An Approach to the Synthesis of (3*R*)- and (3*S*)-2,3-Epoxysqualene

By **Mohamed A. Abdallah** *† and **Jayant N. Shah,** Department of Chemistry, Imperial College, London SW7

In an approach to the synthesis of (3*R*)- and (3*S*)-2,3-epoxysqualene, 4-[(4*R*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]butan-2-one and triphenyl-(4,9,13,17-tetramethyloctadeca-4,8,12,16-tetraenyl)phosphonium iodide have been prepared.

THE intermediacy of 2,3-epoxysqualene in the biogenesis of animal and plant triterpenes carrying a C-3 oxygenated function has been well established.[1-16] Although it had been assumed that 3β-hydroxy-triterpenoids may be produced by cyclisation of (3*S*)-2,3-epoxysqualene,[17,18] little experimental evidence was available to confirm this. However, in 1968, Barton and his co-workers[13] recovered optically active 2,3-epoxysqualene from repeated feedings of yeast with the racemic epoxide. This led us to undertake the synthesis of (3*R*)- and (3*S*)-2,3-epoxysqualene. More recently Suga and his

---

† *Present address:* Laboratoire de Chimie Organique Biologique, Institut de Chimie, Université Louis Pasteur, 67000-Strasbourg, France.

[1] H. H. Rees, L. J. Goad, and T. W. Goodwin, *Tetrahedron Letters*, 1968, 723.

[2] H. H. Rees, L. J. Goad, and T. W. Goodwin, *Biochem. J.*, 1968, **107**, 417.

[3] U. Eppenberger, L. Hirth, and G. Ourisson, *European J. Biochem.*, 1969, **8**, 180.

[4] R. Heintz and P. Benveniste, *Phytochemistry*, 1970, **9**, 1499.

[5] G. Ponsinet and G. Ourisson, *Phytochemistry*, 1968, **7**, 757.

[6] W. O. Godtfredsen, H. Lorck, E. E. van Tamelen, J. D. Willett, and R. B. Clayton, *J. Amer. Chem. Soc.*, 1968, **90**, 208.

[7] E. J. Corey and P. R. Ortiz de Montellano, *J. Amer. Chem.*, *Soc.*, 1967, **89**, 3362.

[8] D. H. R. Barton, A. F. Gosden, G. Mellows, and D. A. Widdowson, *Chem. Comm.*, 1968, 1067.

[9] E. J. Corey, W. E. Russey, and P. R. Ortiz de Montellano, *J. Amer. Chem. Soc.*, 1966, **88**, 4750.

[10] E. J. Corey, K. Lin, and H. Yamamoto, *J. Amer. Chem. Soc.*, 1969, **91**, 2132.

[11] (*a*) E. E. van Tamelen, *Accounts Chem. Res.*, 1968, **1**, 111; (*b*) R. B. Woodward and K. Bloch, *J. Amer. Chem. Soc.*, 1953, **75**, 2023; (*c*) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, 1955, **38**, 1890.

[12] T. T. Tchen and K. Bloch, (*a*) *J. Amer. Chem. Soc.*, 1956, **78**, 1516; (*b*) *J. Biol. Chem.*, 1957, **226**, 921; (*c*) *ibid.*, p. 930.

[13] D. H. R. Barton, G. Mellows, and D. A. Widdowson, personal communication.

[14] E. J. Corey, P. R. Ortiz de Montellano, and H. Yamamoto, *J. Amer. Chem. Soc.*, 1968, **90**, 6254.

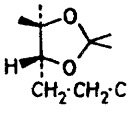
[15] J. W. Cornforth, *Angew. Chem. Internat. Edn.*, 1968, **7**, 903.

[16] E. E. van Tamelen and J. H. Freed, *J. Amer. Chem. Soc.*, 1970, **92**, 7206.

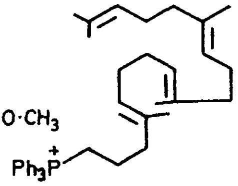
[17] G. P. Moss and S. A. Nicolaidis, *Chem. Comm.*, 1969, 1072.

[18] G. P. Cotterell, T. G. Halsall, and M. J. Wrigglesworth, *J. Chem. Soc.* (*C*), 1970, 739.

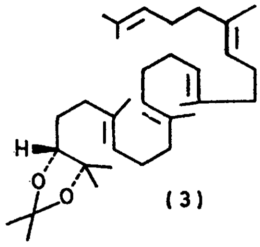
co-workers[19] have reported a similar observation and have demonstrated that a sample of 2,3-epoxysqualene recovered after feeding to minced hog liver was partially resolved, containing an excess of the *R*-isomer.



