Synthesis of (±)-Presqualene Alcohol, (±)-Prephytoene Alcohol, and Structurally Related Compounds

By **Rodwill V. M. Campbell, Leslie Crombie,* David A. R. Findley, Richard W. King, Gerald Pattenden,** and **Donald A. Whiting,** Department of Chemistry, The University, Nottingham NG7 2RD

The stereochemistry of the base-catalysed addition–elimination method for cyclopropane ring synthesis, employing a βγ-unsaturated phenyl sulphone and an αβ-unsaturated ester, has been examined. The olefinic geometry of the βγ-unsaturated sulphone is retained in the product, and the unsaturated side chain and the ester function emerge *trans* about the ring, with substantial stereoselectivity. On the other hand, the geometry of the double bond of the αβ-unsaturated ester becomes equilibrated in the anion addition product. Thus the resulting cyclopropanes are produced without a stereoselective preference based on the geometry of the original αβ-unsaturated ester. This work has led to the synthesis of ethyl 2,2-dimethyl-*trans*-3-[(1*E*,5*E*)-2,6,10-trimethylundeca-1,5,9-trienyl]cyclopropanecarboxylate (40) and the corresponding cyclopropylmethanol (42), representing one side of the presqualene molecule, and to the pair of C-2 epimeric diterpenoid ethyl 2-[(*E*)-4,8-dimethylnona-3,7-dienyl]-2-methyl-*trans*-3-(2-methylprop-1-enyl)cyclopropanecarboxylates (44) and (45) and the corresponding alcohols (47) and (48), representing the other side of the presqualene molecule. Lower prenylogues were also studied.

By using phenyl 3,7,11-trimethyldodeca-2,6,10-trienyl sulphone (37) and ethyl (2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienoate (39; R = Et), the stereochemically controlled synthesis was developed to give two stereoisomers of presqualene esters (49) and (50), which were separated and reduced to give (±)-natural presqualene alcohol (53) and the C-2 epimer (54): tritiated samples were also prepared. Chemical and biological comparison with natural presqualene alcohol, the C_{30} compound involved in squalene biosynthesis, confirmed the identification. An n.m.r. study with shift reagents was used to investigate the stereochemistry of these and related substituted cyclopropanes.

Condensation of the C_{20} sulphone (64) with the C_{20} ester (62) led, in a similar synthesis, to the C_{40} cyclopropane carotenoid precursor (±)-prephytoene alcohol (68) and its C-2 epimer (69).

MANY features of the enzyme-mediated sequence leading from mevalonic acid (1) to squalene (4) are known in detail, largely as a result of the elegant studies by Cornforth, Popják, and their colleagues.[1] Certain stereochemical aspects of the final stage in this sequence, the 'tail-to-tail' coupling of farnesyl pyrophosphate, are well known, but the mechanism by which this coupling is accomplished has, until recent years, remained obscure. The biosynthesis of squalene (4) from farnesyl pyrophosphate (3) requires reduced triphosphopyridine nucleotide (NADPH) and during the process a *pro*-1*S*-hydrogen is lost from one of the farnesyl units and replaced by a *pro*-4*S*-hydrogen (asterisked in the Scheme) from NADPH. Rilling[2] showed that if NADPH is omitted from incubations synthesising squalene from farnesyl pyrophosphate, no squalene is formed but a new compound accumulates. This, when incubated with a fresh microsomal preparation supplied with NADPH, forms squalene. The new compound was considered to be an intermediate on the pathway between squalene and farnesyl pyrophosphate and was designated 'presqualene.' A tentative structure (10) was shown by subsequent synthesis[3] to be incorrect and the structure was later modified to (5a).[4] The same or a similar intermediate was isolated by Popják and his colleagues,[5] and also by Wasner and Lynen.[6] Popják first formulated the intermediate as a glycol pyrophosphate (11), but later modified the structure to (5a).[7]

Recently, two forms of a squalene synthetase have been isolated from yeast;[8] the 'polymeric' form synthesises presqualene and squalene whereas the 'protomeric' form produces only presqualene. Presqualene has also been isolated from bramble (*Rubus fruticosa*) tissue culture.[9]

The early stages in the biosynthesis of carotenoids closely parallel those involved in the biosynthesis of squalene (see Scheme).[10] After formation of farnesyl pyrophosphate (3), head-to-tail condensation with isopentenyl pyrophosphate (2) leads to geranylgeranyl pyrophosphate (6), which by 'tail-to-tail' coupling produces phytoene (9), the first C_{40} carotenoid in the biosynthetic sequence.† The close similarity between events leading to (4) and (9), coupled with the isolation of presqualene, precipitated a search for a similar intermediate in phytoene biosynthesis. During 1972, Rilling[13] and Porter[11] and their respective colleagues

† Barnes *et al.*[11b] have recently presented evidence that lycopersene (8) is a precursor of phytoene (9), and have suggested that lycopersene is therefore the first C_{40} carotenoid; however see ref. 12.

[1] G. Popják and J. W. Cornforth, *Biochem. J.*, 1966, **101**, 553; J. W. Cornforth, *Quart. Rev.*, 1969, **23**, 125; 1973, **2**, 1; R. B. Clayton, *ibid.*, 1965, **19**, 168.

[2] H. C. Rilling, *J. Biol. Chem.*, 1966, **241**, 3233.

[3] E. J. Corey and P. R. Ortiz de Montellano, *Tetrahedron Letters*, 1968, 5113.

[4] H. C. Rilling and W. W. Epstein, *J. Amer. Chem. Soc.*, 1969, **91**, 1041; *J. Biol. Chem.*, 1970, **245**, 4597.

