note: All structures in this and subsequent Schemes, in which stereochemical detail is shown by heavy and/or dotted lines, represent absolute configurations



Scheme 2

That, however, required the regiospecific conversion of the keto-group into an exocyclic methylidene group, a reaction which only became possible with the

advent of Wittig's olefin synthesis. This reaction was then employed independently in Leeds and in Braunschweig to effect partial syntheses of vitamins D (Scheme 3). We in Leeds[5] isomerized the C_{27} epimer mixture (8) to the 5*Z*-



(8) (9)

(10) (11)

Scheme 3

epimers (9) before replacing the keto-group by a methylidene group and separating the epimers to give vitamin D_2. Inhoffen's group[6] separated the 3β-epimer (10) of the C_{26} dienones and converted it in a Wittig reaction into 5*E*-vitamin D_3 (11), which was then isomerized photochemically to give vitamin D_3. Inhoffen's group further effected a synthesis, starting from Hagemann's ester [(61) p. 462], of the $\alpha\beta$-unsaturated aldehyde (7) which had been used to prepare the dienone (10). They thus completed[7] the first total synthesis of a vitamin D by the A → CD approach. However, the magnitude of the overall yield, *ca.* 10^{-6}%, made it clear

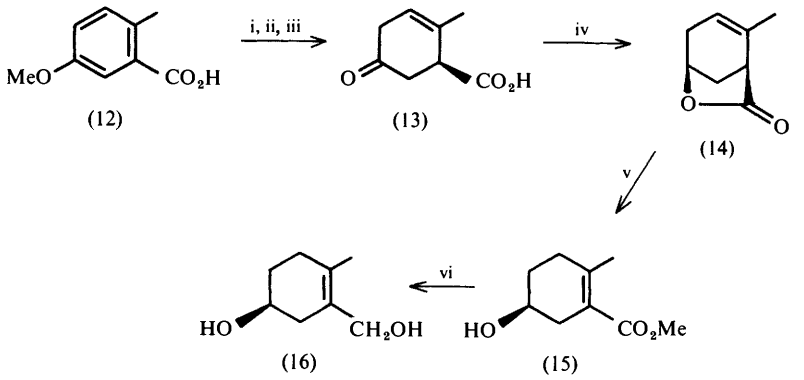
[5] I. T. Harrison and B. Lythgoe, *Proc. Chem. Soc.*, 1957, 261; *J. Chem. Soc.*, 1958, 837.
[6] H. H. Inhoffen, K. Irmscher, H. Hirschfeld, U. Stache, and A. Kreutzer, *Chem. Ber.*, 1958, **91**, 2309.
[7] H. H. Inhoffen, H. Burkhardt, and G. Quinkert, *Chem. Ber.*, 1959, **92**, 1564, and refs. there cited.

that further studies were needed in both stages of the work. For example, in the sequence (7) → (10) → (11) → (2) the configuration at C-3 was established non-stereoselectively, and the mode of establishment of the 5*Z*-geometry was not efficient.

3 Synthesis of Tachysterol$_3$

The next objective to be attained was a partial synthesis of tachysterol$_3$ (3). The presence in this compound of the central *trans*-disubstituted double bond made it probable that the synthesis could be effected by a Wittig reaction between appropriate C_8 and C_{19} fragments. These fragments correspond to the allylic alcohols (16) and (19).

Scheme 4 outlines a route[8] to the monocyclic alcohol (16). Reduction of the



Reagents: i, Li–NH_3; ii, H_3O^+; iii, resolve; iv, $NaBH_4$; H_3O^+; v, NaOMe–MeOH; vi, $LiAlH_3(OEt)$

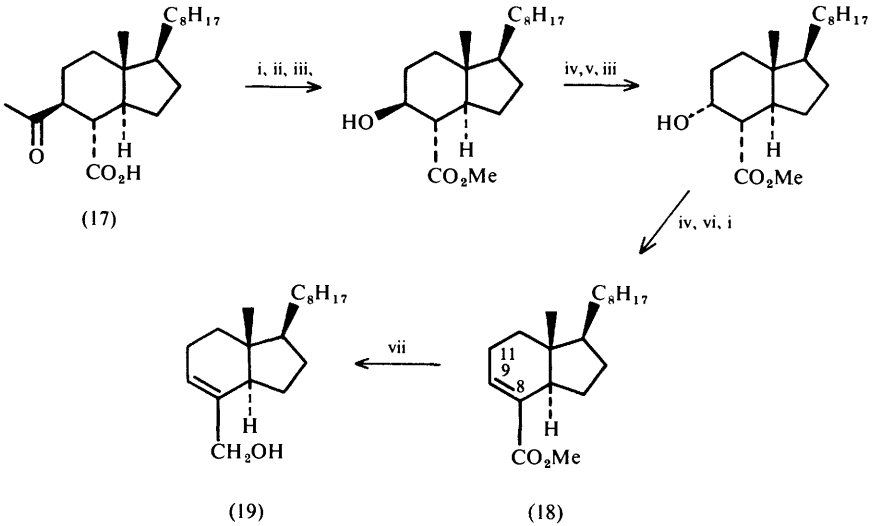
Scheme 4 *Ring* A *fragment for tachysterol*$_3$

aromatic acid (12) with lithium and ammonia, followed by acid hydrolysis, gave the keto-acid *rac*-(13). The required enantiomer (13) was obtained by resolution with quinine. Reduction of the keto-group gave the γ-lactone (14), which on treatment with methanolic sodium methoxide yielded the conjugated ester (15). Reduction then gave the alcohol (16).

The bicyclic alcohol (19) can, on paper, be derived simply from cholesterol by cleavages at the 9,10- and 6,7-positions, but to realise this plan in practice was less easy. Our first attempt[9] used as an intermediate duoannelic acid (17), which can be obtained from cholesterol in low yield by direct oxidation, or in better yield by an indirect method. Its conversion into 8-hydroxymethyl-des-AB-cholest-8-ene (19), using standard methods of alicyclic chemistry, is shown in Scheme 5. It was found that treatment of the conjugated ester (18) with alkali converted it partly

[8] J. Dixon, B. Lythgoe, I. A. Siddiqui, and J. Tideswell, *J. Chem. Soc.*(*C*), 1971, 1301.
[9] R. S. Davidson, W. H. H. Günther, S. M. Waddington-Feather, and B. Lythgoe, *J. Chem. Soc.*, 1964, 4907.

into the $\Delta^{9(11)}$-isomer, illustrating the fact that, owing to conformational factors, the 8,9-double bond occupies a position of high energy.



Reagents: i, CH_2N_2; ii, CF_3CO_3H; iii, NaOMe–MeOH; iv, $PhSO_2Cl$–pyridine; v, Me_2NCHO–H_2O; vi, KOH–EtOH; vii, $LiAlH_3(OEt)$

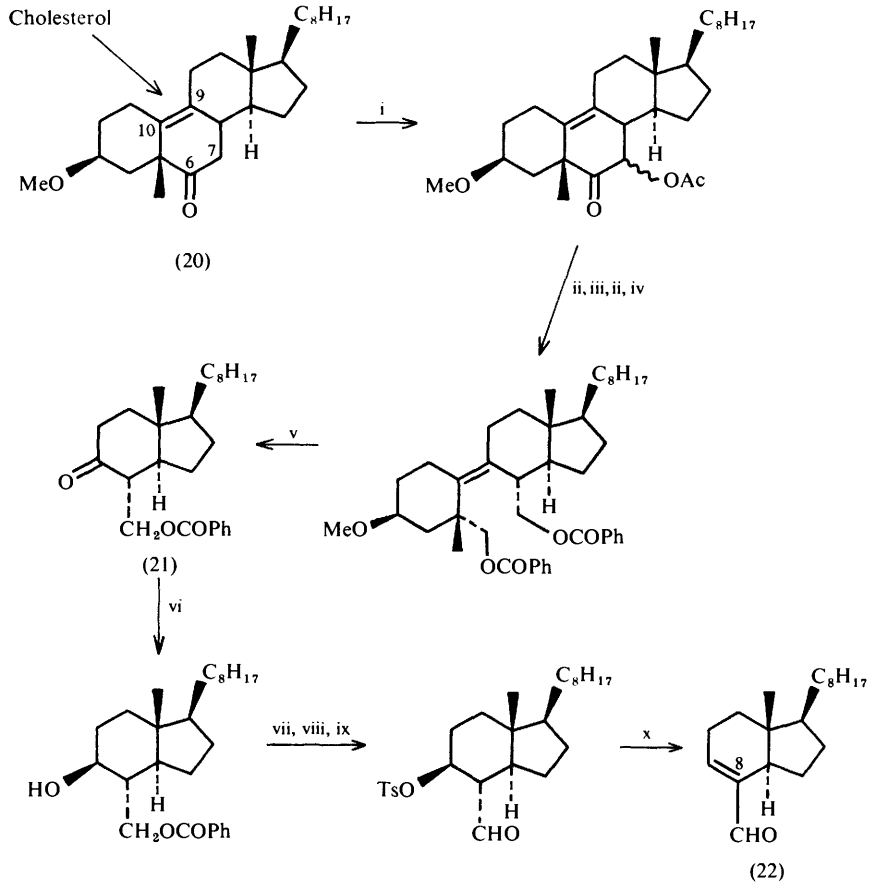
Scheme 5

Later, a more efficient degradative route was found,[10] using as an intermediate the 'Westphalen' methoxy-ketone (20) (Scheme 6). Acetoxylation at C-7 opened the way to an oxidative cleavage of the 6,7-bond; the 9,10-double bond was then ozonized, giving the bicyclic keto-benzoate (21). Normal manipulation of the functional groups in this compound gave the $\alpha\beta$-unsaturated aldehyde (22), which can be obtained from, or converted into, the allylic alcohol (19). The latter was so obtained from cholesterol in an overall yield of 22.5%, and became relatively easily available.

