# Calciferol and its Relatives. Part 27.[1] A Synthesis of 1α-Hydroxyvitamin $D_3$ by way of 1α-Hydroxytachysterol$_3$

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A new synthesis of 1α-hydroxyvitamin $D_3$ is described. The bis-t-butyldimethylsilyl ether (17) † of (3*S*,5*R*)-3,5-dihydroxy-2-methylcyclohex-1-enecarbaldehyde and 8-*p*-tolylsulphonylmethyl-des-AB-cholest-8-ene (4) were combined to give mixed benzoyloxysulphones which, on reductive elimination with sodium amalgam, gave the corresponding bis-ether of 1α-hydroxytachysterol$_3$. This was isomerised photochemically to the bis-ether of 1α-hydroxyprecalciferol$_3$, and then thermally to give the bis-ether of 1α-hydroxyvitamin $D_3$. Removal of protecting groups gave 1α-hydroxyvitamin $D_3$ (21) in 62% yield from the sulphone (4), or 12.8% overall from cholesterol.

THE work now reported formed part of studies made to define a proper strategy for the total synthesis of the hormonal compound 1α,25-dihydroxyvitamin $D_3$ by an A ⟶ CD approach. Until now, direct syntheses [2,3] of D-vitamins by this approach have been based on the union of ring-A and rings-CD fragments so as to generate the 7,8-double bond of the vitamin. A synthesis of precalciferol$_3$,[4] and of 1α-hydroxyprecalciferol$_3$,[5] from which the corresponding vitamins can readily be obtained, has also been effected by the union of appropriate fragments so as to generate the 7,8-single bond of these previtamins. These syntheses have the advantage of using the CD-component, the more complex of the two necessary fragments, in some of its simplest forms.

On the other hand, the synthesis of tachysterol$_3$ [6] and model analogues from two fragments so as to generate the 6,7-double bond was found to be a simple and efficient undertaking; and since tachysterol$_3$ can be converted efficiently into precalciferol$_3$ by fluorenone-sensitised irradiation,[7] it was apparent that an alternative strategy of vitamin synthesis, based on a 6,7-union, deserved evaluation.

Other considerations, too, had a bearing on the question. Synthesis of 1α,25-dihydroxyvitamin $D_3$ by way of a tachysterol derivative would require a CD-fragment derived from the allylic alcohol (1).† Recently,[1] substantial progress has been made in the preparation of 8-hydroxymethyl-des-AB-cholest-8-ene (2), which can now be obtained by degradation of cholesterol in a yield of 22.5%. The preparation from stigmasterol or lithocholic acid of the hydroxylated analogue (1) seemed unlikely to present major difficulties. Moreover, it was apparent that compounds (1) and (2) could be approached also by total synthesis, for example from the hydrindane derivative (3), to which effective access has been provided by Roche workers.[8] The extra carbon atom at C-8 in compounds (1) and (2) is already present in (3), just as it is in the intact sterols, and from such compounds $C_{19}$ intermediates like (1) and (2) should be at least as easily available as $C_{18}$ compounds. Finally, we found that the tachysterol model, (*E*)-1,2-dicyclohex-1-enylethylene, can be efficiently obtained, with stereoselective construction of the central *trans*-double bond, from cyclohexene-1-carbaldehyde and cyclohex-1-enylmethyl phenyl sulphone, using Julia's reductive elimination [9] of β-acyloxy-sulphones. The sulphone (4), appropriate to a similar synthesis of tachysterol$_3$, has now been obtained from the allylic alcohol (2), by reaction of the corresponding chloride with sodium toluene-*p*-sulphinate in dimethylformamide, in 92% yield. These circumstances led us to explore the synthesis of vitamin $D_3$ by way of tachysterol$_3$.