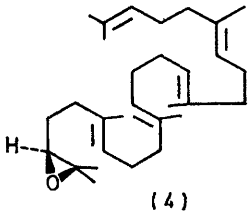
(1)



(2)



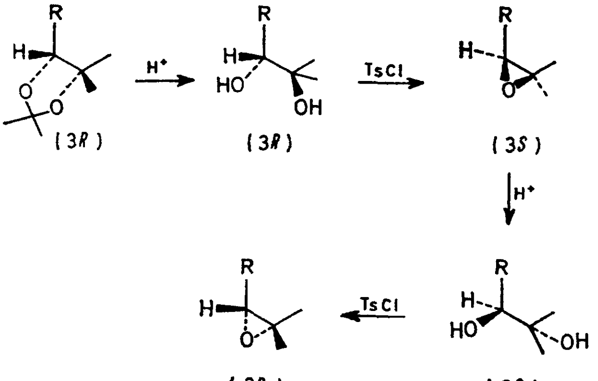
(3)



(4)

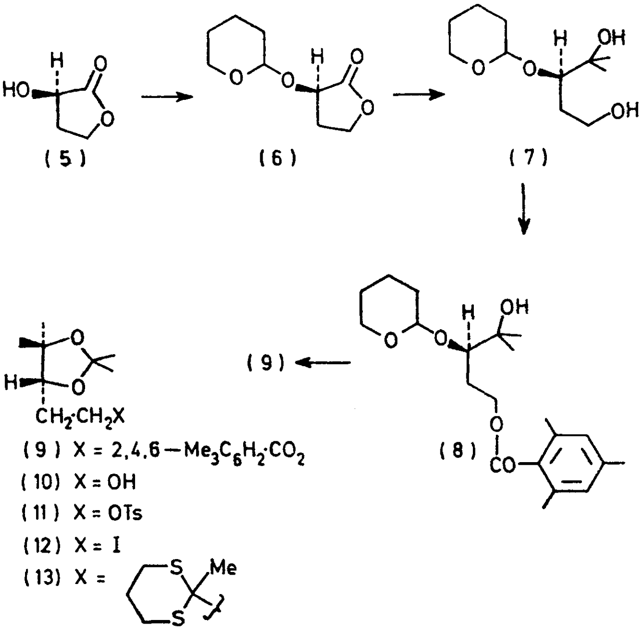
Our approach to the synthesis of (3*S*)-2,3-epoxysqualene involved the preparation of 4-[(4*R*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]butan-2-one (1) (Scheme 2) and its condensation, by a Wittig or equivalent reaction, with the C_{22} unit triphenyl-(4,9,13,17-tetramethyloctadeca-4,8,12,16-tetraenyl)phosphonium iodide (2) (Scheme 4). Mild hydrolysis of the condensation product (3) followed by treatment with tosyl chloride would be expected to yield (3*S*)-2,3-epoxysqualene[13] (4) (Scheme 1).

Racemic 2-hydroxy-γ-butyrolactone[20] was resolved by using brucine[21] to yield the optically pure (2*R*)-isomer (5). The hydroxy-group was then protected by formation of the tetrahydropyranyl ether (6), $[\alpha]_D^{25}$ +15·0°, which reacted with methylmagnesium iodide (2 mol. equiv.) to give (3*R*)-4-methyl-3-(tetrahydropyran-2-yloxy)pentane-1,4-diol (7), $[\alpha]_D^{25}$ +12·6°.



SCHEME 1

It was then necessary to protect the hydroxy-substituents at C-3 and C-4 to enable further reaction to be carried out without any possibility of racemisation at C-3. Treatment of the diol (7) with 2,2-dimethoxypropane yielded mainly a dimer (14), with no free hydroxy-function. Hence it was necessary first to protect the primary hydroxy-group of (7) by esterification. Acetylation with acetyl chloride or acetic anhydride resulted in a transfer reaction yielding a mixture of monoacetates, diacetate, and unchanged material. However esterification with mesitoyl chloride in the presence of sodium hydride in benzene afforded the primary monoester (8) (80%), $[\alpha]_D^{25}$ +60·3°. Treatment of the monomesitoate (8) with 2,2-dimethoxypropane without further purification afforded the acetonide (9), purified by distillation $[\alpha]_D^{25}$ +18·6°. The protecting ester group in (9) was then removed with lithium aluminum hydride, affording 2-[(4*R*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]ethanol (10) ($[\alpha]_D^{25}$ +16·4°) and 2,4,6-trimethylbenzyl alcohol. The mixture was tosylated without separation of the alcohols, with the calculated amount of toluene-*p*-sulphonyl chloride in pyridine. Aqueous work-up separated the water-soluble 2,4,6-trimethylbenzylpyridinium salt from the required tosylate (11) ($[\alpha]_D^{25}$ +17·0°), which was transformed readily into the iodide (12) by displacement with sodium iodide in acetone.



SCHEME 2

In order to extend the carbon chain and to introduce the ketone function, the iodide (12) ($[\alpha]_D^{25}$ +30·2°) was treated with 2-lithio-2-methyl-1,3-dithian in tetrahydrofuran[22,23] to yield the dithian (13). In this reaction any

---

[19] T. Shishibori, T. Fukui, and T. Suga, *Chem. Letters*, **1973**, 1137.

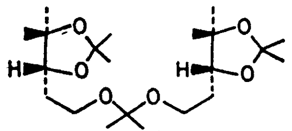
[20] A. C. J. Offermann, B.P. 688,253 (*Chem. Abs.*, 1954, **48**, 3996i).

[21] J. W. E. Glattfeld and F. V. Sander, *J. Amer. Chem. Soc.*, 1921, **43**, 2675.

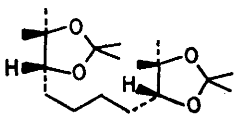
[22] D. Seebach, *Synthesis*, 1969, **1**, 17.

[23] E. J. Corey and D. Seebach, *Angew. Chem. Internat. Edn.*, 1965, **4**, 1075.