[5] G. Popják, J. Edmond, K. Clifford, and V. Williams, *J. Biol. Chem.*, 1969, **244**, 1897.

[6] H. Wasner and F. Lynen, *Fed. European Biochem. Soc. Letters*, 1970, **12**, 54.

[7] J. Edmond, G. Popják, S. M. Wong, and V. Williams, *J. Biol. Chem.*, 1971, **246**, 6254.

[8] A. A. Qureshi, E. Beytia, and J. W. Porter, *J. Biol. Chem.*, 1973, **248**, 1848, 1856.

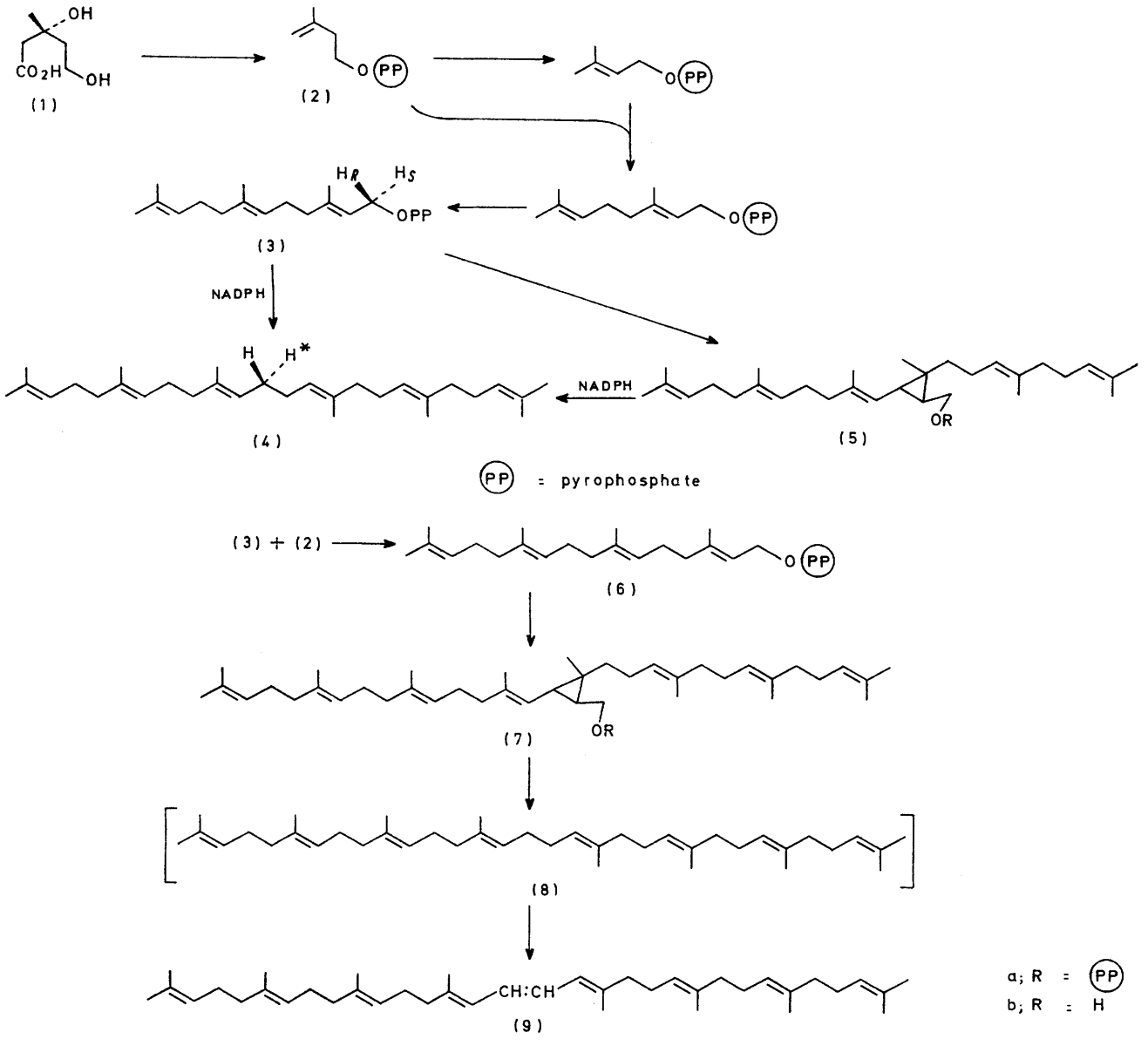
[9] R. Heintz, P. Benveniste, W. H. Robinson, and R. M. Coates, *Biochem. Biophys. Res. Comm.*, 1972, **49**, 1547.

[10] R. W. Goodwin, 'Biosynthesis' in 'Carotenoids,' ed. O. Isler, Birkhauser Verlag, 1971.

[11] (*a*) A. A. Qureshi, F. J. Barnes, and J. W. Porter, *J. Biol. Chem.*, 1972, **247**, 6730; (*b*) F. J. Barnes, A. A. Qureshi, E. J. Semmler, and J. W. Porter, *ibid.*, 1973, **248**, 2755, 2768.

[12] D. E. Gregonis and H. C. Rilling, *Biochemistry*, 1974, **13**, 1538.

[13] L. J. Altman, L. Ash, R. C. Kowerski, W. W. Epstein, B. R. Larsen, H. C. Rilling, F. Muscio, and D. E. Gregonis, *J. Amer. Chem. Soc.*, 1972, **94**, 3257.



