

Calciferol and its Relatives. Part 23.¹ An Alternative Synthesis of Windaus and Grundmann's C₁₉ Ketone

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(-)-(S)-Methyl hydrogen β-methylglutarate was converted into (S)-2,3-dimethylbutyl phenyl sulphone (10).† This was used in combination with the aldehyde (2), obtained by oxidation of 1β-[(R)-2-hydroxy-1-methyl-ethyl]-7αβ-methyl-3αα,4,5,6,7,7αβ-hexahydroindan-4β-yl benzoate (1), to effect a stereospecific synthesis of the secondary alcohol (12) which corresponds to Windaus and Grundmann's C₁₉ ketone.

IN Part 20² we described a total synthesis of the bicyclic monobenzoate (1),† and the transformation of the derived aldehyde (2) into the secondary alcohol (12) which corresponds to Windaus and Grundmann's³ C₁₉ ketone. This transformation commenced with the reaction of the aldehyde (2) with propynylmagnesium bromide and the separation of the resulting C₂₂ epimeric alcohols, each of which was then converted into the alcohol (12) in multi-step processes which did not involve any fresh optically active reagents. It is easy to imagine an alternative approach to the conversion (2) → (12), namely by a reaction of the Wittig type (*i.e.* one which involves an addition, followed by an elimination to generate the 22,23-double bond), using an optically active 2,3-dimethylbutyl fragment activated for carbanion formation at its 1-position. This alternative approach forms the subject of the present paper.

We first considered whether the phosphonium halide (3) would serve our purpose. Under salt-free conditions its ylide would be expected to react with the aldehyde (2) to give mainly the *cis*-isomer of the required compound, but by using Schlosser's modification⁴ of the Wittig method a predominance of the *trans*-isomer would be expected; experiments on the preparation of the phosphonium compound (3) were therefore undertaken. The iodide (7) corresponding to (3) can be obtained without difficulty (see later). However, reaction of the more readily available racemate *rac*-(7) with triphenylphosphine under various conditions failed to give yields of more than 25% of *rac*-(3). This is probably due to the hindrance introduced by the alkyl branch at position

2 of the halide *rac*-(7), together with the considerable steric requirements of the triphenylphosphine and its relatively weak nucleophilic character. The Wittig-Schlosser method was in consequence regarded as unsuitable for our present purpose.

In contrast, the iodide *rac*-(7) reacted readily with sodium benzenethiolate to give a sulphide from which, by oxidation, excellent yields of the sulphone *rac*-(10) were obtained. Two sulphone syntheses have been shown⁵ to give predominantly or exclusively *trans*-disubstituted olefins, and it was then apparent that by use of either it should be possible to effect a synthesis of the proper geometric form of the unsaturated alcohol (12). The preparation of the optically active sulphone (10) was therefore attempted.

Reduction⁶ with diborane of the (-)-monomethyl ester⁷ (4) gave a methyl ester primary alcohol which was benzylated with benzyl chloride and potassium hydroxide; hydrolysis of the ester group then afforded the acid (5). Methylation of the dianion⁸ gave the α-methylated acid (6); its ethyl ester was reduced with lithium aluminium hydride to an alcohol the tosylate of which was again reduced with lithium aluminium hydride to give the benzyl ether of the alcohol (9). Hydrogenolysis to the primary alcohol, followed by oxidation with Jones reagent, gave the acid (8), which was converted by Barton's⁹ lead tetra-acetate method into the iodide (7). Using this, the optically active sulphone (10) was obtained in 38% overall yield from the (-)-monomethyl ester (4).

† All the structures in the present paper represent absolute configurations. Racemates are denoted by the prefix *rac*-; thus *rac*-(3) means the racemate corresponding to (3).

¹ Part 22, B. Lythgoe, T. A. Moran, M. E. N. Nambudiry, J. Tideswell, and P. W. Wright, *J.C.S. Perkin I*, 1978, 590.

² B. Lythgoe, D. A. Roberts, and I. Waterhouse, *J.C.S. Perkin I*, 1977, 1976.