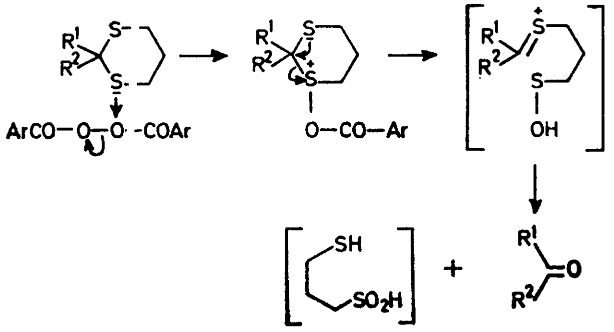
excess of base (n-butyl-lithium) was avoided, as it reacted faster with the iodide (12) than did 2-lithio-2-methyl-1,3-dithian. The lithio-derivative of (12) obtained by this side reaction consumed further iodide to yield a dimer (15). Therefore the percentage of 2-lithio-2-methyl-1,3-dithian in the solution was first estimated by ^1H n.m.r. analysis (D_2O quenching), and the equivalent amount of iodide (12) was then added to furnish dithian (13) in 90% yield $[\alpha]_D^{25}$ +8·6°.



(14)



(15)



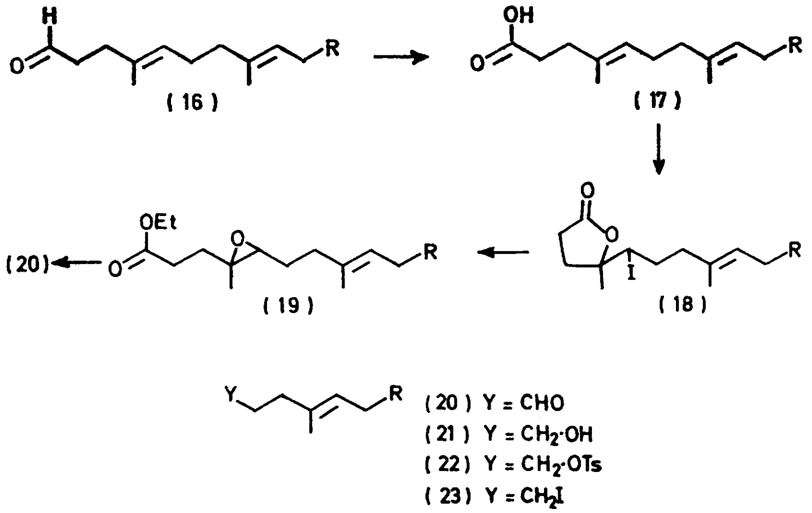
Scheme 3

Cleavage of the dithian (13) to give the ketone (1) was performed by two different procedures. The first[22,23] involved treatment with a mixture of mercury(II) chloride and oxide in aqueous methanol. However, because of initial problems with this method we developed a second, new oxidative cleavage of the dithian with an aroyl peroxide. Two molar equivalents of peroxide are required to complete the cleavage, the sulphenic acid intermediate being oxidised to a sulphinic acid or its oxidative equivalent (Scheme 3).

The physical data (optical rotation excepted) of the *R*-ketone (1) ($[\alpha]_D^{25}$ +10·4°) [overall yield 30% from (6)] were identical with those reported for the racemic material.[24]

The phosphonium salt (2) was first prepared by a controlled degradation of squalene (Scheme 4). The trinorsqualene aldehyde[25,26] (16) (prepared from all-*trans*-squalene) was oxidised by an adaptation of the two-phase oxidation procedure described by H. C. Brown[27] to yield trinorsqualene acid (17). However, this oxidation never proceeded to completion, and hydroxylated by-products were produced. Therefore the reaction was quenched after a few hours, when the conversion into acid was still low. An attempt to oxidise the aldehyde (16) with silver oxide in aqueous tetrahydrofuran was unsatisfactory.[28,29]

The iodo-lactone (18) was then prepared by treatment of the acid (17) with iodine and potassium carbonate in benzene. The product was unstable, and was characterised by spectral data. It was immediately treated with sodium ethoxide in ethanol to afford the pure stable epoxy-ester (19) in 80% yield. Finally, oxidative cleavage of the epoxy-ester (19) with periodic acid in ether gave the octanorsqualene aldehyde (20).[10]



Scheme 4 R = farnesyl

Because of the low overall yield of (20) from squalene, an alternative route[30] was also used. All-*trans*-squalene[31] was epoxidised with peracetic acid in di-

---

[24] G. W. K. Cavill and P. J. Williams, *Austral. J. Chem.*, 1969, **22**, 1737.

[25] R. G. Nadeau and R. P. Hanzlik, *Methods Enzymol.*, 1969, **15**, 346.

[26] E. E. van Tamelen, K. B. Sharpless, J. D. Willett, R. B. Clayton, and A. L. Burlingame, *J. Amer. Chem. Soc.*, 1967, **89**, 3920.

[27] H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, 1961, **83**, 2952.

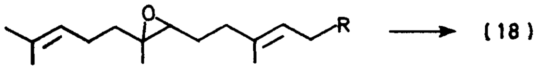
[28] E. J. Corey and K. Achiwa, *Tetrahedron Letters*, 1969, 1837.

[29] E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Amer. Chem. Soc.*, 1968, **90**, 5616.

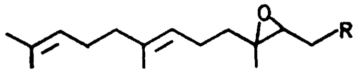
[30] K. B. Sharpless, *Chem. Comm.*, 1970, 1450.