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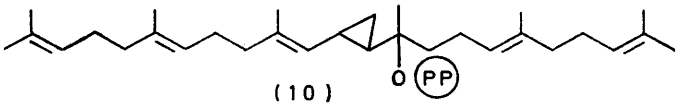
simultaneously reported the presence of such an intermediate between (6) and phytoene. Its formation, like that of presqualene, was increased in incubations devoid of NADPH, and it was converted into phytoene in subsequent incubations supplied with NADPH. Since the conversions appeared analogous to those in squalene biosynthesis, the new carotenoid intermediate was formulated as (7a) and named ' prephytoene.' *

The discovery of presqualene and prephytoene as possible biosynthetic intermediates has stimulated new interest in this area. In 1971, we [14] and others [15,16] reported the first synthesis of ' presqualene alcohol '



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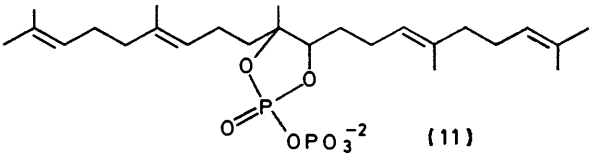

(11)

* The name ' prelycopersene ' has also been used for this intermediate;[11] see footnote †.

[14] R. V. M. Campbell, L. Crombie, and G. Pattenden, *Chem. Comm.*, 1971, 218.

[15] L. J. Altman, R. C. Kowerski, and H. C. Rilling, *J. Amer. Chem. Soc.*, 1971, **93**, 1782.

[16] R. M. Coates and W. H. Robinson, *J. Amer. Chem. Soc.*, 1971, **93**, 1785.

(5b), the structure proposed for the product from cleavage of Rilling's presqualene with lithium aluminium hydride or a phosphatase. Synthesis of (5b) coupled with the demonstration that the corresponding pyrophosphate (5a) of the synthetic alcohol could be enzymically converted into squalene in plant, yeast, and animal systems [17] has been followed by commentary on the formation and cleavage of presqualene,[18-25] and by the isolation of prephytoene (7a).[11-13] The total synthesis of prephytoene alcohol (7b) was reported contemporaneously by Rilling's group [13] and by ourselves.[26] We now present full details of our syntheses of (±)-presqualene alcohol (5b) and (±)-prephytoene alcohol (7b). We also report the synthesis of several structurally related compounds whose spectral and other properties have permitted complete relative stereochemical assignments to be given to natural presqualene and prephytoene.

The cyclopropane carbon framework in presqualene (5a) and prephytoene (7a) bears close structural similarity to that present in the chrysanthemic acid units (12) and (13) of the insecticidal pyrethrin esters found in *Chrysanthemum cinerariaefolium*.[27] Search for synthetic routes to the chrysanthemate skeleton has latterly attracted attention.[28] Martel and his colleagues have successfully developed a route based on sequential Michael-type addition of the anion from the phenyl

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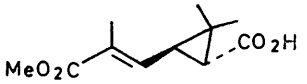

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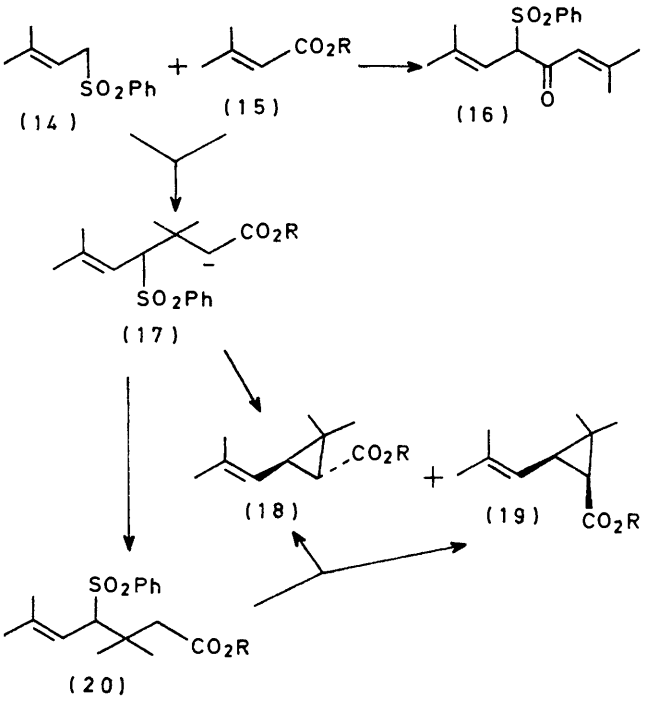
sulphone (14) to the ester (15) leading to an intermediate (17) which then undergoes 1,3-elimination to give the chrysanthemate ester [(18) + (19)].[29,30] This route is remarkably stereoselective and produces largely the *trans*-ester (18). We were attracted by this cyclopropane synthesis as a basis for development towards the ester precursors (21a) and (21b) of presqualene alcohol and prephytoene alcohol. At the outset of our studies in 1969, the detailed stereospecificity of this route and its application to higher isopentanoid analogues required further examination. Presqualene and prephytoene both contain three asymmetric centres, and a total of four stereoisomers resulting from differences in the cyclopropane ring stereochemistry is thus possible. In addition, presqualene contains three, and prephytoene four, trisubstituted double bonds, each capable of



displaying *ZE*-isomerism, which substantially raises the number of possible isomers of the natural products. However, each of the trisubstituted double bonds in squalene and phytoene has been shown to have the *E*-configuration, and it seemed safe to assume that the corresponding double bonds in presqualene and prephytoene would also have the *E*-configuration. We first examined the synthesis of the sesquiterpenoid and diterpenoid compounds (22)—(25).