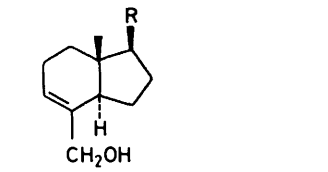
The ring-A component for this purpose was obtained by treatment of the (−)-aldehyde [10] (5) with benzoyl chloride in pyridine to give (*S*)-5-benzoyloxy-2-methylcyclohex-1-ene-1-carbaldehyde (6) as a crystalline solid. Reaction with the lithium derivative of the sulphone (4) in tetrahydrofuran, and treatment of the product with benzoyl chloride, gave in nearly quantitative yield a mixture of the diastereoisomeric benzoyloxysulphones (7). One of the component isomers was isolated by crystallisation in 39% yield; this isomer was used for the preparation of pure tachysterol$_3$. It was reduced with sodium amalgam in tetrahydrofuran and methanol at −20 °C, and the product was hydrolysed to remove the benzoyl group, and re-esterified with 4-methyl-3,5-dinitrobenzoyl chloride. The crystalline 4-methyl-3,5-dinitrobenzoate of tachysterol$_3$ [6,11] was so obtained in a yield of 59% from the sulphone (4).

It has been shown [12] that the behaviour on reductive elimination of diastereoisomeric β-benzoyloxy-sulphones is independent of their relative stereochemistry, so that the non-crystalline mixture, left after removal of most of the crystalline isomer (7), was expected to behave in the same way as that isomer. The product from reductive elimination of the non-crystalline material was hydrolysed, and the crude product (10) was irradiated in benzene containing fluorenone as a sensitiser,[7] in order to effect its photo-equilibration with the 6-*cis*-isomer precalciferol$_3$ (12). After thermal isomerisation of the previtamin the product was separated chromatographically and esterified with 3,5-dinitrobenzoyl chloride, when the crystalline 3,5-dinitrobenzoate [13] of vitamin $D_3$ was obtained in a yield of 47% based on the sulphone (4). These results were thought to warrant the extension of the method to the synthesis of 1α-hydroxyvitamin $D_3$.

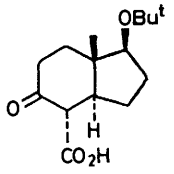
The ring-A component for this purpose was obtained from the (−)-lactone [14] (13). This was first converted,

† All the structures in this paper represent absolute configurations.

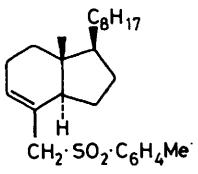
by a modification of the existing method [5] (see Experimental section) into methyl (3*S*,5*R*)-3,5-dihydroxy-2-methylcyclohex-1-ene-1-carboxylate (14). The hydroxy-groups were protected [15] to give the t-butyldimethylsilyl ether (15), and the ester group was then reduced to give the primary alcohol (16). Re-oxidation with manganese dioxide gave the protected aldehyde (17).



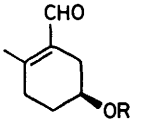
(1) R = CHMe·[CH$_2$]$_3$·CMe$_2$·OH
(2) R = CHMe·[CH$_2$]$_3$·CHMe$_2$



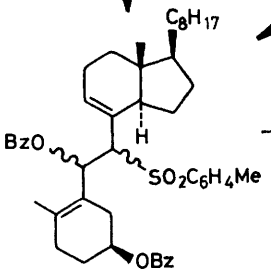
(3)



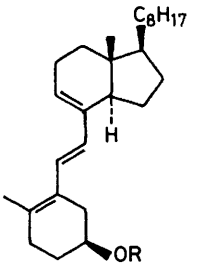
(4)



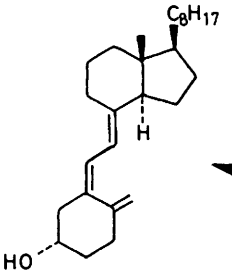
(5) R = H
(6) R = Bz



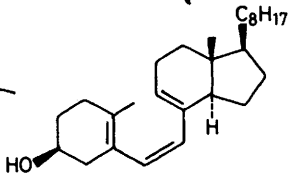
(7)