In principle, either of the two alcohols (16) and (19) can be used to make the phosphorane component for the Wittig reaction, leaving the other to be converted into the aldehyde component. We chose the alcohol (16) for conversion into the phosphorane (23) since this avoided the need for protecting the hydroxy-group. Union of the two components as shown in Scheme 7 gave tachysterol$_3$, isolated in good yield as the crystalline 4-methyl-3,5-dinitrobenzoate.[11]

When Wittig reactions with an allylic phosphorane are used to construct internal disubstituted olefins, a mixture of *cis*- and *trans*-isomers is normally obtained. Here, however, the reaction was *trans*-stereospecific; no precalciferol$_3$

[10] P. J. Kocienski, B. Lythgoe, and D. A. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1980, 897.
[11] R. S. Davidson, S. M. Waddington-Feather, D. H. Williams, and B. Lythgoe, *J. Chem. Soc.*, 1967, 2534.



Reagents: i, trimethylsilyl enol ether treated $Pb(OAc)_4$–Et_3NHF; ii, $LiAlH_4$; iii, $Pb(OAc)_4$; iv, PhCOCl–pyridine; v, O_3, Me_2S; vi, $LiAlH(OBu^t_3)$; vii, $MeC_6H_4SO_2Cl$–pyridine; viii, KOH–H_2O; ix, $(COCl)_2$–Me_2SO, NEt_3; x, KF–NaOAc–Me_2SO

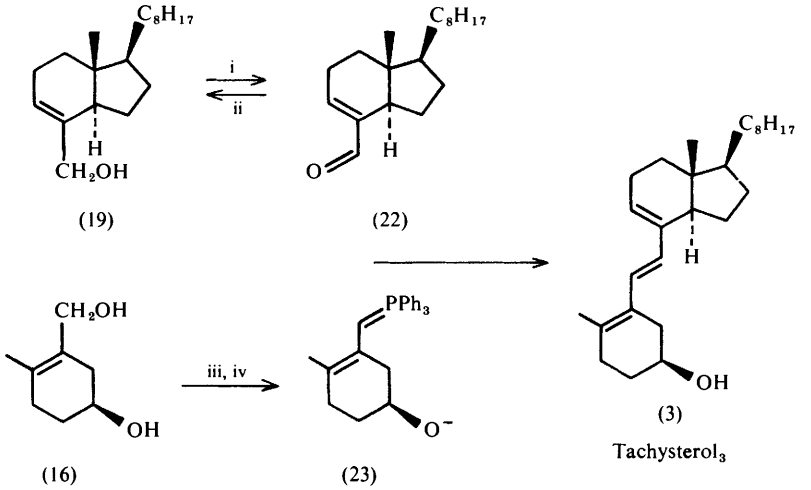
Scheme 6 *Route to* 8-*formyl-des-*AB-*cholest*-8-*ene*

was detected. Two factors seem responsible.[12] Firstly, in such reactions the initial betaine formation is readily reversible. Secondly, owing to the cyclic disposition of the outer double bonds, the product is branched at both positions adjacent to the new (central) double bond. This sets up adverse steric interactions in the transition state leading to the *cis*-isomer, so that the reaction is steered towards formation of the *trans*-isomer.

4 Precalciferol$_3$

The dominating feature of precalciferol$_3$ (1) is the *cis*-geometry of the central

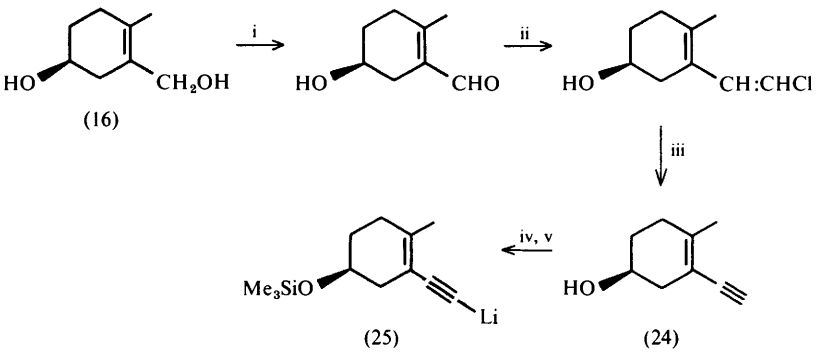
[12] P. J. Kocienski, B. Lythgoe, and I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1045.



Reagents: i, MnO_2–Et_2O; ii, Bu^i_2AlH; iii, $PhCH_2P(OPh)_3Br$–PPh_3; iv, 2BuLi

Scheme 7 *Synthesis of tachysterol*$_3$

double bond. We proposed to secure this feature by using as an intermediate the acetylenic compound (33), constructed by a union at the 7,8-position. It was important for success that the double bond positions in the enynene (33) should be unambiguous. This was achieved for the ring A part by using as a starting material the optically active enyne (24), prepared[13] as shown in Scheme 8 by a one-carbon homologation of the allylic alcohol (16).

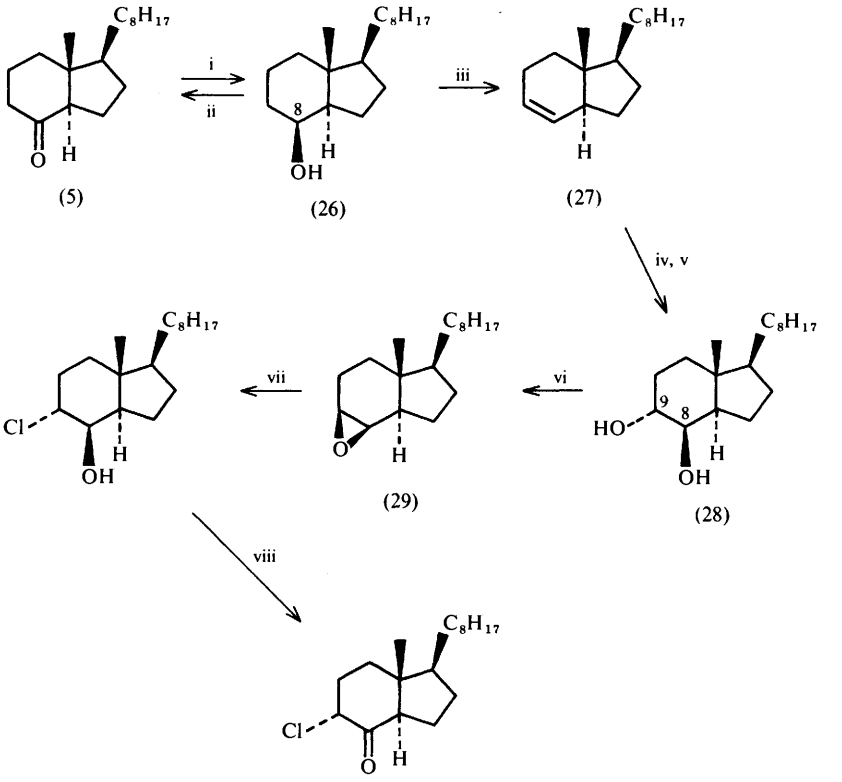


Reagents: i, MnO_2–Me_2CO; ii, $ClCH{:}PPh_3$; iii, $NaNH_2$–NH_3; iv, Me_3SiCl–pyridine–$(Me_3Si)_2NH$; v, BuLi

Scheme 8 *Ring* A *fragment for precalciferol*$_3$

[13] T. M. Dawson, J. Dixon, P. S. Littlewood, and B. Lythgoe, *J. Chem. Soc.* (*C*), 1971, 2352.

The double bond in the ring C part of (33) occupies the high energy 8,9-position. To secure this we used as the hydrindane component 9α-chloro-des-AB-cholestan-8-one (30), prepared initially[14] from des-AB-cholestan-8β-ol (26) by way of des-AB-cholest-8-ene (27), the 8β,9α-diol (28), and the 8β,9β-epoxide (29), as shown in Scheme 9.