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

⁴ M. Schlosser and K. F. Christmann, *Angew. Chem. Internat. Edn.*, 1966, 5, 126; *Annalen*, 1967, 708, 1.

⁵ (a) B. Lythgoe and I. Waterhouse, *Tetrahedron Letters*, 1977, 4223; (b) P. J. Kocienski, B. Lythgoe, and S. Ruston, preceding paper.

⁶ Y. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.*, 1973, 38, 2786.

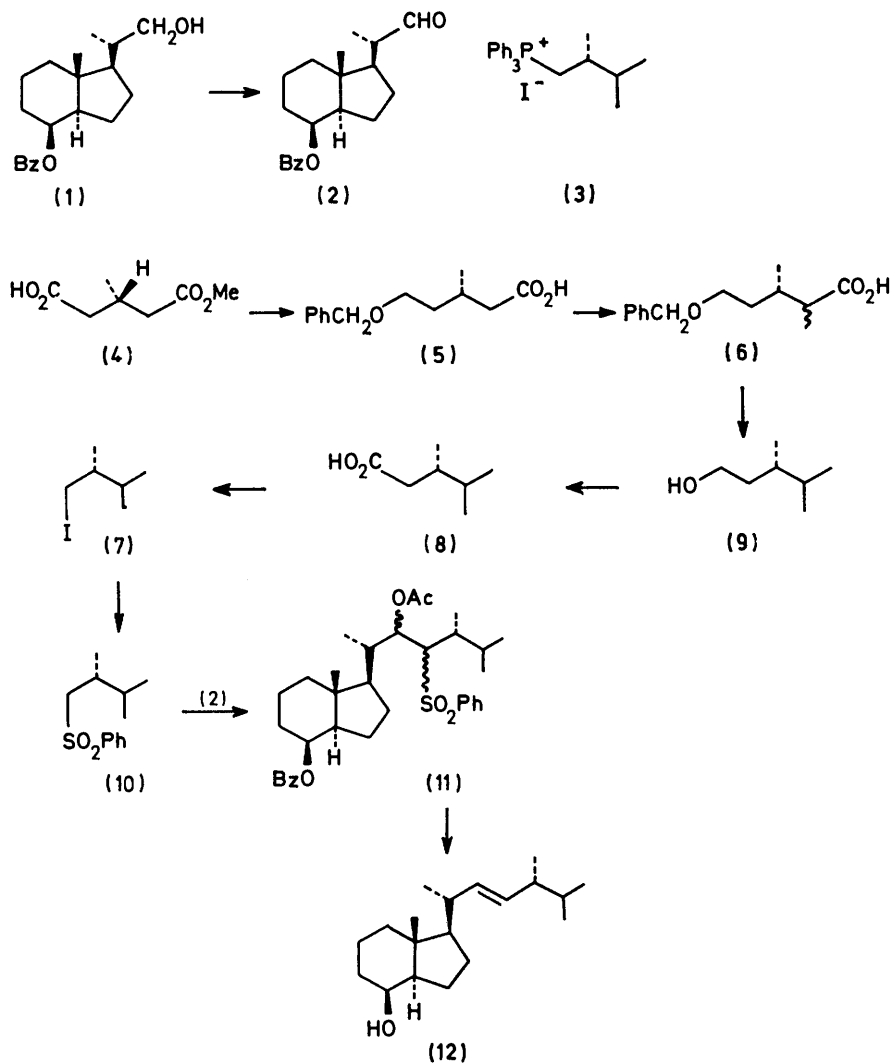
⁷ R. P. Linstead, J. C. Lunt, and B. C. L. Weedon, *J. Chem. Soc.*, 1950, 3333.

⁸ P. E. Pfeffer, L. S. Silbert, and J. M. Chirinko, *J. Org. Chem.*, 1972, 37, 451.

⁹ D. H. R. Barton, H. P. Faro, E. P. Serebryakov, and N. F. Woolsey *J. Chem. Soc.*, 1965, 2438.