[31] N. Nicolaidis and F. Laves, *J. Amer. Chem. Soc.*, 1954, **76**, 2596.

chloromethane to yield a mixture of 2,3-epoxysqualene, *trans*-6,7-epoxysqualene (24), and *trans*-10,11-epoxysqualene (25). Controlled acidic hydrolysis with 7% perchloric acid in t-butyl alcohol selectively hydrolysed the terminal epoxy-group. Purification of the resulting mixture gave the epoxides (24) and (25), which were hydrolysed to the corresponding *erythro*-diols with 30% perchloric acid in t-butyl alcohol, and these were separated by chromatography on a silver nitrate–silica gel column.



(24) (R = farnesyl)



(25) (R = farnesyl)

Oxidative cleavage of *erythro*-6,7-dihydro-6,7-dihydroxysqualene with sodium periodate gave the aldehyde (20) in quantitative yield (overall yield from squalene 10%). Reduction of this with lithium aluminum hydride followed by treatment of the resulting alcohol (21) with toluene-*p*-sulphonyl chloride in pyridine afforded the tosylate (22) which yielded in turn the iodide (23) by displacement with sodium iodide in acetone. Treatment of the iodide (23) with triphenylphosphine in refluxing toluene afforded the phosphonium iodide (2).

Preliminary studies of the Wittig reaction showed that the product consisted of double-bond isomers [$\nu_{max.}$ 890 cm^{-1} (CH_2=)]. Before this problem was solved, the simple resolution system of Boar and Damps[32] was reported, and our approach was therefore discontinued.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Unless otherwise stated i.r. spectra were taken for liquid films or solutions in chloroform; optical rotations were measured with chloroform as solvent; and n.m.r. spectra were measured for solutions in deuteriochloroform with tetramethylsilane as internal standard.

Wherever possible, reactions were followed by t.l.c. on 0·1 mm plates of Merck silica gel GF 254. Preparative layer chromatography (p.l.c.) was carried out on 0·01 × 20 × 20, 0·05 × 20 × 60, or 0·1 × 20 × 60 cm^3 plates of the same material.

Light petroleum, unless otherwise stated refers to the fraction b.p. 60—80°. Solvent mixtures are described in volume ratios. Solvents were dried, where necessary, by standard techniques. Organic solvent extracts were usually dried with anhydrous sodium sulphate.

(+)-(2R)-2-(*Tetrahydropyran*-2-*yloxy*)-γ-*butyrolactone* (6).—To a mixture of (+)-(2*R*)-2-hydroxy-γ-butyrolactone[21] (4·49 g, 0·044 mol) and dry 2,3-dihydropyran (4·71 g, 0·056 mol) at 0 °C was added, under nitrogen and with stirring, toluene-*p*-sulphonic acid (15 mg). After 1 h at 0 °C, the reaction was quenched with 5% sodium hydrogen carbonate solution (20 ml) and the mixture extracted with diethyl ether (3 × 30 ml). The combined extracts were washed with water (3 × 15 ml), dried ($CaCl_2$), and evaporated under reduced pressure to yield the *tetrahydropyranyl ether* (8·2 g, 100%) as a liquid, which was stored at 4 °C under nitrogen, $[\alpha]_D^{25}$ +15·0° (*c* 1·0); $\nu_{max.}$ 1785 cm^{-1}; τ 8·3 (6H, s), 7·2—8·0 (2H, m), 5·7—6·5 (2H, m), 5·0—5·7 (3H, m), and 4·87 (1H, s); *m*/*e* 185 (M^+ − 1) (Found: C, 58·1; H, 7·5. $C_9H_{14}O_4$ requires C, 58·05; H, 7·6%).

(+)-(3R)-4-*Methyl*-3-(*tetrahydropyran*-2-*yloxy*)*pentane*-1,4-*diol* (7).—The lactone (6) (3·72 g, 0·02 mol) was dissolved in dry tetrahydrofuran (25 ml) and added, under nitrogen, during 15 min to a solution of methylmagnesium iodide [from magnesium turnings (1·5 g) and methyl iodide (14·52 g)] in dry ether (25 ml). The mixture was then stirred under reflux for 1·5 h and cooled, and a saturated solution of ammonium chloride was added dropwise. After 0·5 h, the tetrahydrofuran was evaporated off and the aqueous phase was continuously extracted with ether for 12 h to give an oil (4·2 g). The product was purified by column chromatography on grade IV alumina (180 g). The column was first eluted with benzene (50 ml) and then with anhydrous ether. The glycol fractions were combined and evaporated to yield the *diol* (7) (3·8 g, 88%), $[\alpha]_D^{25}$ +12·6° (*c* 1·0); $\nu_{max.}$ 3425 cm^{-1}; τ 8·8 (6H, s), 7·9—8·65 (8H, m), 6·85 (2H, s, D_2O exchanged), 5·85—6·65 (5H, m), and 5·36br (1H, s); *m*/*e* 159 (M^+ − CH_3 − CH_2=CHOH) (Found: C, 60·55; H, 10·0. $C_{11}H_{22}O_4$ requires C, 60·5; H, 10·15%).