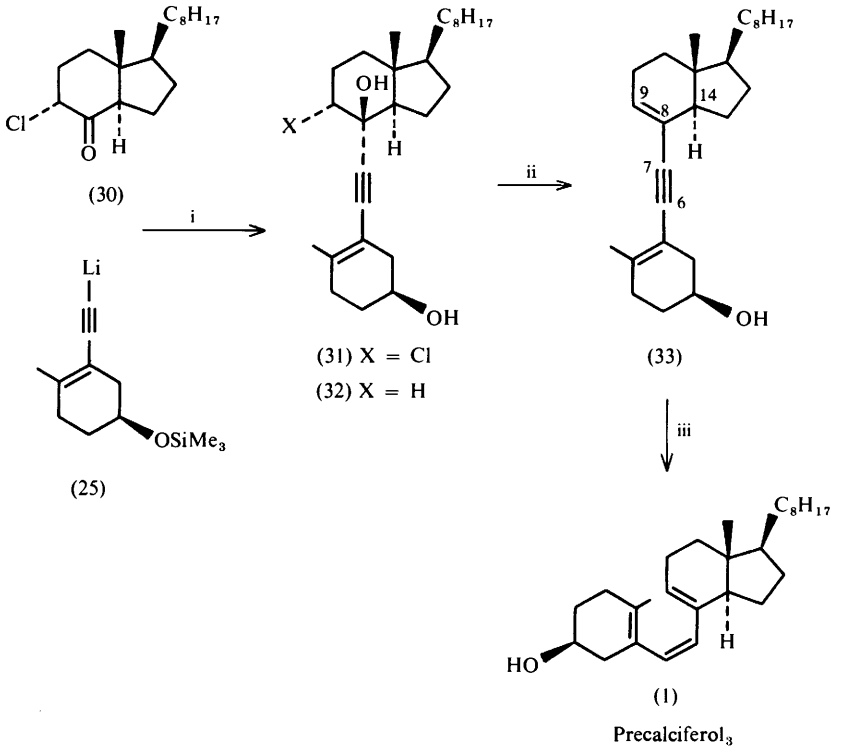


Reagents: i, $LiAlH_4$; ii, CrO_3–pyridine; iii, heat benzoate to 360 °C; iv, $ClC_6H_4CO_3H$; v, $HClO_4$–H_2O–Me_2CO; vi, KOH–MeOH on the 9α-monotosylate; vii, HCl–dioxan; viii, $Na_2Cr_2O_7$–H_2SO_4–H_2O–Et_2O

Scheme 9 CD-*fragment for precalciferol*[3]

The two components were then united[15] (see Scheme 10) by reaction of the protected lithium derivative (25) of the enyne (24) with the chloro-ketone (30) to give, after de-protection, the vicinal chlorohydrin (31). The elimination of the

[14] P. S. Littlewood, B. Lythgoe, and A. K. Saksena, *J. Chem. Soc.* (*C*), 1971, 2955.
[15] T. M. Dawson, J. Dixon, P. S. Littlewood, B. Lythgoe, and A. K. Saksena, *J. Chem. Soc.* (*C*), 1971, 2960.



Reagents: i, reaction product treated H_3O^+; ii, compound (31) treated with bis(ethylenediamine)chromium(II)-Me_2NCHO; iii, 1 H_2–Lindlar Pd

Scheme 10 *Synthesis of precalciferol*$_3$

elements of hypochlorous acid to generate the 8,9-double bond was effected by Kochi's[16] method. The resulting enynene (33) was semihydrogenated over Lindlar's catalyst to give precalciferol$_3$, isolated as the 3,5-dinitrobenzoate in *ca.* 21% yield from the chloro-ketone (30). Thermal equilibration of the synthetic material provided vitamin D_3; this was the first occasion on which it had been obtained without the intervention of photochemical methods.

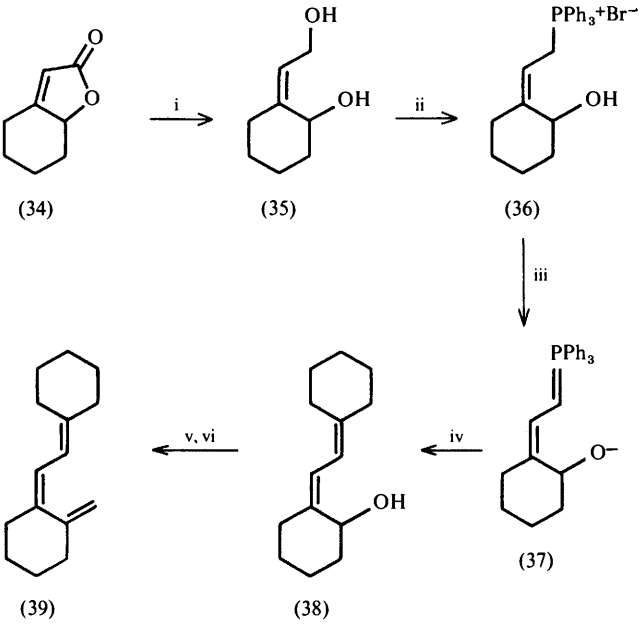
At first sight it may seem that the above result could be more simply achieved by using in place of the chloro-ketone (30) the more readily available ketone[17] (5). This should lead to the tertiary alcohol (32), from which the elimination of the elements of water could, in theory at any rate, yield the enynene (33). However, conformational and hyperconjugational influences would be expected to direct this elimination towards the $\Delta^{8(14)}$-isomer of (33). For this reason the

[16] J. K. Kochi and D. Singleton, *J. Am. Chem. Soc.*, 1968, **90**, 1582.
[17] H. Brockman and A. Busse, *Z. Physiol. Chem.*, 1938. **256**. 252.

chloro-ketone (30), which permits unambiguous control of the ring C double bond position, was used in the synthesis.

5 A Stereoselective Route to the Vitamins D

The lack of stereoselectivity inherent in the routes of Scheme 3 led us to study another approach, in which the two component fragments were to be united to construct the 7,8-double bond, This plan allows the ring A component to contain from the outset the proper *S*-chirality at the hydroxy-centre, and the 5*Z*-trisubstituted double bond. It was tested in a synthesis[18] of the model conjugated *Z*-triene (39) (Scheme 11).



Reagents: i, $LiAlH_4$; ii, $PhCH_2P(OPh)_3Br$, PPh_3; iii, 2 BuLi; iv, cyclohexanone; v, MnO_2; vi, CH_2:PPh_3

Scheme 11

Reduction of the butenolide (34) gave the allylic diol (35), the primary hydroxy-group of which was selectively converted into a phosphonium bromide group. The derived phosphorane (37) reacted with cyclohexanone to give the conjugated dienol (38), from which the triene (39) was obtained in two routine steps.

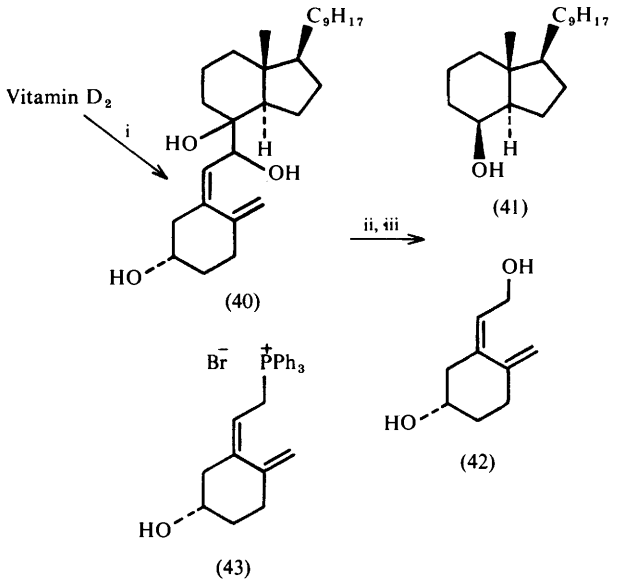
The sequence (35) → (38) provided the first demonstration that an allylic alcohol with the less stable *Z*-geometry can be converted into a Wittig reagent, and used to make a conjugated diene, with essentially complete retention of the

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

original allyl geometry. The method has since found applications in general synthetic work. Although normally practicable, it is not always free from experimental difficulty. The rather weakly nucleophilic nature of triphenylphosphine requires for the quaternization step the allylic bromide rather than the more stable chloride, and this can occasion partial loss of geometry. Moreover, phosphonium halides are difficult to purify by conventional methods, particularly when other polar groups (*e.g.* OH) are present. These difficulties are minimized in a method described below (p. 460).

At first it seemed possible to carry out a synthesis of vitamin D_3 on the lines of Scheme 11, starting with the appropriate hydroxy-derivative of the butenolide (34) and, at the correct step, using the C_{18} ketone (5) in place of cyclohexanone. However, experiments with the appropriate hydroxyderivative of (35) failed to provide a pure phosphonium bromide corresponding to (36). It seemed necessary to reduce the number of hydroxy-groups in the ring A component, and our attentions were therefore turned to the *Z*-dienediol (42).