The lithio-derivative of the sulphone (10) was allowed to react at low temperature with the aldehyde (2), and the cold mixture was treated with acetic anhydride to

(2,3-Dimethylbutyl)triphenylphosphonium Iodide *rac*-(3).—The iodide *rac*-(7) (212 mg) and triphenylphosphine (314 mg) were heated under reflux in dry toluene (5 cm³) for 24 h,



give the β -acetoxy-sulphone (11). Reduction¹⁰ with sodium amalgam in methanol-ethyl acetate (2:1) at -20°C gave an olefinic product which on hydrolysis furnished the alcohol (12). This was characterised as the known¹¹ crystalline 3,5-dinitrobenzoate; no *cis*-olefinic product was detected. The 3,5-dinitrobenzoate was obtained in 48% yield overall from the monobenzoate (1). These results illustrate how difficulties which sometimes attend the Wittig olefination method can be avoided by a synthesis based on sulphones.

EXPERIMENTAL

Optical rotations refer to solutions in chloroform, and n.m.r. data to solutions in deuteriochloroform. T.l.c. and p.l.c. were carried out with Kieselgel GF₂₅₄. Light petroleum means the fraction b.p. 60–80 $^\circ\text{C}$ unless otherwise specified.

¹⁰ M. Julia and J.-M. Paris, *Tetrahedron Letters*, 1973, 4833; ref. 5b.

after which the toluene was removed under reduced pressure. The residue was extracted with hot benzene (3 \times 10 cm³), and the residual oil (324 mg) was subjected to t.l.c. to give the crude phosphonium salt as an oil (200 mg). The iodide *rac*-(3) separated from aqueous ethanol as prisms (104 mg, 22%), m.p. 152–154 $^\circ$, ν_{max} (Nujol) 1115s, 1440s, and 1585w cm⁻¹, τ 1.95–2.35 (15 H, m, ArH), 6.35–6.65 (2 H, m, CH₂·P), 9.10 (3 H, d, *J* 7 Hz, CHMe), 9.15 (3 H, d, *J* 7 Hz, CHMe), and 9.20 (3 H, d, *J* 7 Hz, CHMe) (Found: C, 60.75; H, 5.95; P, 6.5; I, 26.4. C₂₄H₂₈IP requires C, 60.8; H, 5.95; P, 6.5; I, 26.75%).

(S)-3,4-Dimethylpentan-1-ol (9).—To the (–)-half ester (4) (15 g) in dry tetrahydrofuran (100 cm³) at -18°C under nitrogen, 1.8M-diborane in tetrahydrofuran (60 cm³) was added with stirring during 30 min. The mixture was stirred at 20 $^\circ\text{C}$ for 16 h, and then cooled to 0 $^\circ\text{C}$ during addition of water (100 cm³). The tetrahydrofuran was removed under reduced pressure, the solution was extracted

¹¹ H. H. Inhoffen, G. Quinkert, S. Schütz, G. Friedrich, and E. Tober, *Chem. Ber.*, 1958, **91**, 781; ref. 2.

with ether, and the extract was washed with dilute hydrochloric acid and with aqueous sodium hydrogen carbonate, and was then dried and evaporated. The oily hydroxy-ester (12.8 g, 86%) was homogeneous to g.l.c. and showed ν_{\max} (film) 1 740s and 3 415s cm^{-1} , τ 6.34 (3 H, s, CO_2Me), 6.35 (2 H, t, J 8 Hz, CH_2O), and 9.04 (3 H, d, J 7 Hz, CHMe).

The hydroxy-ester (15.4 g) in toluene (250 cm^3) containing benzyl chloride (100 g) and powdered potassium hydroxide (40 g) was heated under reflux with vigorous stirring and continuous removal of water for 20 h. Water was added to the cooled mixture, and the product was isolated with ether; it was an oil, ν_{\max} 1 740s cm^{-1} . It was kept at room temperature for 8 h with ethanol (200 cm^3) and potassium hydroxide (50 g) and then the solvent was removed, water (200 cm^3) was added, neutral products were removed with ether, and, after acidification with 6*N*-hydrochloric acid, the benzyloxy-acid (5) was isolated with ether. It formed an oil (22.63 g, 96%), ν_{\max} 700m, 735m, 1 100s, 1 710s, and 3 100 cm^{-1} , τ 2.70 (5 H, s, ArH), 5.52 (2 H, s, ArCH_2O), 6.48 (2 H, t, J 7 Hz, $\text{O}\cdot\text{CH}_2$), and 9.02 (3 H, d, J 7 Hz, CHMe) (Found: M^+ , 222.124 97. Calc. for $\text{C}_{13}\text{H}_{18}\text{O}_3$: M , 222.125 59).