(8) R = Bz
(9) R = CO·C$_6$H$_2$Me(NO$_2$)$_2$
(10) R = H



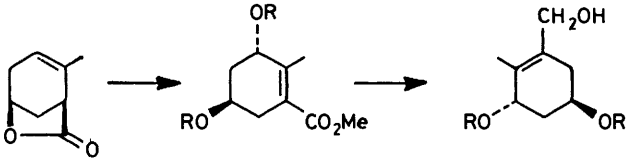
(11)



(12)

Reaction of the aldehyde in the usual way with the lithium derivative of the sulphone (4) provided a mixture of the isomeric benzoyloxy-sulphones (18) from which the tachysterol derivative (19) was obtained on reductive elimination. It was subjected first to the photochemical,[7] and then to thermal equilibration. After a brief chromatographic purification the protecting silyl groups were removed with tetra-n-butylammonium fluoride in tetrahydrofuran, and 1α-hydroxyvitamin D$_3$ (21) was isolated by crystallisation. A further amount was obtained from the mother-liquor material by a repetition of the photochemical and thermal isomerisation processes, so that the combined yield of the recrystallised material was 62% based on the *p*-tolyl sulphone (4), or 57% based on the allylic alcohol (2).

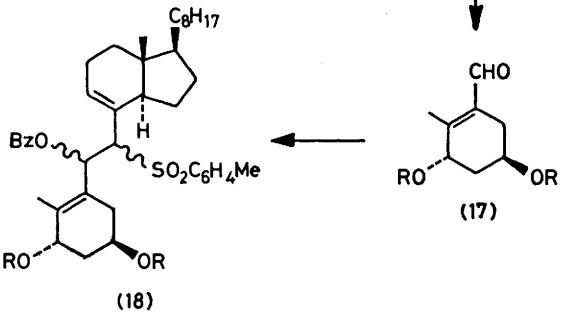
Since the allylic alcohol (2) has been obtained [1,16] by total synthesis, the foregoing work represents a formal total synthesis of 1α-hydroxyvitamin D$_3$. It is, however also of interest to regard it as a transformation of cholesterol, from which the 1α-hydroxyvitamin was obtained in a yield of 12.8%. This may be compared with some yields cited in the current literature for the same transformation effected by using as intermediates 1α-hydroxycholesterol and/or 1α-hydroxy-7-dehydrocholesterol derivatives. An improved route [17] *via*



(13)

(14) R = H
(15) R = Bu$^t$Me$_2$Si

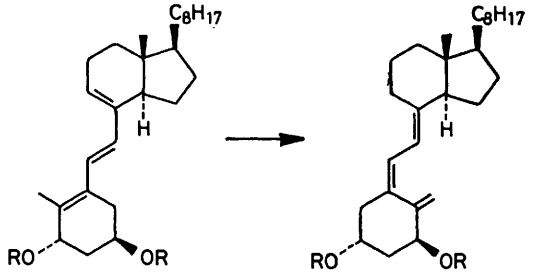
(16)



(17)



(18)



(19)

(20) R = SiMe$_2$Bu$^t$
(21) R = H

R = Bu$^t$Me$_2$Si unless otherwise stated

cholesta-1,5,7-trien-3-one and 1α-hydroxy-7-dehydrocholesterol gave the latter compound in a yield of 14% from cholesterol. Barton's [18] original method *via* 1α-hydroxycholesterol gave 1α-hydroxy-7-dehydrocholesterol in 9% yield from cholesterol, but more recent

modifications [19] are said to give 20%. Yields quoted for the final photochemical and thermal steps from 1α-hydroxy-7-dehydrocholesterol to 1α-hydroxyvitamin $D_3$ are generally modest, for example [17] 15%; but it should be noted that Eyley and Williams [20] obtained 28% for the corresponding reactions leading to crystalline vitamin $D_2$, and that recently,[21] using their method, 22,23-epoxyvitamin $D_2$ has been obtained from its provitamin in 58% yield. It is therefore likely that the usual 'intact steroidal approach' is capable of giving 1α-hydroxyvitamin $D_3$ from cholesterol in yields of 12% or more. However, the present method, using the A ⟶ CD approach, can be regarded as relatively efficient, and possibly suitable for extension to the synthesis of 1α,25-dihydroxyvitamin $D_3$.