(+)-(3R)-4-*Hydroxy*-4-*methyl*-3-(*tetrahydropyran*-3-*yloxy*)-*pentyl* 2,4,6-*Trimethylbenzoate* (8).—To a stirred suspension of sodium hydride [50% in oil; 1·5 g (washed free of oil)] in dry benzene (80 ml) at room temperature was added dropwise under nitrogen a solution of the glycol (7) (2·18 g, 10 mmol) in benzene (15 ml). After 1·5 h, freshly distilled 2,4,6-trimethylbenzoyl chloride (1·82 g, 10 mmol) in benzene (10 ml) was added. After 6 h at room temperature, the mixture was diluted with water and extracted with benzene. Removal of the solvent left the *monomesitoate* (8) (2·9 g, 80%) as an oil, $[\alpha]_D^{25}$ +60·3° (*c* 2·0); $\nu_{max.}$ 3470, 1720, 1610, and 1270 cm^{-1}; τ 8·8 (6H, s), 7·9—8·65 (8H, m), 7·7 (9H, s), 6·0—6·7 (4H, m), 5·3—5·7 (3H, m), and 3·1 (2H, s); *m*/*e* 364 (M^+) (Found: C, 69·35; H, 8·8. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·85%).

(+)-2-[(4R)-2,2,5,5-*Tetramethyl*-1,3-*dioxolan*-4-*yl*]*ethyl* 2,4,6-*Trimethylbenzoate* (9).—To the monoester (8) (2·73 g, 7·5 mmol) in dry acetone (30 ml) at room temperature were added 2,2-dimethoxypropane (8 ml) and toluene-*p*-sulphonic acid (10 mg), and the solution was left in the dark for 18 h at room temperature. Aqueous sodium hydrogen carbonate (10%; 15 ml) was added, the solvent was removed under reduced pressure, and the mixture was extracted with diethyl ether (3 × 100 ml). The combined extracts were washed with water (3 × 20 ml), dried, and evaporated. The remaining oil was distilled (bath temperature 160—180° at 0·1 mmHg) to yield the *acetonide* (9) (1·9 g, 80%) as white crystals, m.p. 38—39°, $[\alpha]_D^{25}$ +18·6° (*c* 1·0); $\nu_{max.}$ 1720, 1610, 1385, and 1270 cm^{-1}; τ 8·9 (3H, s), 8·75 (3H, s), 8·67 (3H, s), 8·59 (3H, s), 8·08 (2H, m), 7·65 (9H, s), 6·70 (1H, t, *J* 6·5 Hz), 5·5 (2H, t, *J* 6·5 Hz), and 3·05 (2H, s); *m*/*e* 320 (M^+) (Found: C, 71·35; H, 8·7. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%).

(+)-2-[(4R)-2,2,5,5-*Tetramethyl*-1,3-*dioxolan*-4-*yl*]*ethanol*

---

[32] R. B. Boar and K. Damps, *Tetrahedron Letters*, 1974, 3731.

(10).—To the dioxolan (9) (1·6 g, 5 mmol) in dry ether (30 ml) was added lithium aluminum hydride (190 mg) in small portions during 15 min. The mixture was stirred for 2 h at room temperature, and water (1·1 ml) was added. The inorganic residue was filtered off and the solvent removed under reduced pressure to yield equimolecular amounts of the *alcohol* (10) and 2,4,6-trimethylbenzyl alcohol (1·5 g). The dioxolan (10) had R_F 0·30 (ethyl acetate–light petroleum, 1 : 1), $[\alpha]_D^{25}$ +16·4° (*c* 2·0 in EtOH); $\nu_{max.}$ 3430 and 1380 cm^{-1}; τ 8·9 (3H, s), 8·75 (3H, s), 8·67 (3H, s), 8·59 (3H, s), 8·2—8·45 (2H, m), 7·56br (1H, s, D_2O exchanged), and 6·0—6·28 (3H, m); *m/e* 159 ($M^+ - CH_3$) (Found: C, 62·25; H, 10·2. $C_9H_{18}O_3$ requires C, 62·05; H, 10·4%).

(+)-2-[(4R)-2,2,5,5-*Tetramethyl*-1,3-*dioxolan*-4-*yl*]*ethyl Toluene*-p-*sulphonate* (11).—The foregoing mixture of alcohols (1·08 g) was dissolved in dry pyridine (2·4 ml) and toluene-*p*-sulphonyl chloride (1·6 g) was added in small portions during 15 min while the solution was stirred at −20 °C. The mixture was stirred for 48 h at 0 °C. Water (5 ml) was added, and the tosylate extracted with diethyl ether (3 × 25 ml). The combined extracts were washed with water, dried, and evaporated to yield crystalline *tosylate* (11) [1·0 g, 85% with respect to the starting dioxolan (9)]; m.p. 67° (needles from light petroleum); $[\alpha]_D^{25}$ +17·0° (*c* 1·0); $\nu_{max.}$ 1170 and 1370 cm^{-1}; τ 9·0 (3H, s), 8·82 (3H, s), 8·78 (3H, s), 8·70 (3H, s), 8·30 (2H, q, *J* 6 Hz), 7·6 (3H, s), 6·3 (1H, t, *J* 6 Hz), 5·8 (2H, t, *J* 6 Hz), 2·7 (2H, d, *J* 6 Hz), and 2·25 (2H, d, *J* 6 Hz); *m/e* 313 ($M^+ - CH_3$) (Found; C, 58·35; H, 7·45; S, 9·9. $C_{16}H_{24}O_5S$ requires C, 58·55; H, 7·35; S, 9·75%).