Access to compound (42) was first gained[19] by a degradation of vitamin D_2 (Scheme 12). Hydroxylation of the vitamin gives[20] the triol (40); cleavage with



Reagents: i, $KMnO_4$; ii, $Pb(OAc)_4$; iii, $NaAlH_2(OCH_2CH_2OMe)_2$

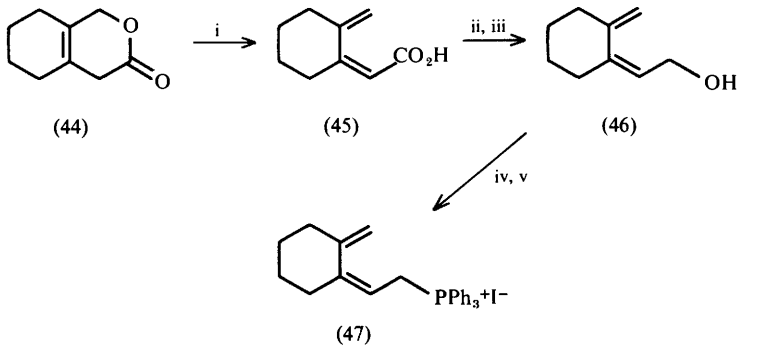
Scheme 12

[19] J. V. Frosch, I. T. Harrison, B. Lythgoe, and A. K. Saksena, *J. Chem. Soc. Perkin Trans. 1*, 1974, 2005.

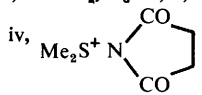
[20] Y. Wang, H.-S. Ting, J. J. Huang, Y.-C. Chow, and Y.-T. Huang, *Acta Chim. Sin.*, 1958, **24**, 126.

lead tetra-acetate and reduction of the products gave a mixture of the bicyclic alcohol (41) and the dienediol (42) from which the dienediol was separated by virtue of its water-solubility, and was obtained crystalline. From it we prepared a phosphonium bromide which appeared to have the desired structure (43). However, it did not take part in Wittig reactions with carbonyl compounds.

As it was thought possible that the secondary hydroxy-group in (42) might be responsible for the difficulty, we prepared the simpler dienol (46) by a sequence[19] in which the key reaction (Scheme 13) was the base-induced ring-opening of the



(44) (45) (46) (47)

Reagents: i, $LiNPr^i_2$, H_3O^+; ii, CH_2N_2; iii, $NaAlH_2(OCH_2CH_2OMe)_2$; iv,  Cl^-; v, PPh_3–NaI–Me_2CO

Scheme 13

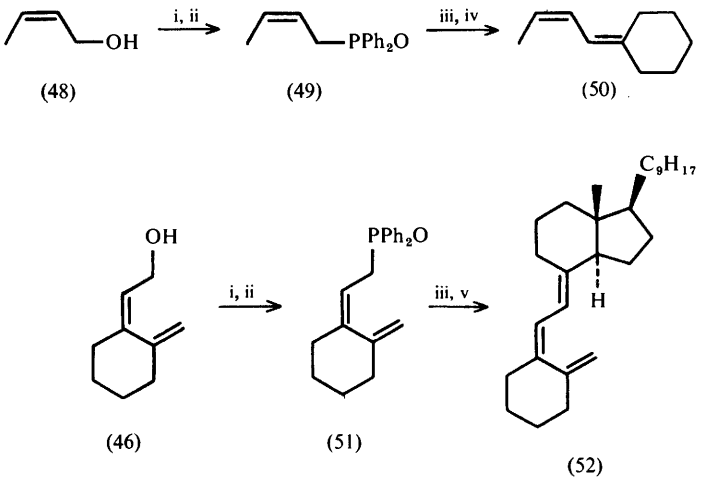
$\beta\gamma$-unsaturated δ-lactone (44) to give the *Z*-dienoic acid (45). From the *Z*-dienol (46) we prepared the phosphonium iodide (47). This compound, too, failed to participate in Wittig olefin syntheses.

Although the cause of these failures is unclear, a way of circumventing them was found[21] in turning from Wittig's method with phosphonium halides to the related Horner's method which uses phosphine oxides. In the two examples just discussed, the use of phosphine oxides seems essential, but we have also found that, in general,[22] allylic diphenylphosphine oxides have marked advantages for the synthesis of conjugated dienes of defined geometry. The phosphine oxides are easily prepared from the relatively stable allylic chlorides, or the even more stable 2,6-dichlorobenzoates, by reaction with lithium diphenylphosphide, followed by oxidation with hydrogen peroxide. The high nucleophilicity of the diphenyl-

[21] B. Lythgoe, T. A. Moran, M. E. N. Nambudiry, S. Ruston, J. Tideswell, and P. W. Wright, *Tetrahedron Lett.*, 1975, 3863.

[22] B. Lythgoe, T. A. Moran, M. E. N. Nambudiry, and S. Ruston, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2386.

phosphide anion allows the reaction to proceed at low temperatures, minimizing the risk of loss of allyl geometry. The phosphine oxides are easily purified. The elimination phase of the olefin synthesis takes place below 25 °C, and the by-product, lithium diphenylphosphinate, is water-soluble and easily removed. Two examples of the use of this convenient method are outlined in Scheme 14. In the



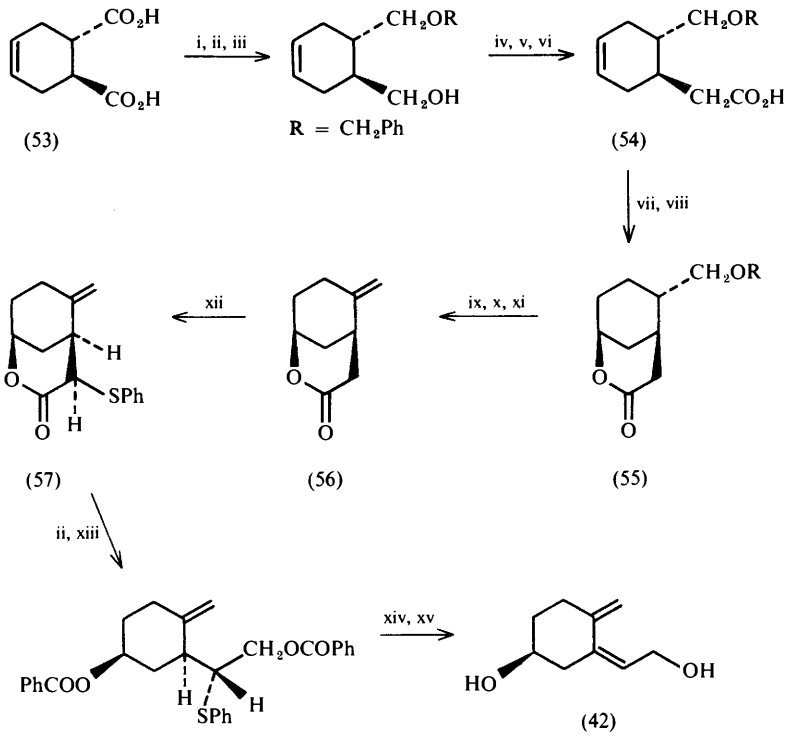
Reagents: i, 2,6-dichlorobenzoate treated with $LiPPh_2$–THF; ii, H_2O_2–$CHCl_3$; iii, BuLi; iv, cyclohexanone; v, compound (4)

Scheme 14 *Allylic phosphine oxides as precursors of conjugated dienes of defined geometry*

first, *cis*-crotyl alcohol (48) was converted into the phosphine oxide (49) and then into *cis*-crotylidenecyclohexane (50). In the second, the *Z*-dienol (46) was similarly converted into the phosphine oxide (51). The lithium derivative reacted without difficulty with Windaus and Grundmann's ketone (4) to give a single conjugated triene, which was shown to have the structure of 3-deoxyvitamin D_2 (52).

It was next necessary to obtain the *Z*-dienediol (42) by total synthesis.[23] This presented two stereochemical problems. The first, that of securing the proper *S*-chirality at the secondary hydroxy-centre, was solved by using as the starting material the readily available *S*-cyclohex-4-ene-1,*trans*-2-dicarboxylic acid (53) (Scheme 15). It contains eight of the nine carbon atoms present in the required dienediol; the ninth was introduced in a nitrile homologation step leading to the

[23] B. Lythgoe, R. Manwaring, J. R. Milner, T. A. Moran, M. E. N. Nambudiry, and J. Tideswell, *J. Chem. Soc., Perkin Trans. 1*, 1978, 387.