## EXPERIMENTAL

Unless otherwise specified, light petroleum means the fraction of b.p. 60—80 °C. $^1$H N.m.r. data refer to solutions in $CDCl_3$. T.l.c. and p.l.c. were carried out with Kieselgel $GF_{254}$.

8-p-*Tolysulphonylmethyl-des*-AB-*cholest*-8-*ene* (4).—The *p*-nitrobenzoate (1.90 g) of the allylic alcohol (2) was hydrolysed for 1 h at 20 °C in methanol (20 cm$^3$) with potassium hydroxide (0.8 g) in the minimum volume of water, and the product (2) (1.23 g) was isolated with ether. Its solution in benzene (1 cm$^3$) was added dropwise at 0 °C to a stirred suspension of chloromethylenedimethylammonium chloride, prepared by the slow addition of oxalyl chloride (0.525 cm$^3$) to dimethylformamide (0.5 cm$^3$) in benzene (5 cm$^3$) at 0 °C with stirring. After 30 min the mixture was poured into water, and the crude allylic chloride was isolated with ether. It was stirred at 60 °C for 3 h with sodium toluene-*p*-sulphinate (1.5 g) in dimethylformamide (4 cm$^3$); the cooled mixture was then poured into water and the product was isolated with ether–light petroleum (1 : 1). Crystallisation from methanol gave in two crops the p-*tolyl sulphone* (4) (1.71 g, 92%) as plates, m.p. 85—86°, $[\alpha]_D^{19}$ −25.4° ($CHCl_3$); $\nu_{max.}$ ($CCl_4$) 1 155s and 1 325s cm$^{-1}$; τ 2.23 (2 H, d, *J* 8 Hz, ArH), 2.66 (2 H, d, *J* 8 Hz, ArH), 4.74 br (1 H, =CH–), 6.19 and 6.42 (each 1 H, d, *J* 16 Hz, $ArSO_2CH_2$), and 7.53 (3 H, s, $ArCH_3$) (Found: C, 74.85; H, 9.85; S, 7.85. $C_{26}H_{40}O_2S$ requires C, 75.0; H, 9.7; S, 7.7%).

(S)-5-*Benzoyloxy*-2-*methylcyclohex*-1-*ene*-1-*carbaldehyde* (6).—The crude aldehyde (5) was treated at 22 °C in the usual way with benzoyl chloride in pyridine. The oily product solidified on trituration with light petroleum; crystallisation from ether–light petroleum gave the *benzoyloxy-aldehyde* (6) as prisms m.p. 85—86 °C, $[\alpha]_D^{20}$ +9.1° ($CHCl_3$); $\nu_{max.}$ ($CCl_4$) 1 100s, 1 265s, 1 640m, 1 670s, and 1 718s cm$^{-1}$; τ −0.18 (1 H, s, CH=O), 1.8—2.7 (5 H, m, ArH), 4.68 (1 H, m, >C*H*·OBz), 7.80 (3 H, s, $CH_3C$=), and 8.00 (2 H, d, *J* 7 and 13 Hz, $>CH_2$) (Found: C, 73.65; H, 6.55. $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.6%).