Investigations by Martel on the synthesis of alkyl chrysanthemates [(18) and (19)] from the C_5 precursors (14) and (15) have established that optimum yields can be realised when the ester (15) and sulphone (14) react in a 2 : 1 molar ratio in dimethylformamide (DMF) as solvent in the presence of 3 mol. equiv. of potassium t-butoxide at 25°. Conditions are important since use of equimolar quantities of reactants results only in the formation of the intermediate (20) [which

[17] See refs. 14—16 and G. H. Beastall, H. H. Rees, and T. W. Goodwin, *Fed. European Biochem. Soc. Letters*, 1972, **28**, 243.

[18] H. C. Rilling, C. D. Poulter, W. W. Epstein, and B. Larsen, *J. Amer. Chem. Soc.*, 1971, **93**, 1783.

[19] E. E. Van Tamelen and M. A. Schwartz, *J. Amer. Chem. Soc.*, 1971, **93**, 1780.

[20] R. E. Dugan and J. W. Porter, *Arch. Biochem. Biophys.*, 1972, **152**, 28.

[21] A. A. Qureshi, E. Beytia, and J. W. Porter, *J. Biol. Chem.*, 1973, **248**, 1848, 1856.

[22] L. Crombie, P. A. Firth, R. P. Houghton, D. A. Whiting, and D. K. Woods, *J.C.S. Perkin I*, 1972, 642.

[23] B. M. Trost, P. Conway, and J. Stanton, *Chem. Comm.*, 1971, 1639.

[24] R. M. Coates and W. H. Robinson, *J. Amer. Chem. Soc.*, 1972, **94**, 5920.

[25] C. D. Poulter, O. J. Muscio, C. J. Spillner, and R. G. Goodfellow, *J. Amer. Chem. Soc.*, 1972, **94**, 5922.

[26] L. Crombie, D. A. R. Findley, and D. A. Whiting, *J.C.S. Chem. Comm.*, 1972, 1045.

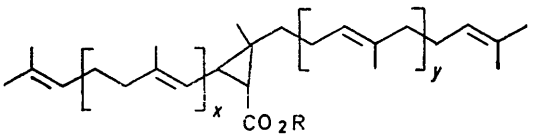
[27] M. Elliott and N. F. Janes, 'Chemistry of the Natural Pyrethrin,' in 'Pyrethrum, the Natural Insecticide,' ed. J. E. Casida, Academic Press, 1973; L. Crombie and M. Elliott, *Fortschr. Chem. org. Naturstoffe*, 1961, **19**, 120.

[28] For recent approaches see R. W. Mills, R. D. H. Murray, and R. A. Raphael, *J.C.S. Perkin I*, 1973, 133; E. J. Corey and M. Jautelat, *J. Amer. Chem. Soc.*, 1967, **89**, 3912; ref. 27.

[29] J. Martel, C. Huynh, E. Toromanoff, and G. Nominé, *Bull. Soc. chim. France*, 1967, 982; J. Martel and C. Huynh, *ibid.*, p. 985; *cf.* M. Julia and A. Guy-Rouault, *Bull. Soc. chim. France*, 1967, 1411.

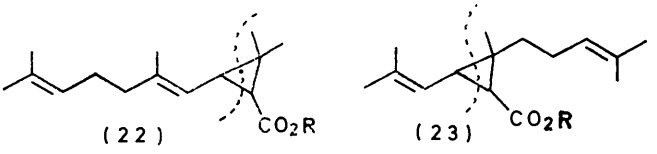
[30] L. Velluz, J. Martel, and G. Nominé, *Compt. rend.*, 1969, **268**, 2199; Fr. Pat. 1,488,209, 1,505,423 (*Chem. Abs.*, 1969, **70**, 37,280, 68,572).

can be treated further to give (18) and (19)] and other base–solvent systems lead to significant amounts of the 1,2-addition (16) and other products.



(21)

a; $x = 2, y = 1$
b; $x = 3, y = 2$



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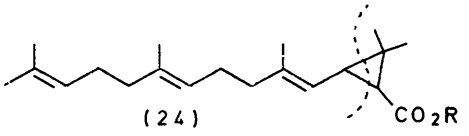

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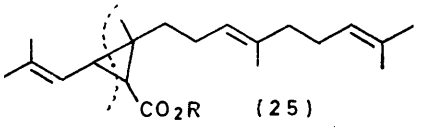
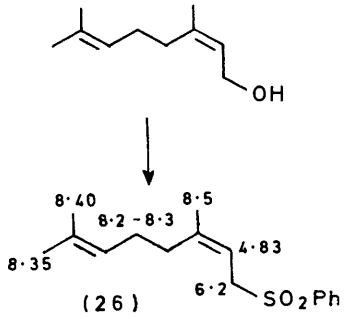


(25)

In our early studies we briefly re-examined the synthesis of (18) and (19) from (14) and (15) under conditions similar to those described by Martel and his colleagues. In tetrahydrofuran, condensation between equimolar amounts of (14) and (15), in the presence of 2 mol. equiv. of potassium t-butoxide, indeed led to a complex mixture of products from which the phenyl sulphones (16) and (20) and the chrysanthemate (18) could be separated and characterised. In DMF, and with a 1 : 2 : 3 molar ratio of sulphone (14), ester (15), and butoxide, reasonably reproducible yields of chrysanthemate (18) were obtained without the accompaniment of significant amounts of by-products; the formation of (18; R = Me or Et) from (15; R = Me or Et) was always accompanied by production of the corresponding t-butyl ester (18; R = Bu^t), resulting from ester exchange. In only a few reactions were we able to obtain evidence for the co-formation of *cis*-chrysanthemate (19) and the *trans*-isomer (18) in these preliminary studies. The presence of (19) was easily demonstrated by the appearance of an additional olefinic proton doublet at τ 4·63 (*cf.* τ 5·1 for the *trans*-isomer) in the n.m.r. spectra of crude products.[31] When such a doublet resonance was detected, integration showed that never more than 10% of (19) was present; to this extent therefore we were able to confirm that the condensation leading to (18) was largely (*trans*) stereospecific.