Reagents: i, CH_2N_2; ii, $LiAlH_4$; iii, Na–dioxan, $PhCH_2Br$; iv, $MeC_6H_4SO_2Cl$–pyridine; v, NaCN–Me_2SO; vi, KOH–H_2O–EtOH; vii, KI_3 on Na salt; viii, Ph_3SnH; ix, H_2–Pd; x, NaI–Me_2CO on tosylate; xi, diazabicycloundecene; xii, $LiNPr^i_2$, PhSSPh; xiii, PhCOCl–pyridine; xiv, $NaIO_4$; xv, heat to 120 °C; KOH–H_2O–MeOH

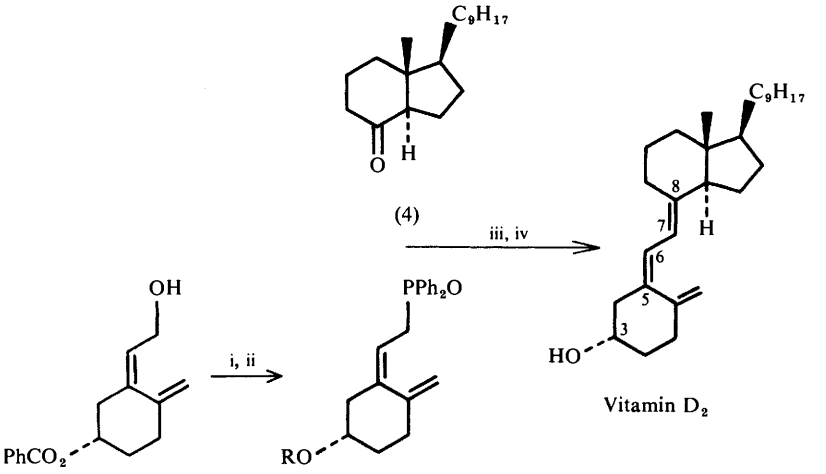
Scheme 15 *Ring* A *fragment for the vitamins D*

acid (54). When this acid was converted into the lactone (55) chirality was transferred to provide that required at the secondary hydroxy-centre in the end-product (42). To solve the second problem, that of securing the *Z*-geometry of the trisubstituted double bond, we used a stereospecific sulphoxide thermolysis. Introduction[24] of a phenylthio-group adjacent to the lactonic carbonyl group of (56) gave two epimers. The major epimer (57), which was that with the desired configuration, crystallized and was readily isolated; as it was also the more stable

[24] B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.*, 1973, **95**, 6840.

of the two, further amounts were obtained by base-catalysed equilibration of the residual mixture. It was then converted as shown into the *Z*-dienediol (42).

The two hydroxy-groups in the dienediol (42) have widely different reactivities, which enable the preparation of the secondary monobenzoate (58). The synthesis[25] of vitamin D_2 from this compound is shown in Scheme 16. The mono-



Reagents: i, $ClCH{:}NMe_2{}^+Cl^-$–Me_2NCHO; ii, $LiPPh_2$–THF;H_2O_2; iii, compound (60) treated with BuLi, then with compound (4); iv, AcOH–H_2O

Scheme 16 *Synthesis of vitamin D_2*

benzoate was first converted into the crystalline phosphine oxide (59) and then into the acetal-protected analogue (60). The lithium derivative of the latter reacted with Windaus and Grundmann's ketone (4) to give, after de-protection, crystalline vitamin D_2 in *ca.* 60% yield. A similar reaction, employing the C_{18} ketone (5), gave vitamin D_3.

In these syntheses, no significant amounts of vitamin D stereoisomers were produced. The *S*-configuration at C-3 and the *Z*-geometry of the 5,6-double bond, already present in the dienediol (42), were preserved in the vitamins. The 7,8-double bond, formed in the phosphine oxide olefin synthesis, had exclusively the natural *E*-geometry; the reasons for this have been discussed.[12] Thus in its major aspects the synthetic route is highly stereoselective.

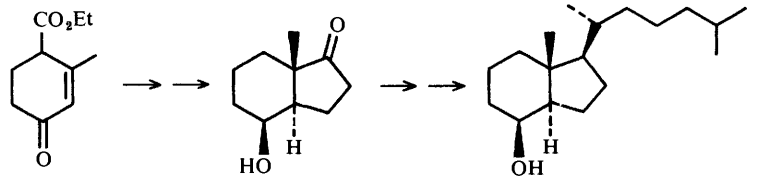
6 Synthesis of Des-AB-cholestane and Des-AB-ergostane Derivatives

The partial syntheses, described in the preceding three Sections, of the 9,10-seco-

[25] B. Lythgoe, T. A. Moran, M. E. N. Nambudiry, J. Tideswell, and P. W. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1978, 590.

sterols of the vitamin D_3 series made use of the des-AB-cholestane derivatives (5), (22), and (30), whilst that of vitamin D_2 made use of des-AB-ergost-22-en-8-one (4). In this Section synthetic routes to these compounds are described so that the syntheses making use of them become total.

All three of the des-AB-cholestane derivatives can be prepared[14] by standard methods from simple compounds such as des-AB-cholest-8-ene (27), the 8β,9α-diol (28), or, less easily, from the 8β-ol (26). The 8β-ol (26) had indeed already been obtained by a total synthesis in which Hagemann's ester (61) (Scheme 17) was first elaborated to give[26] the *trans*-perhydroindan-1-one (62), the keto-group of which was then used as a means of adding, in a series of steps, the iso-octyl side-chain.[7] However, the overall yield in the sequence of Scheme 17 was low (*ca.* 0.001%). We therefore attempted to obtain the related 8β,9α-diol (28) by a more convergent route.



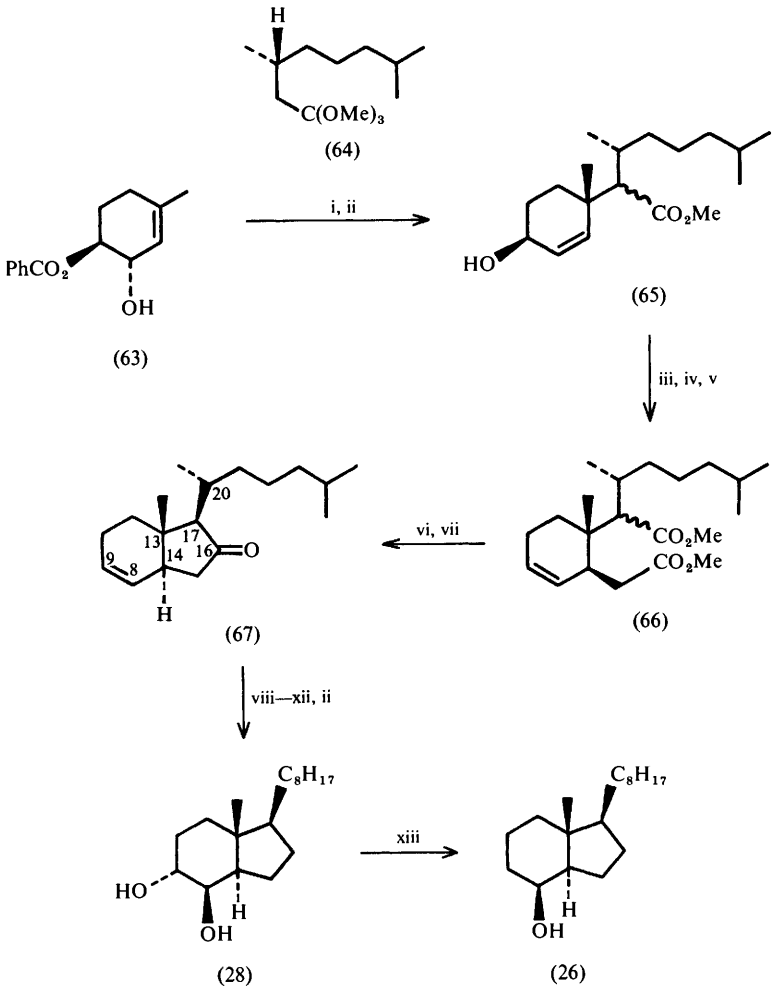
(61) (62) (26)

Scheme 17

The plan of the synthesis[27] can be understood by reference to the dibasic ester (66) (Scheme 18). Cyclization was expected to afford a hydrindenone mixture which, after equilibration, would contain some 85% of the isomer (67) having the correct chirality at C-17. In the ester (66) ten of the nineteen skeletal carbon atoms (the north-east sector) have the same structural and stereochemical arrangement as those in *R*-dihydrocitronellic acid [*cf.* the orthoester (64)]. We proposed to use a derivative of that acid to provide that sector of the ester (66), so ensuring the correct chirality at C-20 in the ketone (67).

An acceptable way of uniting the ten-carbon fragment with the future ring C was found in the orthoester variant[28] of the Claisen rearrangement of allylic alcohols. Reaction of the orthoester (64) with the allylic alcohol[29] (63) gave, after debenzoylation, a new allylic alcohol (65) which was then used in a second Claisen rearrangement to provide the dibasic ester (66). The rearrangements proceed stereospecifically with respect to the cyclohexane ring, so that the

[26] H. H. Inhoffen, S. Schütz, P. Rossberg, O. Berges, K. H. Nordsiek, H. Plenio, and E. Höroldt, *Chem. Ber.*, 1958, **91**, 2626.
[27] I. J. Bolton, R. G. Harrison, and B. Lythgoe, *J. Chem. Soc.* (*C*), 1971, 2950.
[28] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Am. Chem. Soc.*, 1970, **92**, 741.
[29] I. J. Bolton, R. G. Harrison, B. Lythgoe, and R. S. Manwaring, *J. Chem. Soc.* (*C*), 1971, 2944.