A solution of lithium di-isopropylamide was prepared at -20°C under nitrogen from the amine (12.5 g) and ethereal 1.75*M*-*n*-butyl-lithium (72 cm^3) in tetrahydrofuran (50 cm^3). It was stirred and cooled to 0°C during the slow addition of the benzyloxy-acid (11.1 g) in tetrahydrofuran (40 cm^3) and during the addition of hexamethylphosphoramide (12.5 cm^3) in tetrahydrofuran (20 cm^3). After 30 min methyl iodide (10.5 g) was added rapidly at 0°C ; the mixture was then stirred for $1\frac{1}{2}$ h after which water (20 cm^3) was added. The organic solvents were then removed under reduced pressure, and water (50 cm^3) was added. The aqueous mixture was extracted with ether, and then acidified with hydrochloric acid, and the acidic product was isolated with ether. The acid (6) formed an oil (11.54 g, 98%), ν_{\max} (film) 700m, 735m, 1 100s, 1 710s, and 3 100s cm^{-1} , τ 2.70 (5 H, s, ArH), 5.52 (2 H, s, ArCH_2O), 6.48 (2 H, t, J 7 Hz, $\text{O}\cdot\text{CH}_2$), 8.92 (3 H, s, J 7 Hz, CHMe), and 9.10 (3 H, d, J 7 Hz, CHMe) (Found: M^+ , 236.140 5. Calc. for $\text{C}_{14}\text{H}_{20}\text{O}_3$: M , 236.141 2).

The acid (6) (12.55 g) was converted with ethanol in benzene containing toluene-*p*-sulphonic acid into its ethyl ester, an oil (12.4 g, 89%), ν_{\max} (film) 1 735s cm^{-1} . Reduction of the ester (13.3 g) with lithium aluminium hydride gave a hydroxy benzyl ether as an oil (10.4 g, 100%) homogeneous to t.l.c. (benzene), ν_{\max} (film) 700m, 735m, 1 100s, 1 455m, and 3 400s cm^{-1} , τ 2.70 (5 H, s, ArH), 5.52 (2 H, s, ArCH_2O), 6.51 (4 H, t, J 7 Hz, $2 \times \text{O}\cdot\text{CH}_2$), and 9.1—9.27 (6 H, m, $2 \times \text{CHMe}$). This hydroxy compound (10.7 g) was converted with toluene-*p*-sulphonyl chloride in pyridine into the toluene-*p*-sulphonate, an oil (17.0 g, 95%) which was homogeneous to t.l.c. (benzene), ν_{\max} (film) 665m, 965s, 1 100s, 1 180s, 1 355s, 1 455m, and 1 600w cm^{-1} .

The toluene-*p*-sulphonate (15 g) was reduced with lithium aluminium hydride (6.1 g) in ether (250 cm^3) at room temperature during 3 h, after which normal work-up gave the benzyl ether of the alcohol (9). After chromatography on silica gel (benzene—light petroleum, 1 : 4) it was obtained as an oil (7.4 g, 89%), ν_{\max} (film) 695m, 735m, 1 100s, 1 370w, and 1 460w cm^{-1} , τ 2.70 (5 H, s, ArH), 5.52 (2 H, s, ArCH_2O), 6.51 (2 H, t, J 7 Hz, $\text{O}\cdot\text{CH}_2$), and 9.05—9.25 (9 H, m, $3 \times \text{CHMe}$). Hydrogenolysis of a portion (6.5 g)