To examine further details of the stereochemistry of the Martel reaction we studied the syntheses of the sesquiterpenoid molecules (22) and (23) from the corresponding *Z*- and *E*-C_{10} and C_5 precursors. The *Z*- and *E*-phenyl sulphones (26) and (27) were prepared from nerol and geraniol, respectively, by sequential reaction with phosphorus tribromide and sodium benzenesulphinate. The sulphones were cleanly resolved by g.l.c., and their configurations followed from the method of synthesis and from comparison of their n.m.r. data [see formulae (26) and (27)]; significantly those protons oriented *cis* to the bulky $CH_2{\cdot}SO_2Ph$ group were heavily shielded relative to those orientated *trans* (τ_{Me} 8·7 and 8·5; $\tau_{[OH_4]_2}$ 8·2—8·3 and 7·9—8·1).

Condensations between the sulphones (26) and (27) and ethyl 3-methylbut-2-enoate (15; R = Et) were carried out in DMF with potassium t-butoxide as base, and molar ratios of sulphone, ester, and base of 1 : 2 : 3. From each condensation a single product was isolated,* both homogenous in g.l.c. and cleanly separated from one another in mixed g.l.c. Each compound displayed analytical and spectral data consistent with the expected C_{15} skeleton (22). The olefinic proton regions of the n.m.r. spectra of the two products gave no suggestion of doublet resonances at τ *ca.* 4·6 associated with the presence of a C-1′ olefinic proton orientated *cis* to the



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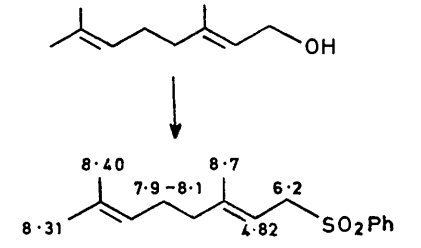


(27)

ester function. In addition, as in the formation of (18) from (14) and (15), the condensations between (26) and (15) and between (27) and (15) were essentially stereoselective with regard to cyclopropane geometry and led to ester products where the ethoxycarbonyl and C_9 side-chains adopt a *trans*-relationship. The ^1H

* All synthetic compounds are (±).

[31] A. F. Bramwell, L. Crombie, P. Hemesley, G. Pattenden, M. Elliott, and N. F. Janes, *Tetrahedron*, 1969, **25**, 1727.

n.m.r. spectra of the two esters were closely similar, but small differences could be discerned in the τ 7—10

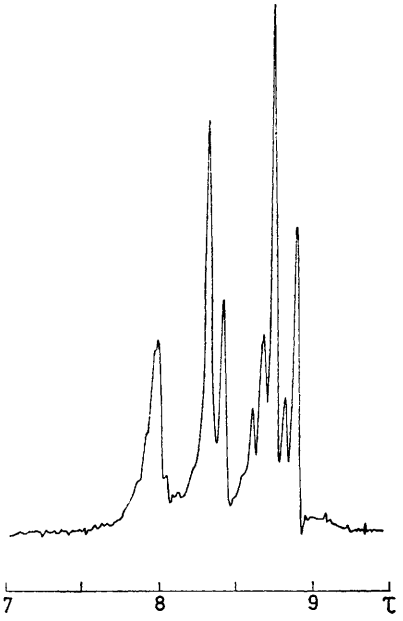


FIGURE 1 N.m.r. spectrum (τ 7—10) of the cyclopropane ester (29)

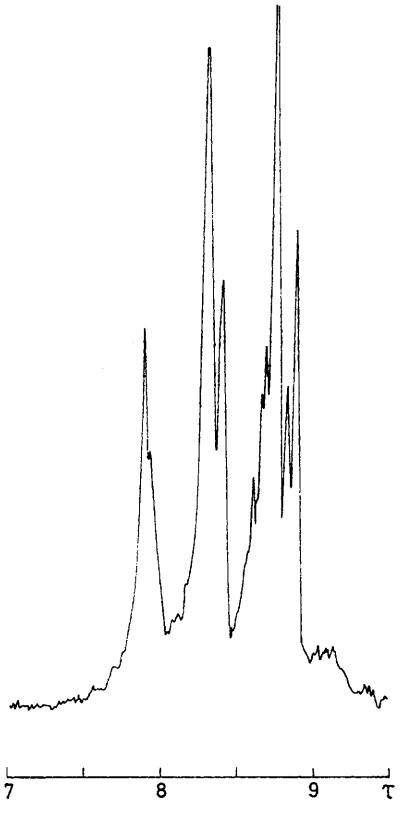
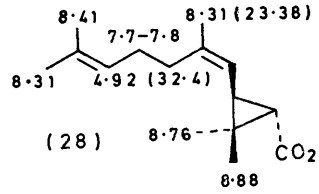