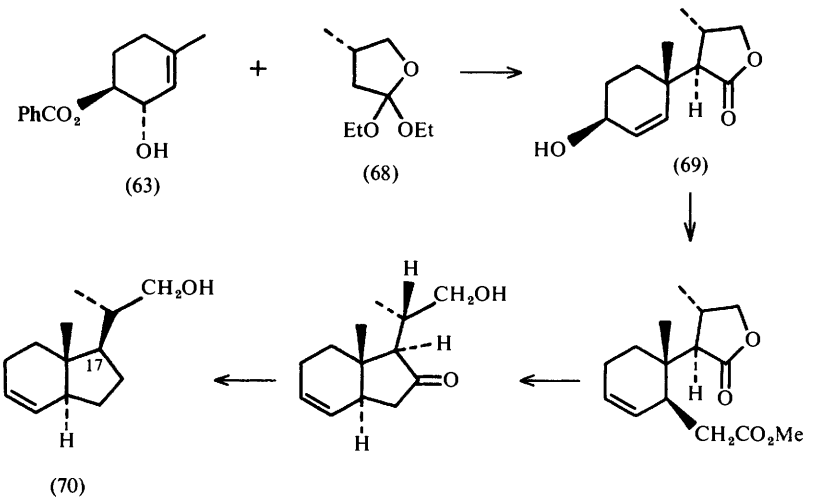
Reagents: i, catalytic $EtCO_2H$ at 140 °C; ii, $NaOH-H_2O$; iii, $MeC(OMe)_2NMe_2$; iv, KOH–EtOH; v, CH_2N_2; vi, NaH–Me_2SO; vii, $MeC_6H_4SO_3H-H_2O$–AcOH; viii, $ClC_6H_4CO_3H$; ix, $H_2SO_4-H_2O$; x, Ac_2O–pyridine; xi, $HSCH_2CH_2SH-BF_3.Et_2O$; xii, Raney Ni; xiii, convert into compound (29) and treat with $LiAlH_4$

Scheme 18 *Synthesis of des-*AB*-cholestanes*

compound (63) is seen to contain in code the absolute configurations at C-13 and C-14 of the ketone (67), which was thus obtained relatively briefly from it in a yield of over 30%. The application of standard methods then gave the 8β,9α-diol (28). This has been converted into the β-epoxide (29) and the chloro-ketone (30) as shown in Scheme 9, and into the 8β-ol (26) as shown in Scheme 18.

When a similar synthesis of the alcohol (41), corresponding to Windaus and Grundmann's ketone, was considered, it was apparent that the analogue of (67) would contain double bonds in both ring c and the side-chain, and that the selective functionalization of the first of them would present difficulties. The route was therefore modified so as to lead initially to the compound (70) in which the side-chain, though abbreviated, has facilities for later extension.

This was effected[30] as shown in Scheme 19. The allylic alcohol (63) was first



Scheme 19

allowed to react in a Claisen rearrangement with the cyclic orthoester (68). Such cyclic orthoesters are readily obtained by applying Meerwein's[31] method to the appropriate δ- or, as in this case, γ-lactone. The rearrangement product gave on debenzoylation the γ-lactone (69) which was transformed, in a series of unexceptional steps, into the unsaturated primary alcohol (70). For identification, this compound was also prepared by a degradation of vitamin D_2.

The stereochemical results[32] of the reactions of allylic alcohols with cyclic orthoesters, although occasionally surprising, can in general be interpreted in terms of the expected transition states. The initial reaction in Scheme 19 is stereospecific and, taking place by way of a boat-shaped transition state, results in the *R*-configuration shown at the new chiral centre adjacent to the lactonic carbonyl group of compound (69). This configuration was maintained during the

[30] C. B. Chapleo, P. Hallett, B. Lythgoe, I. Waterhouse, and P. W. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1211.

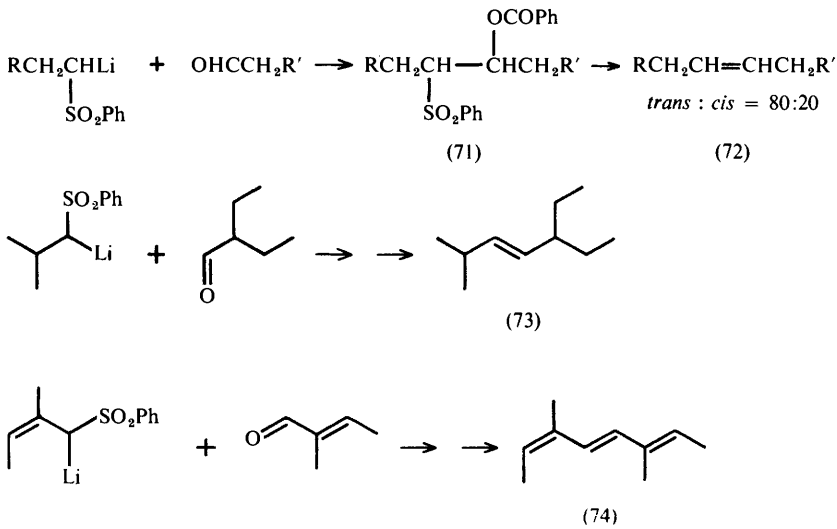
[31] H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt, and J. Spille, *Chem. Ber.*, 1956, **89**, 2060.

[32] R. J. Cave, B. Lythgoe, D. A. Metcalfe, and I. Waterhouse, *J. Chem. Soc., Perkin Trans.* 1, 1977, 1218.

rest of the synthesis, so that the 17β-configuration in compound (70) is a result of asymmetric induction rather than, as in compound (28) of Scheme 18, a result of equilibration.

The primary alcohol (70) was converted[33] by standard methods into the benzoyloxyaldehyde (77). The proper way of completing the synthesis then appeared to lie in a use of Schlosser's[34] modified Wittig reaction, in order to obtain the new double bond in the *trans*-configuration. However, although the required optically active halide (75) proved readily available, yields of the corresponding phosphonium halide were disappointing. By contrast, reaction with sodium thiophenoxide gave, in excellent yield, a thio-ether which was oxidized quantitatively to give the sulphone (76).

Metallated alkyl aryl sulphones react with carbonyl compounds to give, after acetylation or benzoylation, diastereoisomeric β-acyloxy-sulphones. On treatment with sodium amalgam in methanol these undergo loss of both functional groups, forming olefins.[35] In a study[36] of the stereochemistry of the reaction, when used for the formation of acyclic internal disubstituted olefins, we observed (Scheme 20) first that for unbranched olefins, *e.g.* (72), the *trans*:*cis* ratio of the



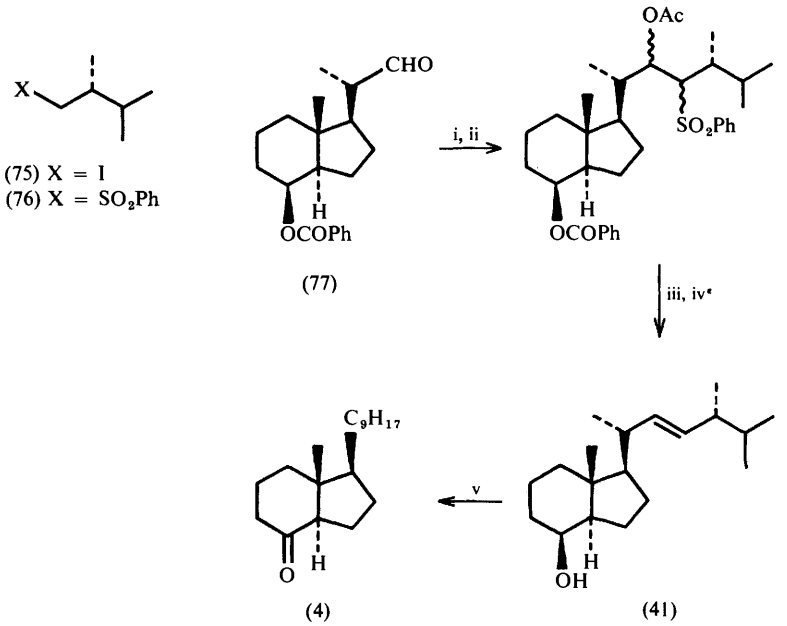
Scheme 20 *Stereochemistry of the β-benzoyloxysulphone elimination*

product is *ca.* 80:20 for each of the intermediate acyloxysulphone diastereoisomers (71). Secondly, when substituents are introduced into the starting materials at positions adjacent either to the aldehyde group, or to the methylene

[33] B. Lythgoe, D. A. Roberts, and I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2608.
[34] M. Schlosser and K. F. Christmann, *Liebigs Ann. Chem.*, 1967, **708**, 1.
[35] M. Julia and J.-M. Paris, *Tetrahedron Lett.*, 1973, 4833.
[36] P. J. Kocienski, B. Lythgoe, and S. Ruston, *J. Chem. Soc., Perkin Trans. 1*, 1978, 829; see also ref. 12.

group bearing the sulphonyl function, the *trans*-selectivity of the reaction is markedly increased. Two examples will illustrate this effect. The reaction partners isobutyl phenyl sulphone and 2-ethylbutyraldehyde, both of which contain substituents of the type in question, gave rise to an olefin consisting almost exclusively of the *trans*-isomer (73). Similarly, *Z*-2-methylbut-2-enyl phenyl sulphone and *E*-2-methylbut-2-enal gave rise almost exclusively to (2*E*, 4*E*, 6*Z*)-3,6-dimethylocta-2,4,6-triene (74), in which the original geometries of the starting materials were preserved, and the new, central double bond had the *trans*-configuration. The reasons for this *trans*-selectivity have been discussed.[12]

These observations formed the basis for the stereoselective construction[37] (Scheme 21) of the *trans*-double bond in the alcohol (41) which corresponds to



Reagents: i, Li derivative of (76); ii, Ac_2O; iii, Na/Hg–MeOH–EtOAc; iv, KOH–EtOH–H_2O; v, CrO_3–pyridine

Scheme 21 *Synthesis of Windaus and Grundmann's ketone*

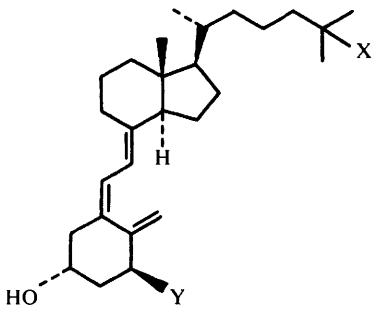
Windaus and Grundmann's ketone (4), starting from the benzoyloxyaldehyde (77) and the optically active sulphone (76). By virtue of this work the synthesis of vitamin D_2 described in the preceding section became formally total.