*The Benzoyloxy-sulphones* (7).—1.5M-n-Butyl-lithium in hexane (0.7 cm$^3$) was added dropwise to a stirred solution of the sulphone (4) (416 mg) in tetrahydrofuran (6.0 cm$^3$) at −78 °C. After a further 30 min at the same temperature a solution of the benzoyloxy-aldehyde (5) (244 mg) in tetrahydrofuran (1 cm$^3$) was added dropwise, and after a further 15 min benzoyl chloride (0.35 cm$^3$) was added. Stirring was continued for 2 h while the temperature was allowed to rise from −78 to 0 °C; 3-dimethylaminopropylamine (0.2 cm$^3$) was then added to destroy the excess of benzoyl chloride. The mixture was distributed between 1N-hydrochloric acid (20 cm$^3$) and ether (30 cm$^3$) at 0 °C; the ether layer was washed with aqueous sodium hydrogencarbonate and aqueous ammonium chloride, and then dried and evaporated. Crystallisation of the residue from ether gave 3β,6-*dibenzoyloxy*-7-p-*tolylsulphonyl*-9,10-*seco*-*cholesta*-5(10),8-*diene* (7) as prisms (300 mg, 39%), m.p. 198—202 °C, $[\alpha]_D^{20}$ −15.2° ($CHCl_3$); $\nu_{max.}$ ($CCl_4$) 1 150s, 1 265vs, 1 305m, 1 315s, and 1 720vs cm$^{-1}$; τ 2.2—3.1 (14 H, m, ArH), 3.62 (1 H, d, *J* 10 Hz, BzOC*H*·$CHSO_2$), 3.88br (1 H, =CH), 4.9br (1 H, >C*H*·OBz), 5.75 (1 H, d, *J* 10 Hz, $>CHSO_2$), 7.85 (3 H, s, $ArCH_3$), and 8.13 (3 H, s, $=CCH_3$) (Found: C, 74.95; H, 7.95; S, 4.2. $C_{48}H_{60}O_6S$ requires C, 75.4; H, 7.9; S, 4.2%).

The mother-liquor material (495 mg) which contained some of the above isomer, and was not separated from it on t.l.c., had spectral characteristics which indicated the presence of diastereoisomers of the crystalline compound.

*Tachysterol*$_3$ 4-*Methyl*-3,5-*dinitrobenzoate* (9).—In this experiment materials were handled under argon with strict exclusion of air. The crystalline isomer (7) (100 mg) was stirred at —20 °C for 1.5 h with 5.65% sodium amalgam (300 mg) in methanol (2 cm$^3$) and tetrahydrofuran (2 cm$^3$). The decanted solution was evaporated under reduced pressure and the residue dissolved in chloroform (2 cm$^3$), and chromatographed on silica gel (1.5 × 3 cm) with elution by chloroform (15 cm$^3$). The residue left by evaporation of the solvent was hydrolysed in the usual way with potassium hydroxide in ethanol, and the product was re-esterified with 4-methyl-3,5-dinitrobenzoyl chloride in pyridine. Crystallisation from acetone–methanol (9 : 1) gave tachysterol$_3$ 4-methyl-3,5-dinitrobenzoate (9) [44 mg, 59% from the sulphone (4)], m.p. 137—139 °C, $[\alpha]_D^{20}$ +33.0° (benzene); $\lambda_{max.}$ (EtOH) 270 (ε 25 400), 281 (30 600), and 290 nm (25 200); τ 1.42 (2 H, s, ArH), 3.23 and 4.02 (each 1 H, d, *J* 16 Hz, CH=CH), 4.28 br (1 H, =CH–), 4.65br (1 H, >CH–O), 7.36 (3 H, s, $ArCH_3$), and 8.14 (3 H, s, $=C{\cdot}CH_3$).

*Vitamin* $D_3$ 3,5-*Dinitrobenzoate*.—The non-crystalline mixture of the diastereoisomeric benzoyloxy-sulphones (7) (495 mg) was converted, as described for the crystalline isomer, into crude tachysterol$_3$ (169 mg); it was handled with exclusion of air (argon). Its solution in degassed benzene (80 cm$^3$) containing fluorenone (90 mg) was irradiated at 10 °C for 45 min with a Hanovia medium-pressure mercury-vapour lamp (450 W); the solution was then heated under reflux for 3 h, the solvent was evaporated, and the residue was chromatographed on silica gel (2 × 10 cm) with chloroform. The first eluate contained the fluorenone; this was followed by vitamin $D_3$ and a less-polar compound. They were separated by p.l.c. (methylene chloride), and the vitamin fraction (110 mg) was esterified with 3,5-dinitrobenzoyl chloride in pyridine. Crystallisation of the product from acetone–methanol gave vitamin $D_3$ 3,5-dinitrobenzoate [169 mg, 47% from the sulphone (4)], m.p. 127—129.5 °C, $[\alpha]_D^{20}$ +95° ($CHCl_3$).