with 10% palladised charcoal in ethanol (100 cm^3) containing a little concentrated hydrochloric acid gave (S)-3,4-dimethylpentanol (3.5 g, 96%), as an oil, homogeneous to t.l.c. (5% ethyl acetate in benzene), ν_{\max} (film), 1 060s, 1 380m, 1 470m, and 3 325s cm^{-1} , τ 6.32 (2 H, t, J 7 Hz, $\text{O}\cdot\text{CH}_2$) and 9.02—9.23 (9 H, m, $3 \times \text{CHMe}$). The 3,5-dinitrobenzoate separated from light petroleum (b.p. $40\text{--}60^\circ\text{C}$) as needles, m.p. $54\text{--}55^\circ$, $[\alpha]_{\text{D}}^{22} -14.3^\circ$ (Found: C, 54.05; H, 5.7; N, 9.1. $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_6$ requires C, 54.2; H, 5.85; N, 9.0%).

(S)-3,4-Dimethylpentanoic Acid (8).—A solution of the alcohol (9) (1.16 g) in acetone (20 cm^3) was stirred during the addition of Jones reagent (2.67*M*; 8.2 cm^3) and for a further 10 min, after which propan-2-ol (1 cm^3) was added. The acetone was removed under reduced pressure, and the residue was distributed between water (20 cm^3) and ether (50 cm^3). Acidic material (8) was isolated from the ether phase in the usual way; it formed an oil (1.11 g, 85%), ν_{\max} (film) 1 295m, 1 710s, and 3 100 cm^{-1} , τ 8.98—9.22 (9 H, m, $3 \times \text{CHMe}$). The *p*-bromophenacyl derivative of (S)-3,4-dimethylpentanoic acid separated from light petroleum (at -30°C) as needles, m.p. $42\text{--}43^\circ$, $[\alpha]_{\text{D}}^{27} -4.1^\circ$ (Found: C, 54.85; H, 5.8; Br, 24.2. $\text{C}_{15}\text{H}_{19}\text{Br}_3\text{O}$ requires C, 55.05; H, 5.85; Br, 24.4%).

(S)-2,3-Dimethylbutyl Phenyl Sulphone (10).—The acid (8) (1.3 g) was heated under reflux in dry carbon tetrachloride (148 cm^3) containing lead tetra-acetate (5.57 g) and the solution was irradiated with two 100 W tungsten filament lamps while iodine (2.23 g) was added in small portions at intervals; decolourisation was allowed to take place before each further addition. Heating was continued for a further $\frac{1}{2}$ h, and the solution was cooled, filtered through Celite, washed with aqueous sodium thiosulphate, and then dried and freed from most of the carbon tetrachloride by distillation through a packed column.

In one experiment, a sample of the iodide (7) was obtained by rapid distillation; it had b.p. $156\text{--}158^\circ$ at 750 mmHg, ν_{\max} (film) 1 190s, 1 270w, 1 380m, and 1 460s cm^{-1} , τ 6.62—6.98 (2 H, m, CH_2I), and 8.95—9.22 (9 H, m, $3 \times \text{CHMe}$) (Found: M^+ , 212.005 98. Calc. for $\text{C}_6\text{H}_{13}\text{I}$: M , 212.006 38).

The concentrated solution of the iodide (7) in carbon tetrachloride, prepared as described above, was stirred at room temperature with a freshly prepared solution of sodium benzenethiolate [from ethanol (30 cm^3), sodium (0.26 g), and benzenethiol (1.2 g)] for 1 h; the solution was then cooled, diluted with water (120 cm^3), and extracted with light petroleum ($2 \times 30 \text{ cm}^3$). Evaporation, chromatography on silica gel (light petroleum), and bulb-to-bulb distillation at 0.3 mmHg (bath temperature 100°C) gave (S)-2,3-dimethylbutyl phenyl sulphide as an oil [1.61 g, 83% from (8)], $[\alpha]_{\text{D}}^{25} -39.4^\circ$, τ 2.5—2.9 (5 H, m, ArH), 6.95 (1 H, dd, J 6 and 13 Hz, CH_2S), 7.29 (1 H, dd, J 8 and 13 Hz, CH_2S), and 8.2—8.9 (9 H, $3 \times \text{CHMe}$) (Found: M^+ , 194.113 35. $\text{C}_{12}\text{H}_{18}\text{S}$ requires M , 194.112 92).