7 1α-Hydroxyvitamin D_3

During the past decade important advances have been made in understanding

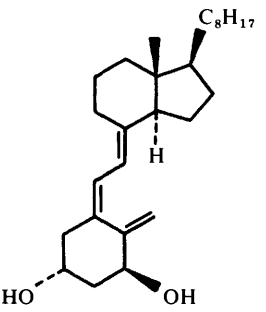
[37] P. J. Kocienski, B. Lythgoe, and D. A. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1978, 834.

the mode of action of vitamins D.[38] The full physiological activity of vitamin D_3 is developed only after its metabolic hydroxylation, at first in the liver to give 25-hydroxyvitamin D_3, and then in the kidneys to give 1α,25-dihydroxyvitamin D_3 (79) (Scheme 22), the hormonal form, which is very potent and rapidly acting.



(78) X = OH, Y = H
25-Hydroxyvitamin D_3

(79) X = Y = OH
1α,25-Dihydroxyvitamin D_3



(80)
1α-Hydroxyvitamin D_3

Scheme 22

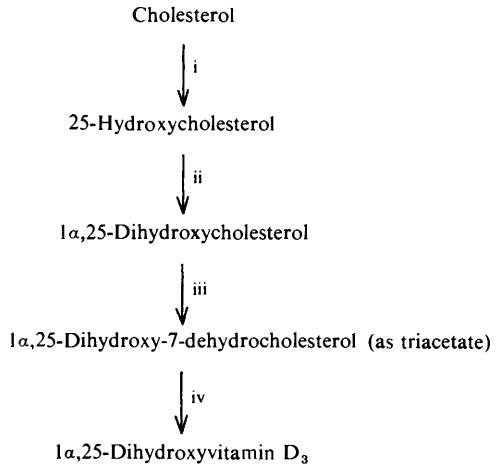
The dihydroxyvitamin (79) is clinically effective in those cases of osteodystrophy where, because the kidneys fail to effect the 1α-hydroxylation step, the vitamin itself is ineffective. 1α-Hydroxyvitamin D_3 (80) is similarly effective, since it can be converted *in vivo* into the hormone (79). These and related observations have greatly stimulated experiments on the chemical preparation of hydroxylated vitamin D derivatives.

The hormone (79) was first obtained in well characterized and crystalline form by the route[39] outlined in Scheme 23. Its central feature was the novel and elegant sequence which was used to effect the 1α-hydroxylation step (ii); step (i) derives from earlier work, and steps (iii) and (iv) use methods parallel to those normally used for the preparation of vitamin D_3 from cholesterol. Most other routes to the hormone (79) follow a similar synthetic strategy, although starting materials, methods, and sequence may be different.

It was of interest to consider whether the approaches described in earlier Sections of this lecture have relevance to the preparation of the hormone (79). For vitamin D_3 itself, total synthesis is so much longer than partial synthesis from cholesterol that it is ineffective as a preparative method. When, however,

[38] For reviews, see *inter al.* H. F. DeLuca and H. K. Schnoes, *Ann. Rev. Biochem*, 1976, **45**, 631; P. E. Georghiou, *Chem. Soc. Rev.*, 1977, **6**, 83.

[39] D. H. R. Barton, R. H. Hesse, M. M. Pechet, and E. Rizzardo, *J. Chem. Soc., Chem. Commun.*, 1974, 203.



Scheme 23

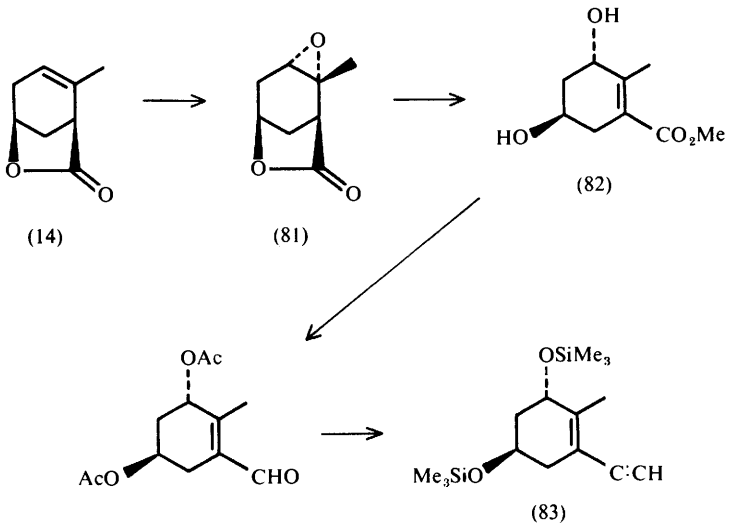
as in Scheme 23 and its relatives, a starting material must be modified at two separate sites in order to prepare it for the subsequent transformations (iii) and (iv), an element of linearity is introduced which can diminish, although it may not completely abolish, the advantage of partial synthesis. Moreover, total synthesis is often advantageous for the preparation of labelled compounds, useful in biological work.

We therefore explored synthetic routes to 1α-hydroxyvitamin D_3 (80). The first, an extension of the work of Scheme 10, proceeded by way of 1α-hydroxyprecalciferol$_3$, and required as the ring A component the enyne (83). This was prepared from the lactone (14) as shown in Scheme 24. The lactone bridge directs the attack of *m*-chloroperbenzoic acid to the opposite face of the molecule, so that the epoxide (81) is the major product, thus providing the correct configuration at the second hydroxy-centre in the dihydroxy-ester (82), and in the enyne (83), which were then obtained by standard methods.

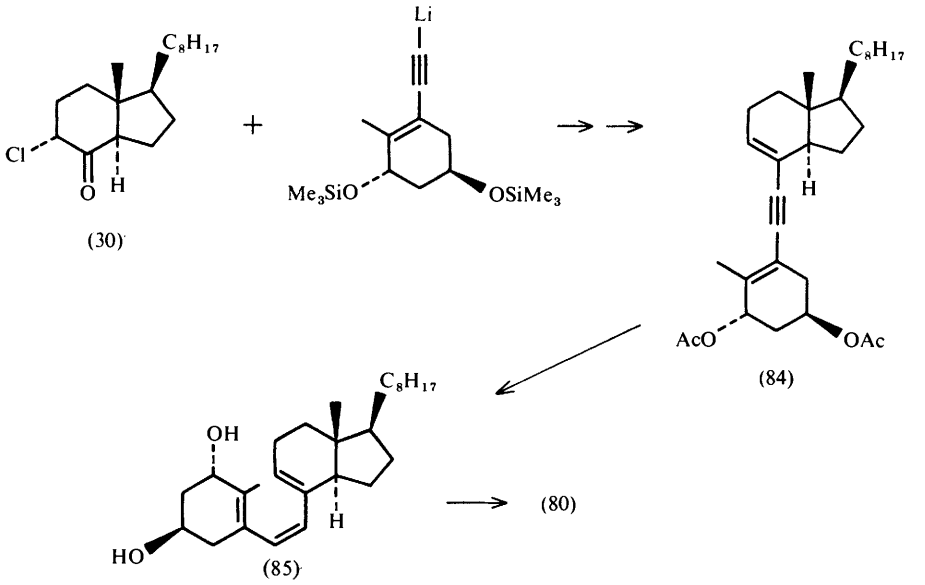
The lithium derivative of the enyne (83) and the chloro-ketone (30) were used[40] (Scheme 25) to obtain, in analogy with earlier work, the diacetoxyenynene (84), which was converted successively into 1α-hydroxyprecalciferol$_3$ (85) and 1α-hydroxyvitamin D_3 (80).

In a second route,[41] shown in Scheme 26, a 1α-hydroxytachysterol$_3$ derivative (88) was first prepared by a Julia olefin synthesis using the components (86) and (87). The *p*-tolyl sulphone, from which the lithium derivative (86) is derived, was obtained from the allylic alcohol (19); the protected aldehyde (87) was obtained by standard methods from the dihydroxy-ester (82). Tachysterol derivatives such

[40] R. G. Harrison, B. Lythgoe, and P. W. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2654.
[41] P. J. Kocienski and B. Lythgoe, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1400.