*Methyl* (3S,5R)-3,5-*Dihydroxy*-2-*methylcyclohex*-1-*enecarboxylate* (14).—A solution of the (−)-lactone (13) (2.2 g) in methylene chloride (25 cm$^3$) was stirred at 0 °C during the gradual addition of 85% *m*-chloroperbenzoic acid (3.23 g). The mixture was allowed to reach room temperature during 3.5 h, ether (100 cm$^3$) was added, and the mixture was washed with aqueous sodium hydrogensulphite and aqueous sodium hydrogencarbonate, the aqueous phases being re-extracted with methylene chloride. The com-

bined organic phases were dried and evaporated, and the crystalline residue was chromatographed on silica gel (10% ethyl acetate–light petroleum). The less polar product separated from ether–light petroleum giving 5α,6α-epoxy-6-methylcylohexane-1β,3β-carbolactone [5] (1.66 g, 67%), m.p. 67—69 °C, $[\alpha]_D^{20}$ −215° ($CHCl_3$). The more polar product separated from ether–chloroform giving *5β,6β-epoxy-6-methylcyclohexane-1β,3β-carbolactone* as prisms (0.5 g, 20%), m.p. 118—120 °C, $[\alpha]_D^{20}$ +10.4° (acetone); $\nu_{max.}$ ($CCl_4$) 1 770 $cm^{-1}$; τ 5.30 br (1 H, >CH·OCO), 6.70 (1 H, d, *J* 4 Hz, >CH·O), 7.12 (1 H, d, *J* 6 Hz, >CH·COO), and 8.47 (3 H, s, $CH_3$) (Found: C, 62.0; H, 6.65. $C_8H_{10}O_3$ requires C, 62.3; H, 6.5%).

The α-epoxy-carbolactone (1.52 g) was kept at room temperature for 12 h with 0.64N-methanolic sodium methoxide (25 $cm^3$). Acetic acid (1 $cm^3$) was added, the mixture was evaporated under reduced pressure, and the residue was dissolved in water (100 $cm^3$), which was then continuously extracted with ether for 7 h; the extract was dried and concentrated (*ca.* 15 $cm^3$) and cooled to −20 °C. The crystals were recrystallised from acetone–ether, giving the *dihydroxy-ester* (14) (1.65 g, 90%), m.p. 84—86°, $[\alpha]_D^{20}$ −139° ($CHCl_3$); $\nu_{max.}$ ($CCl_4$) 1 240s, 1 635m, 1 710s, and 3 450s $cm^{-1}$; τ 6.23 (3 H, s, $OCH_3$) and 7.89br (3 H, s, $CH_3$) (Found: C, 58.2; H, 7.55. $C_9H_{14}O_3$ requires C, 58.05; H, 7.6%).

*The Aldehyde* (17).—The ester (14) (0.89 g), t-butyldimethylsilyl chloride (1.81 g) and imidazole (1.7 g) were kept together at room temperature in dimethylformamide (4 $cm^3$) for 36 h. The mixture was added to water (50 $cm^3$), which was extracted with ether–light petroleum (1 : 1, 2 × 30 $cm^3$). The dried extract was evaporated to give an oil which was dissolved in ether (15 $cm^3$) and the solution was added dropwise with stirring to lithium aluminium hydride (250 mg) in ether (15 $cm^3$). The mixture was heated under reflux for 2 h, and then cooled to 20 °C and stirred during the addition of powdered sodium sulphate decahydrate (3.5 g) in portions. After a further 30 min the mixture was filtered, and the ether was removed. Crystallisation of the residue from light petroleum (b.p. 30—40 °C) at −40 °C gave the *bis(t-butyldimethylsilyl) ether* (16) of (1S,5R)-3-*hydroxymethyl*-4-*methylcyclohex*-3-*ene*-1,5-*diol* as needles (1.56 g, 84%), m.p. 88—89 °C, $[\alpha]_D^{20}$ −66.5° ($CHCl_3$); $\nu_{max.}$ ($CCl_4$) 1 120s, 1 250s, 3 520w, and 3 580w $cm^{-1}$; τ 5.9br (4 H, $CH_2$·OH and 2 >CH·O), 8.07 and 8.08 (each 9 H, s, 2 × $Bu^t$), 8.23br (3 H, s, $CH_3$), and 9.89 and 9.92 (each 6 H, s, $Me_2Si$) (Found: $M^+$, 386.267 78. $C_{20}H_{42}O_3Si_2$ requires *M*, 386.267 24).