To a stirred solution of the above sulphide (1.10 g) in methylene chloride (25 cm^3), *m*-chloroperbenzoic acid (85%; 2.3 g) was added in portions at room temperature. After a further 1 h the solution was washed with aqueous ammonia and then with water, and was then dried and evaporated. Bulb-to-bulb distillation at 0.3 mmHg (bath temperature 130°C) gave (S)-2,3-dimethylbutyl phenyl sulphone (10) (1.26 g, 93%) as an oil, $[\alpha]_{\text{D}}^{40} -12^\circ$, ν_{\max} (CCl_4) 1 250s, 1 310s, and 1 325s cm^{-1} , τ 2.0—2.2 (2 H, m, ArH), 2.3—2.6 (3 H, m, ArH), 6.90 (1 H, dd, J 4 and 14 Hz, $\text{CH}_2\cdot\text{SO}_2$), 7.27 (1 H, dd, J 8 and 14 Hz, $\text{CH}_2\cdot\text{SO}_2$), and

9.0, 9.2, and 9.25 (each 3 H, d, J 7 Hz, $CHMe$) (Found: M^+ , 226.103 29. $C_{12}H_{18}O_2S$ requires M , 226.102 74).

Synthesis of the Bicyclic Alcohol (12).—To a stirred solution of the sulphone (10) (0.226 g) in tetrahydrofuran (5 cm³) at -78°C under nitrogen, 1.3M-*n*-butyl-lithium in hexane (0.8 cm³) was added. After 10 min at -78°C the aldehyde (2) [freshly prepared from the monobenzoate (1) (316 mg) by oxidation with pyridinium chlorochromate¹²], dissolved in tetrahydrofuran, was added dropwise. Stirring was continued at the same temperature for 30 min, and then acetic anhydride (200 mg) was added. After 4 h the mixture was allowed to attain room temperature, and stirring was continued for a further 1 h; saturated aqueous ammonium chloride (5 cm³) was then added, the mixture was extracted with ether (3 \times 15 cm³), and the extract was washed with water, dried, and evaporated to give the oily acetoxy-sulphone (11) (550 mg), ν_{max} (CCl_4) 1 150s, 1 260s, 1 320s, 1 330s, and 1 750s cm^{-1} , τ 4.35 (1 H, m, $CH\cdot OAc$), 4.6br (1 H, $CH\cdot OBz$) 6.4 (1 H, m, $CH\cdot SO_2$), and 7.95 (3 H, s, OAc). It was used immediately in the next step.

A solution of the acetoxy-sulphone in methanol (4 cm³) and ethyl acetate (2 cm³) was stirred at -20°C with 5.65%

sodium amalgam (1.0 g) for 8 h; the mixture was then poured into water (25 cm³) and the product was isolated with ether and chromatographed on a column of silica gel (30 g) and benzene. Elution with 4% ethyl acetate-benzene gave the amorphous benzoate (220 mg) of the alcohol (12); it was homogeneous to t.l.c. and had ν_{max} (CCl_4) 975s, 1 120s, 1 270s, and 1 730s cm^{-1} , τ 1.9–2.1 (2 H, m, ArH), 2.6–2.8 (3 H, m, ArH), 4.65br (1 H, $W_{\frac{1}{2}}$ 6 Hz, $CH\cdot OBz$), and 4.75–4.9 (2 H, m, $=CH-$). It was hydrolysed with hot ethanolic aqueous potassium hydroxide, and the resulting alcohol (12), isolated in the usual way, was converted into the 3,5-dinitrobenzoate, which separated from light petroleum as plates (229 mg, 48% overall), m.p. 135–139°. Twice recrystallised material (191 mg) had m.p. 139–141°, $[\alpha]_D^{30} +68.7^\circ$, and i.r. and ^1H n.m.r. spectra identical with those of authentic material, m.p. 140–141°, $[\alpha]_D^{25} +69.2^\circ$.

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¹² E. J. Corey and J. W. Suggs, *Tetrahedron Letters*, 1975, 2647