(+)-2-[(4R)-2,2,5,5-*Tetramethyl*-1,3-*dioxolan*-4-*yl*]*ethyl Iodide* (12).—The tosylate (11) (1·0 g, 3·04 mmol) was dissolved in a saturated solution of sodium iodide in acetone (60 ml) and stirred at room temperature in the dark. After 24 h, aqueous 5% sodium thiosulphate was added, the solvent was removed under reduced pressure, and the aqueous phase was extracted with light petroleum. The extract was washed with aqueous 5% sodium thiosulphate and water, then dried and evaporated. The residual oil was distilled to yield the *iodide* (12) (800 mg, 92%), b.p. 50° at 13 mmHg; $[\alpha]_D^{25}$ +30·2° (*c* 1·0); $\nu_{max.}$ 1375 and 1380 cm^{-1}; τ 8·9 (3H, s), 8·70 (3H, s), 8·62 (3H, s), 8·55 (3H, s), 8·30—7·65 (2H, m), 6·80—6·30 (2H, m), and 6·10 (1H, dd, *J* 5 and 10 Hz); *m/e* 269 ($M^+ - CH_3$) (Found: C, 38·3; H, 5·95. $C_9H_{17}IO_2$ requires C, 38·05; H, 6·05%).

(+)-(4R)-2,2,5,5-*Tetramethyl*-4-[2-(2-*methyl*-1,3-*dithian*-2-*yl*)*ethyl*]-1,3-*dioxolan* (13).—To 2-methyl-1,3-dithian (400 mg, 2·99 mmol) in dry tetrahydrofuran (2 ml), under argon, was added n-butyl-lithium (2·73 mmol) in hexane. After 3 h at −20 °C, the iodide (12) (710 mg, 2·5 mmol) in dry tetrahydrofuran (2 ml) was added, and stirring was continued for 18 h at 0 °C. The reaction was quenched with water and the mixture extracted exhaustively with light petroleum. The extract was washed with water, dried (K_2CO_3), and evaporated and the residual oil was distilled to yield the *dithian* (13) (650 mg, 90%), b.p. 115° at 0·5 mmHg; $[\alpha]_D^{25}$ +8·6° (*c* 1·0); $\nu_{max.}$ 1380 cm^{-1}; τ 8·88 (3H, s), 8·72 (3H, s), 8·62 (3H, s), 8·55 (3H, s), 8·35 (3H, s), 8·3—7·5 (6H, m), 7·2—6·9 (4H, m), and 6·25 (1H, t, *J* 6 Hz); *m/e* 290 (M^+) (Found: C, 57·75; H, 9·0; S, 22·0. $C_{14}H_{26}O_2S_2$ requires C, 57·9; H, 9·05; S, 22·05%).

(+)-4-[(4R)-2,2,5,5-*Tetramethyl*-1,3-*dioxolan*-4-*yl*]*butan*-2-*one* (1).—(*a*) A mixture of the dithian (13) (580 mg, 2 mmol), mercury(II) chloride (1·2 g), and mercury(II) oxide (650 mg) in aqueous 90% ethanol (24 ml) was refluxed for 2 h. The solution was filtered through Celite and the inorganic residue was thoroughly washed with light petroleum. The combined organic extract was washed with water, 5% ammonium acetate solution, and water, then dried and evaporated. The residual oil was distilled to yield the *ketone* (1) (320 mg, 80%), b.p. (bath temperature) 116—117° at 20 mmHg, $[\alpha]_D^{25}$ +10·4° (*c* 1·0); $\nu_{max.}$ 1715, 1373, and 1380 cm^{-1}; τ 8·88 (3H, s), 8·72 (3H, s), 8·65 (3H, s), 8·58 (3H, s), 8·2 (2H, t, *J* 7 Hz), 7·8 (3H, s), 7·15—7·55 (2H, m), and 6·35 (1H, dd, *J* 7·5 and 5·5 Hz); *m/e* 185 ($M^+ - CH_3$) (Found: C, 66·05; H, 10·15. $C_{10}H_{17}O_3$ requires C, 65·95; H, 10·05%).

(*b*) The dithian (13) (84·6 mg, 0·292 mmol) was dissolved in aqueous 10% acetone (0·5 ml) and treated with freshly recrystallised dibenzoyl peroxide (143 mg, 0·591 mmol). The solution was stirred for 16 h at room temperature. Solid sodium hydrogen carbonate (200 mg) was added, the mixture was stirred for 2 h, the solvent was removed under reduced pressure, and the residue was exhaustively extracted with light petroleum. The extract was concentrated and applied to a column of alumina (grade V) (8 g) made up in the same solvent. The column was eluted with increasing amounts of benzene in light petroleum (10—50%) yielding the pure ketone (1) (34 mg, 60%) having the same characteristics as above.

4,8,13,17,21-*Pentamethyldocosa*-4,8,12,16,20-*pentaenoic Acid* (17).—To the trinorsqualene aldehyde [25,26] (16) (600 mg, 1·56 mmol) dissolved in ether was added an equimolecular amount of Brown's reagent.[27] The two-phase mixture was vigorously stirred at room temperature under nitrogen. After 8—10 h, the ethereal layer was separated and the aqueous solution was extracted with diethyl ether. The combined extracts were washed with water, dried, and evaporated. The crude oil was shaken with aqueous 4N-sodium hydroxide and continuously extracted with light petroleum for 18 h. The extract, containing non-acidic impurities, was discarded. The aqueous alkaline phase was acidified and re-extracted with ether. The extract was evaporated and the crude oil was chromatographed on a silica gel column (50 g SiO_2 containing 20% water) made up in light petroleum. The column was eluted with 5—20% ethyl acetate in light petroleum, and the acid thus obtained was re-purified on silica gel plates eluted with 20% benzene in ethyl acetate. The yield of pure *acid* (17) was only 20%; R_F 0·5 (acetic acid–methanol–benzene, 1 : 2 : 47); $\nu_{max.}$ 1710 cm^{-1}; τ 8·42 (18H, s), 8·0br (16H, s), 7·55—7·80 (4H, m), 4·92br (5H, s), and 1·1 (1H, s, D_2O exchanged); *m/e* 400 (M^+) (Found: C, 80·8; H, 11·35. $C_{27}H_{44}O_2$ requires C, 80·95; H, 11·05%).