FIGURE 2 N.m.r. spectrum (τ 7—10) of the cyclopropane ester (28)

regions, particularly in those resonances (τ 7·8—8·1 and 7·7—8·0) due to the vinyl methylene protons [see Figures 1 and 2, and formula (28) and (29) for a summary of these data]. Little differential shielding of those protons (2′-Me and 3′-H_2) orientated *cis* to the cyclopropane ring was observed in the ^1H n.m.r. spectra. By contrast, in the corresponding ^{13}C n.m.r. spectra [δ values in parentheses on formula (28) and (29)] carbon atoms *cis* to the cyclopropane ring were significantly shielded in comparison with those oriented *trans*. The absence of *cis–trans* isomerism about the cyclopropane rings in the products of reaction between (26) and (15; R = Et) and between (27) and (15) established that the difference between the two compounds must be due to *ZE*-isomerism about their C-1′ trisubstituted



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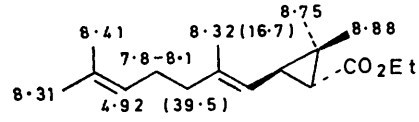
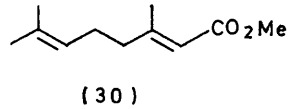


(29)

double bonds. This study clearly showed, then, that the geometries about the double bonds in the βγ-unsaturated sulphones (26) and (27) were completely preserved during condensations producing the chrysanthemate carbon framework, and led to the formation of the *Z*- and *E*-isomers (28) and (29).

The geometrical isomers of methyl 3,7-dimethylocta-2,6-dienoate (30) and (31) have been described previously.[32] In the present studies, a mixture of the



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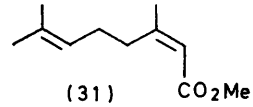


(31)

two isomers was prepared from commercial citral (a 2 : 1 mixture of *E*- and *Z*-isomers) by oxidation with silver oxide and esterification with dimethyl sulphate. The individual isomers were separated by chromatography, and each displayed spectral data consonant with the configurations assigned. Reaction between the *E*-ester (30) and the C_5 sulphone (14), led to a cyclopropanecarboxylate which was homogenous in g.l.c. analysis but showed two cyclopropyl methyl singlet resonances in its n.m.r. spectrum at τ 8·75 and 8·89 (ratio *ca.* 2 : 3). The absence of absorptions at τ *ca.* 4·6 established that the methylpropenyl and methoxycarbonyl substituents were *trans* to each other; this is in keeping with the results from the earlier studies.

[32] J. W. K. Burrell, R. F. Garwood, L. M. Jackman, E. Oskay, and B. C. L. Weedon, *J. Chem. Soc.* (*C*), 1966, 2144.

Repeated chromatography separated two isomers differing in their *cis–trans* stereochemistry about the cyclopropane ring. Since n.m.r. data unequivocally established the *trans*-orientation of the C-1 and C-3 substituents in the two isomers, the difference must be due to the relative orientations of the C-1 and C-2 substituents. Consideration of the chemical shifts of the cyclopropyl methyl protons of the two isomers, and comparison with those in methyl *trans*-chrysanthemate,[31] established that the least polar isomer (τ_{Me} 8·89; major product) has the geometry shown in (33) whereas the other isomer (τ_{Me} 8·75) has that shown in (32). The τ 7—9 regions of the spectra of the isomeric esters are reproduced in Figures 3 and 4, and the relevant data are compared with those of methyl *trans*-chrysanthemate in formulae (32)—(34).

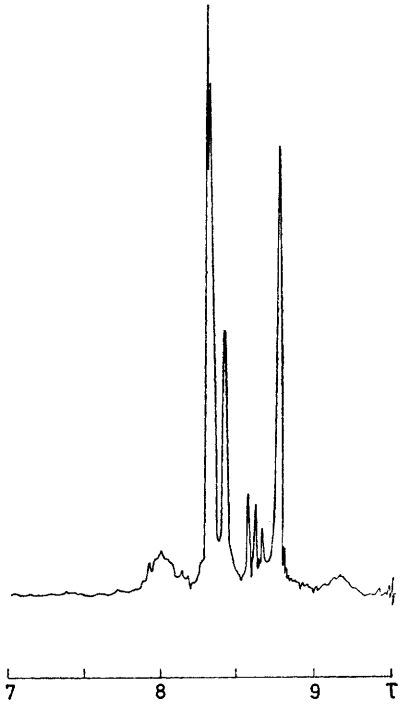


FIGURE 3 N.m.r. spectrum (τ 7—9) of the cyclopropane ester (32)

A similar reaction between the *Z*-ester (31) and the C_5 sulphone (14) produced the same proportion of isomers (32) and (33) as that obtained from the *E*-ester (30). These studies clearly established that the geometries of the *E*- and *Z*-double bonds in (30) and (31) were not preserved during reactions with (14); equilibration of the intermediate carbanion [corresponding to (17)] occurs giving rise to a mixture of C-2 epimers of the cyclopropanecarboxylate product.

We next turned to the application of the C_{15} sulphone [*viz.* (37)] and C_{15} ester [*viz.* (30)] precursors to presqualene alcohol synthesis. For these studies it was imperative that geometrically pure (2*E*,6*E*)-sulphone (37) and (6*E*)-ester (39) were used. The stereochemistry at the 2,3-bond in (39) is not, however, important since our previous studies, with (30) and (31), demonstrated that the stereochemistry about this bond is lost.