The alcohol (16) (310 mg) was stirred in light petroleum (b.p. 30—40 °C; 5 $cm^3$) with active manganese dioxide (1.0 g) for 8 h; the solution was filtered and evaporated, and the residue was distilled from bulb-to-bulb at 180 °C (bath temp.) and 0.05 mmHg to give the aldehyde (17) as an oil (301 mg, 97%), $\nu_{max.}$ (film) 775s, 840s, 1 080s, 1 255s, 1 640w, and 1 680s $cm^{-1}$; τ −0.17 (1 H, s, −CH=O), 5.5—6.1 (2 H, m, >CH·OSi), 7.85br (3 H, s, =C·$CH_3$), 8.2 (2 H, apparent t, >$CH_2$), 9.08 and 9.11 (each 9 H, s, $Bu^t$), and 9.86 and 9.93 (each 6 H, s, $Me_2Si$). The aldehyde was used at once for the next step.

*1α-Hydroxyvitamin* $D_3$ (21).—The sulphone (4) (292 mg) and the aldehyde (17) (288 mg) were brought into reaction as described for the preparation of the isomers (7) to give diastereoisomeric benzoyloxy-sulphones (18) as an amorphous mixture (620 mg). It was dissolved in tetrahydrofuran (6 $cm^3$) and methanol (2 $cm^3$) and the solution was stirred at −20 °C under nitrogen for 2 h with 5.65% sodium amalgam (1.5 g). Following this, strictly anaerobic conditions were used (argon). The solution was separated, the solvents were removed under reduced pressure, and the residue was distributed between saturated aqueous ammonium chloride (3 $cm^3$) and benzene (3 $cm^3$). The benzene layer was applied to a column (1.5 × 6 cm) of silica gel (benzene); the aqueous layer was extracted with more benzene (3 × 3 $cm^3$), and each extract was applied under argon to the column, the benzene eluates from the column being led directly into a photochemical vessel. After dilution with benzene (to 50 $cm^3$), fluorenone (126 mg) was added, and the solution was irradiated as described earlier for 20 min at 10 °C. It was then heated under reflux for 3.5 h, and after concentration under reduced pressure it was applied to a column (1.5 × 6 cm) of silica gel (benzene). Elution with benzene (20 $cm^3$) gave a mixture (607 mg) of seco-steroids, the fluorenone remaining on the column. The mixture was kept under nitrogen for 4 h with tetrahydrofuran (10 $cm^3$) and tetra-n-butylammonium fluoride trihydrate (630 mg). The solvent was removed under reduced pressure and the residue was distributed between ether and water. The ether phase was washed, dried, and evaporated. The residue, dissolved in light petroleum (b.p. 30—40 °C) and cooled, gave a crop of crystalline 1α-hydroxyvitamin $D_3$. The mother-liquor material was dissolved in benzene (25 $cm^3$) containing fluorenone (50 mg) and was irradiated as before. Heat treatment and chromatography were conducted as before, the first eluate containing the fluorenone; further elution (20% ethyl acetate–benzene) gave the seco-steroids. Evaporation and crystallisation as before gave a second crop of 1α-hydroxyvitamin $D_3$.

The combined crops were recrystallised from light petroleum (6.5 $cm^3$) giving 1α-hydroxyvitamin $D_3$ (174.5 mg, 62% overall), m.p. 133—136°, $[\alpha]_D^{20}$ +29° ($CHCl_3$). The $^1H$ n.m.r. spectrum was identical with that of authentic [5] material.

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