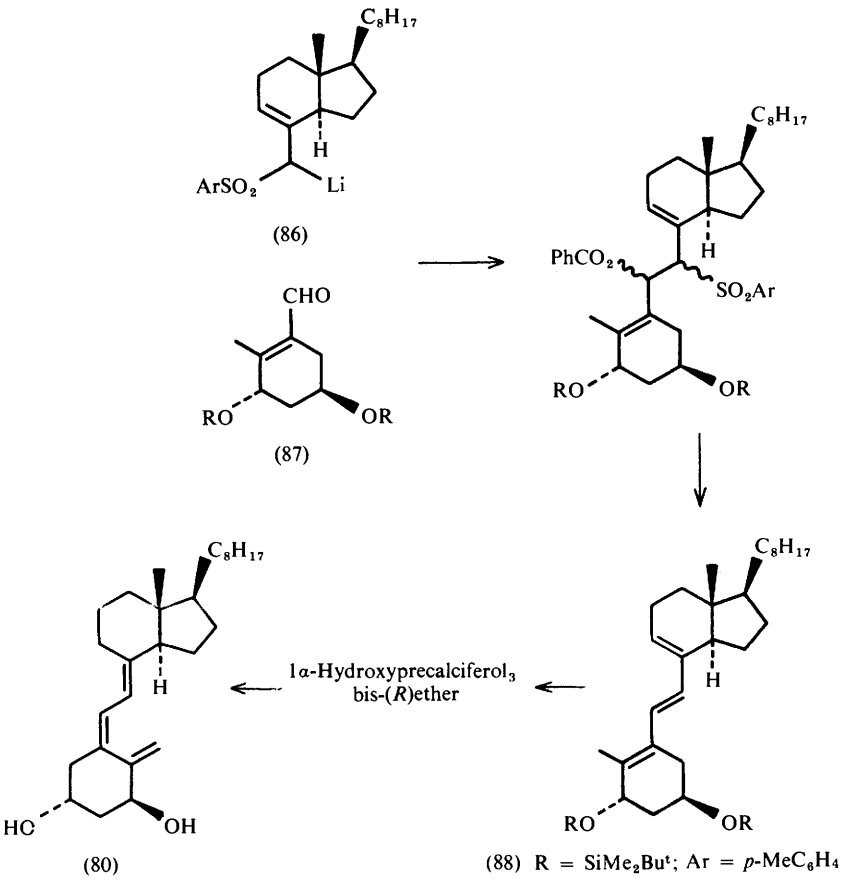
Scheme 24



Scheme 25 1α-*Hydroxyvitamin* D_3 *by way of* 1α-*hydroxyprecalciferol*$_3$

as (88) can be converted very efficiently by fluorenone-sensitized irradiation[42] into the corresponding precalciferol derivatives. Following this conversion, the

[42] A. E. C. Snoeren, M. R. Daha, J. Lugtenburg, and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, 1970, **89**, 261.

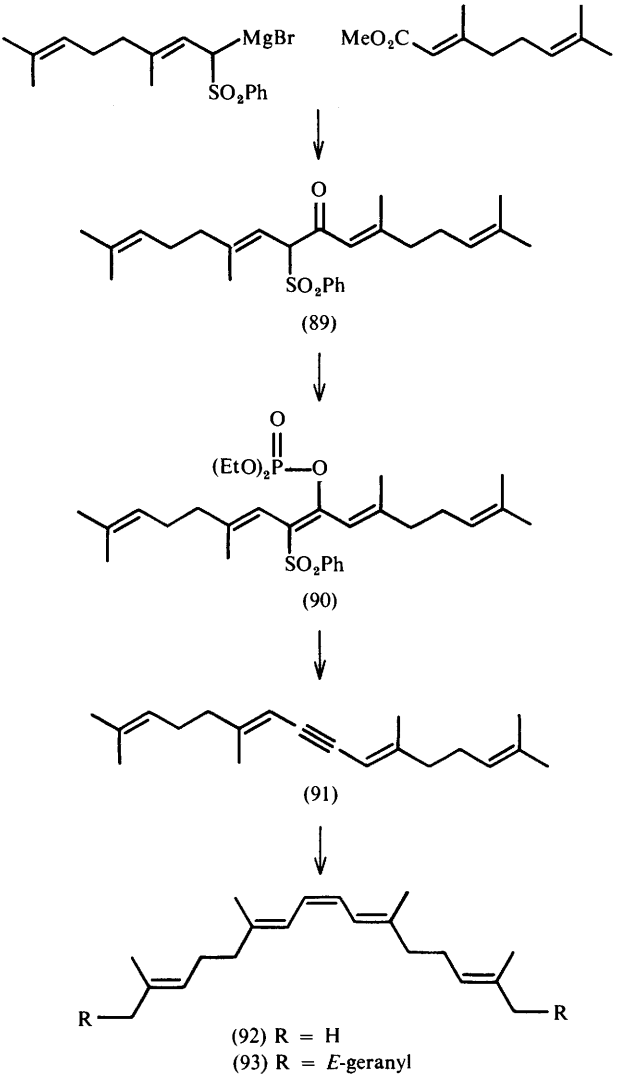


Scheme 26 *1α-Hydroxyvitamin D_3 by way of a 1α-hydroxytachysterol$_3$ derivative*

1α-hydroxyvitamin (80) was obtained in a yield of 57% from the allylic alcohol (19) or 12.8% overall from cholesterol. This compares favourably with many of the yields reported in the current literature; admittedly, however, more steps were needed in our method.

As in the synthesis of tachysterol$_3$ (Scheme 7), and for similar reasons, the 6-*trans*-compound (88) was formed essentially stereospecifically. It would clearly be of great value if a similar addition–elimination sequence were available for the stereoselective construction of an internal disubstituted double bond with *cis*-geometry. This result can of course be achieved by use of the 'salt-free' Wittig method, but only in those cases where the phosphorane used is not allylic; it can not be used to construct the central double bond in such conjugated trienes as natural 15*Z*-phytoene (93) or precalciferol$_3$. We were not able to devise a direct

method for the purpose in question, but a method was found[43] for constructing an internal acetylenic link which, by adding a semihydrogenation step, permitted the desired result to be achieved indirectly. The method is illustrated by the synthesis[44] of the conjugated triene (92) (Scheme 27).



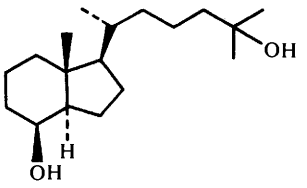
Scheme 27 *Synthesis of conjugated enynenes*

[43] B. Lythgoe and I. Waterhouse, *Tetrahedron Lett.*, 1978, 2625. For a related synthesis, see P. A. Bartlett, F. R. Green III, and E. H. Rose, *J. Am. Chem. Soc.*, 1978, **100**, 4852.
[44] B. Lythgoe and I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2429.

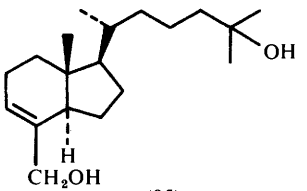
Reaction of the magnesium bromide derivative of *E*-geranyl phenyl sulphone with methyl *E*-geranate gave the β-oxo-sulphone (89); its lithium enolate reacted with diethyl phosphorochloridate to give the enol phosphate (90). When this was treated with sodium amalgam in tetrahydrofuran–dimethyl sulphoxide, 1,2-elimination of both functional groups took place giving the enynene (91), in which the *E*-geometry of both starting materials was preserved. Semihydrogenation over Lindlar's catalyst then gave the conjugated *E,Z,E*-triene (92), which is an analogue of 15*Z*-phytoene (93).

In an exactly similar manner, the bis-t-butyldimethylsilyl ether of the ester (82) and the *p*-tolyl sulphone corresponding to (86) were used to prepare[45] the conjugated enynene (84) from which, as previously described, 1α-hydroxyprecalciferol$_3$ and 1α-hydroxyvitamin D$_3$ were obtained in turn.

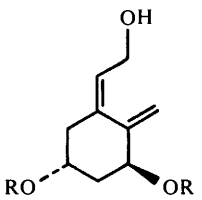
Although these experiments have not so far been extended to yield 1α,25-dihydroxyvitamin D$_3$, they are clearly serviceable for that purpose, and it may be useful to point to two routes as the most promising. The first, analogous to that of Scheme 16, constructs the 7,8-double bond of the metabolite by interaction of the diphenylphosphine oxide corresponding to an allylic alcohol (96) with a suitably protected ketone corresponding to the alcohol (94). This latter alcohol has been obtained by total synthesis[33] (although probably not by the most efficient available route) as well as from vitamin D$_3$.[46] A second route to the metabolite (79) requires the preparation of the allylic alcohol (95) and the use of a suitable phosphorus or sulphur derivative of it in an olefin synthesis with the aldehyde (87). As in Scheme 26, the resulting tachysterol derivative would then be converted into the vitamin D analogue.



(94)



(95)



(96)

Scheme 28

[45] B. Lythgoe and I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1405.
[46] Z. Cohen, E. Berman, and Y. Mazur, *J. Org. Chem.*, 1979 **44**, 3077.

I wish to thank sincerely the numerous and skilful collaborators, named in the references, whose experiments form the basis for this lecture.