4-*Methyl*-4-(1-*iodo*-4,9,13,17-*tetramethyloctadeca*-4,8,12,16-*tetraenyl*)-γ-*butyrolactone* (18).—A mixture of the trinorsqualene acid (17) (120 mg, 0·3 mmol) and powdered anhydrous potassium carbonate (170 mg, 1·23 mmol) in benzene (20 ml) was refluxed for 5 h and then stirred at room temperature for 8—10 h. An equivalent amount of iodine in benzene was then added at +10 °C, under nitrogen, during 15 min. After 4 h at +10 °C, the mixture was filtered through Celite and the solution was washed with aqueous 5% sodium disulphite and water, dried, and evaporated at room temperature. The *iodo-lactone* (18) thus obtained was immediately used for the next reaction; R_F 0·4 (5% ethyl acetate in benzene); $\nu_{max.}$ 1780 cm^{-1} (Found: M^+, 526·2312. $C_{27}H_{43}IO_2$ requires *M*, 526·2310).

Ethyl 4,5-*Epoxy*-4,8,13,17,21-*pentamethyldocosa*-

8,12,16,20-*tetraenoate* (19).—The foregoing iodo-lactone (18) dissolved in absolute ethanol (1 ml) at 0 °C was treated with 1·5 equiv. of sodium ethoxide in anhydrous ethanol and stirred for 1 h at 0 °C. After sequential addition of isopropenyl acetate (100 mg) in absolute ethanol (1 ml) and light petroleum (5 ml), the mixture was filtered through a column of alumina (grade V) and the column was eluted with ethyl acetate to yield the *epoxy-ester* (19) (90 mg, 68%); R_F 0·5 (5% ethyl acetate in benzene); $\nu_{max.}$ 1735 cm^{-1}; τ 8·72 (3H, s), 8·72 (3H, t, J 7 Hz), 8·35—8·25 (15H, m), 7·87—8·10 (16H, m), 5·82 (2H, q, J 7 Hz), 7·10—7·80 (5H, m), and 4·82br (4H, s); m/e 444 (M^+) (Found: C, 78·2; H, 10·65. $C_{29}H_{48}O_3$ requires C, 78·35; H, 10·9%).

4,9,13,17-*Tetramethyloctadeca*-4,8,12,16-*tetraenal* (20).—To the epoxy-ester (19) (90 mg, 0·203 mmol) dissolved in ether, was added at room temperature an equivalent amount of ethereal periodic acid. After 1 h, water was added, and the aqueous phase was extracted with light petroleum. The organic extract was washed with water, dried, and evaporated. The residual oil was distilled (bath temperature 200 °C at 3 × 10^{-4} mmHg) to yield the aldehyde (20) (50 mg, 78%); R_F 0·65 (5% ethyl acetate in benzene); $\nu_{max.}$ 1720 cm^{-1}.

Squalene Oxides.—To 90% hydrogen peroxide (8·83 ml) in dichloromethane (38 ml) at 0 °C, was added concentrated sulphuric acid (1 drop), followed, during 90 min, by acetic anhydride (40 g). After 30 min at room temperature, dichloromethane (25 ml) was added, then anhydrous sodium acetate (4·3 g). The 44% peracetic acid solution thus obtained was dried (Na_2SO_4) before use.

To an ice-cold stirred mixture of all-*trans*-squalene (100 g) and powdered anhydrous sodium carbonate (145 g) in dichloromethane (750 ml) was added 44% peracetic acid (0·6—0·7 mol) during 60 min. After 30 min at room temperature, the mixture was filtered and the inorganic residues were washed with dichloromethane. The dichloromethane extract was washed with aqueous 5% sodium thiosulphate, aqueous 5% potassium hydroxide, and water, dried ($MgSO_4$), and evaporated to yield a crude oil (110 g) mainly composed of squalene (R_F 0·75), a mixture of squalene internal monoepoxides (R_F 0·5), and 2,3-epoxysqualene (R_F 0·43 in benzene).

To the crude mixture of squalene oxides (105 g) in t-butyl alcohol (3 l) and water (2 l) was added 7% perchloric acid (250 ml) at 27 °C. The reaction was quenched after 12—15 min with 4N-sodium hydroxide, and the mixture was diluted with water and extracted with light petroleum. The extract was washed with water, dried, and evaporated to yield a crude oil (100 g) containing mainly squalene (R_F 0·75), squalene internal monoepoxides (R_F 0·5) and squalene-2,3-diol (R_F 0·0) (benzene). The glycol was removed by thiourea clathration followed by decomposition of the clathrate with water. The product thus obtained (45 g) was chromatographed on a silica gel column (1000 g of SiO_2 containing 10% water). Elution with light petroleum gave unchanged squalene. Elution with benzene furnished the mixture of squalene internal monoepoxides (20 g).