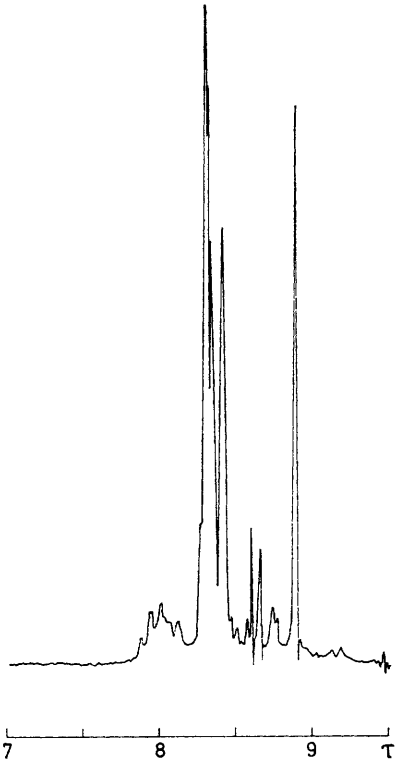
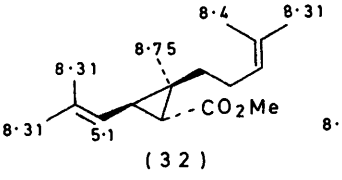


FIGURE 4 N.m.r. spectrum (τ 7—9) of the cyclopropane ester (33)

The stereochemistry of the farnesols has been examined in detail, and assignments of the four isomeric structures can frequently be made on the basis of the relative intensities of the vinyl proton resonances in their n.m.r. spectra.[32,33] The proportions of isomers in commercial farnesol vary from one supplier to another. We systematically examined several samples of commercial farnesols, by a combination of g.l.c. and n.m.r. analysis,



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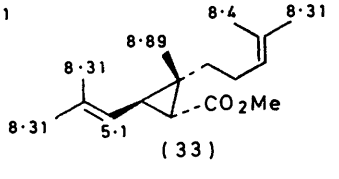

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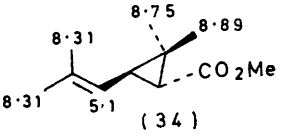
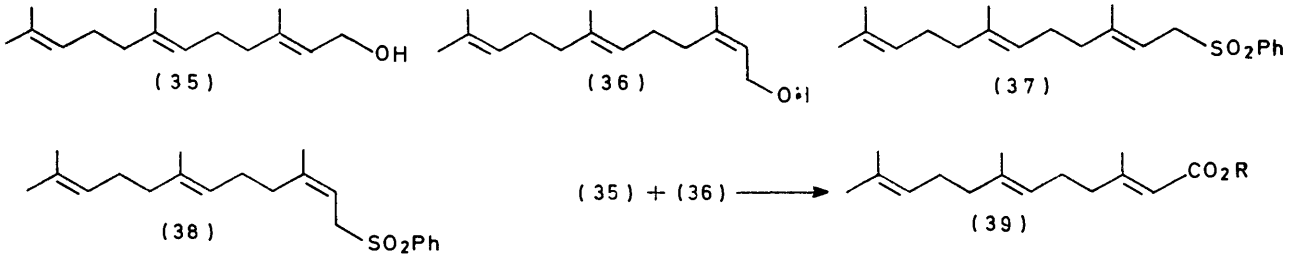


(34)

and used for the synthesis of the sulphone (37) a sample composed largely of the (2*E*,6*E*)-isomer (35) (>60%) and the (2*Z*,6*E*)-isomer (36) (>30%); it was estimated

[33] R. B. Bates, D. M. Gale, and B. J. Grunar, *J. Org. Chem.*, 1963, **28**, 1086.

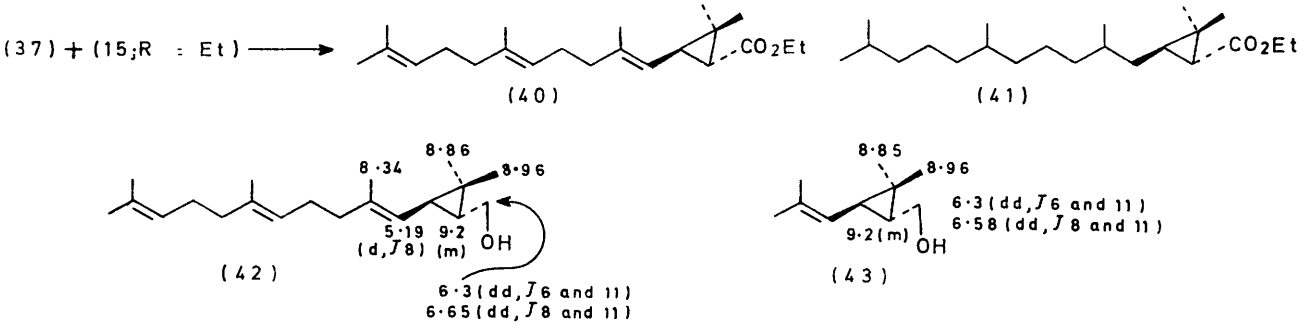
that less than 5% of (6*Z*)-isomers of the farnesols was present. Bromination of the isomeric farnesols, with phosphorus tribromide, and subsequent reaction with sodium benzenesulphinate produced a mixture of isomeric farnesyl phenyl sulphones, from which the isomeric (2*E*,6*E*)- (37) and (2*Z*,6*E*)- (38) sulphones were separated by chromatography. The two sulphones, (37)