Squalene Diols.—To the mixture of squalene internal monoepoxides (20 g) dissolved in t-butyl alcohol (2 l) and water (1·75 g), was added aqueous 30% perchloric acid (200 ml). After 1·5 h at room temperature, the reaction was quenched by addition of aqueous 4N-sodium hydroxide. Water was added and the mixture extracted with light petroleum. The extract was washed with water, dried, and evaporated under reduced pressure to give a mixture of *erythro*-diols (20 g). The product was then chromatographed on a column of silica gel (1000 g of SiO_2 containing 7·5% silver nitrate) made up in light petroleum. The solvent polarity was gradually increased with ethyl acetate, beginning with ethyl acetate–light petroleum (1 : 9). Squalene-6,7-*erythro*-diol (8 g) was thus readily eluted with ethyl acetate–light petroleum (1 : 4 to 3 : 7).

4,9,13,17-*Tetramethyloctadeca*-4,8,12,16-*tetraenal* (20).—To squalene-6,7-*erythro*-diol (3·5 g, 7·9 mmol) in tetrahydrofuran (50 ml) and water (18 ml) at room temperature, under nitrogen, was added sodium periodate (5·15 g, 24 mmol). After 1·5 h, water was added and the mixture extracted with light petroleum. The extract was washed with water, dried, and evaporated and the crude oil distilled to yield the octanorsqualene aldehyde (20) (2 g, 80%), b.p. (bath temperature) 200° at 3 × 10^{-4} mmHg; R_F 0·65 (5% ethyl acetate in benzene); $\nu_{max.}$ 1720 cm^{-1}; m/e 316 (M^+).

4,9,13,17-*Tetramethyloctadeca*-4,8,12,16-*tetraen*-1-*ol* (21).—To the octanorsqualene aldehyde (20) (2 g, 6·32 mmol) in ether, under nitrogen, was added lithium aluminum hydride (120 mg) in small portions. After 30 min, water was carefully added, the inorganic residue was filtered off and the solvent was removed to yield almost quantitatively the octanorsqualenol (21); R_F 0·2 (5% ethyl acetate in benzene); $\nu_{max.}$ 3350 cm^{-1}; τ 8·2—8·55 (15H, m), 7·7—8·1 (15H, m, 1H D_2O exchanged), 7·25—7·5 (2H, m), 6·35 (2H, t, J 7 Hz), and 4·88br (4H, s); m/e 318 (M^+).

4,9,13,17-*Tetramethyloctadeca*-4,8,12,16-*tetraenyl Toluene*-p-*sulphonate* (22).—To the octanorsqualenol (21) (2 g, 6·28 mmol) in dry pyridine (2·25 ml) was added toluene-*p*-sulphonyl chloride (1·5 g, 7·9 mmol) at −20 °C. After 18 h at 0—5 °C, the solution was diluted with water, pyridine was removed under reduced pressure, and the aqueous phase was extracted with light petroleum. The extract was washed with water, dried, and evaporated to yield the tosylate (22) (2·37 g, 80%); R_F 0·56 (5% ethyl acetate in benzene); $\nu_{max.}$ 1190, 1195, and 1370 cm^{-1}; τ 8·67—8·17 (15H, m), 8·17—7·65 (16H, m), 7·55 (3H, s), 6·0 (2H, t, J 7 Hz), 4·99br (4H, s), 2·64 (2H, d, J 8 Hz), and 2·17 (2H, d, J 8 Hz); m/e 472 (M^+).

4,9,13,17-*Tetramethyloctadeca*-4,8,12,16-*tetraenyl Iodide* (23).—The tosylate (22) (2·35 g, 4·96 mmol) in a saturated solution of sodium iodide in acetone (150 ml) was stirred in the dark for 24 h. Aqueous 5% sodium thiosulphate was added, acetone was removed under reduced pressure, and the aqueous phase was extracted with light petroleum. The extract was washed with aqueous 5% sodium thiosulphate and water, then dried. Removal of the solvent gave the *iodide* (23) (2 g, 94%); R_F 0·56 (benzene–light petroleum, 1 : 4); τ 8·25—8·50 (15H, m), 7·85—8·15 (14H, m), 7·3—7·6 (2H, m), 6·75—7·15 (2H, m), and 4·92br (4H, s); m/e 428 (M^+) (Found: C, 61·4; H, 8·45. $C_{22}H_{37}I$ requires C, 61·7; H, 8·7%).

Triphenyl-(4,9,13,17-*tetramethyloctadeca*-4,8,12,16-*tetraenyl*)*phosphonium Iodide* (2).—The iodide (23) (103 mg, 0·24 mmol) and triphenylphosphine (232 mg, 0·89 mmol) were dissolved in dry toluene (0·5 ml) and refluxed for 24 h under argon. The solution was cooled, dry ether was added, and the solid which separated was washed several times with dry diethyl ether and then with dry light petroleum until no more triphenylphosphine was extracted. The yield of solid phosphonium salt (2) was 160 mg (96%); τ 8·2—8·62 (m, Me), 7·2—8·2 (m, methylene envelope), 6·2—6·7 (m, CH_2), 4·9br (s, vinyl), and 2·6—2·0 (m, Ph).

We gratefully acknowledge the interest shown by Professor Sir Derek Barton and Dr. D. A. Widdowson and thank them for invaluable advice and discussions. This work was carried out during the tenure of an M.R.C. grant (to J. N. S.).

[4/1661 *Received*, *7th August*, 1974]