and (38), showed spectral data closely similar to those obtained for geranyl and neryl phenyl sulphones, (27) and (26) respectively, and each formed one major band (>95%) on g.l.c. analysis. The relative integrals for the 'in-chain' (τ 8·32) and 'terminal' (τ 8·4) vinyl methyl proton absorptions in the n.m.r. spectrum of the (2*E*)-sulphone (37) showed that these were in the ratio 2 : 1,[34] consistent with expectation for a (6*E*)-double bond. Ethyl (2*E*,6*E*)-farnesoate (39) was obtained by

resulted in the uptake of 3 mol. equiv. of hydrogen and produced (41), whilst reduction with lithium aluminium hydride led smoothly to the corresponding *trans*-cyclopropylmethanol (42). The chemical shifts and the multiplicities of the resonance lines associated with the protons of the chrysanthemyl alcohol unit in (42) were superimposable on those observed in the n.m.r. spectrum of *trans*-chrysanthemyl alcohol (43);[31] these relevant data are summarised on formulae (42) and (43).

The reaction between (2*E*,6*E*)-farnesoate (39; R = Et) and the C_5 sulphone (14), like that between geranoate (30) and (14), led to a mixture of isomeric cyclopropanecarboxylates corresponding to the geometries (44) and (45). These assignments followed conclusively from n.m.r. data and from comparison with similar data obtained for the previously synthesised compounds (32)



chromatography from a mixture of the (2*E*,6*E*)- and (2*Z*,6*E*)-isomers kindly supplied by Hofmann LaRoche, or alternatively could be separated from a mixture of isomers prepared from commercial farnesol by the Corey procedure.[35] The (*E*,*E*)-ester showed one peak in g.l.c. analysis, and displayed n.m.r. data closely similar to those recorded previously.[32]

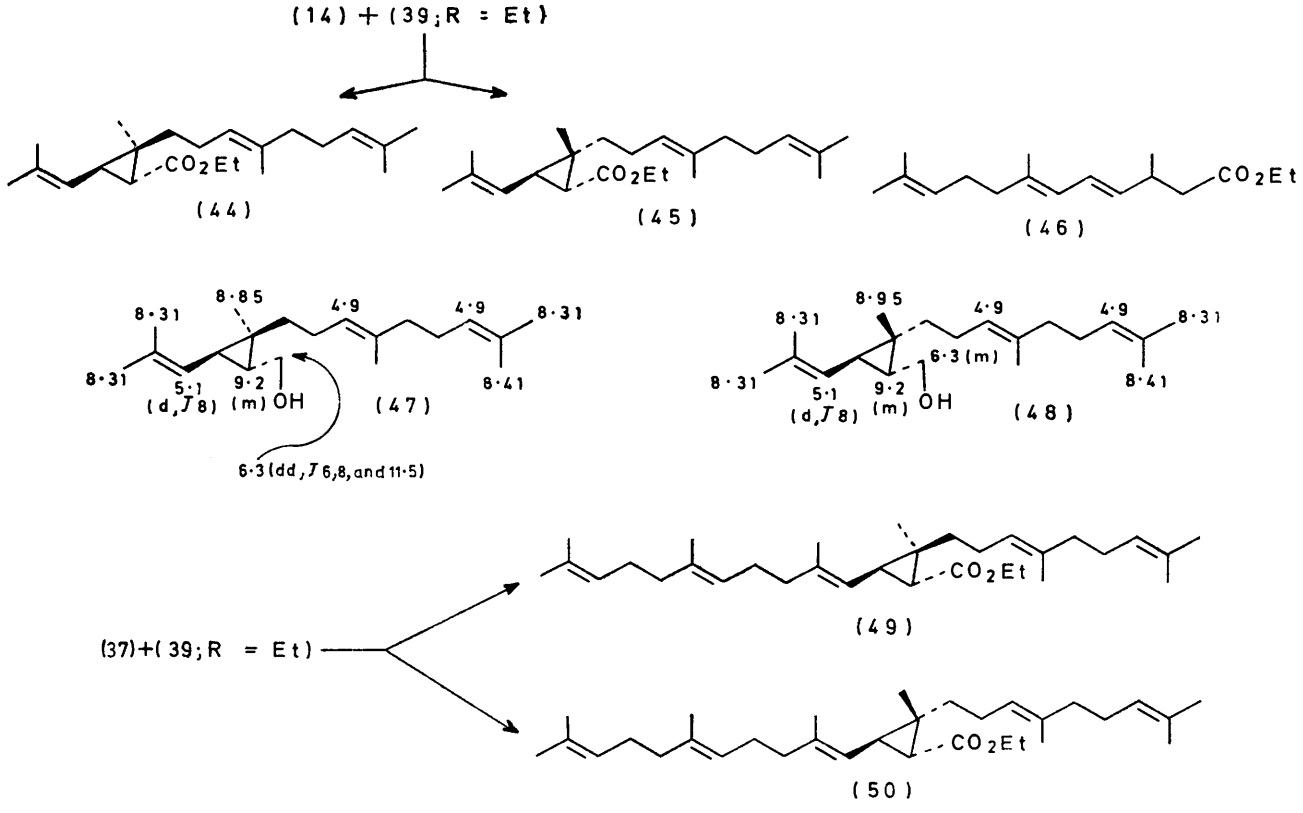
Condensation between the (2*E*,6*E*)-farnesyl sulphone (37) and 3-methylbut-2-enoate (15; R = Et) produced the diterpenoid cyclopropyl ester (40). The ester showed one band in g.l.c. analysis (>98%) and displayed n.m.r. data similar to those obtained for the lower isoprenylogues (18) and (29); once more the absence of absorption in the region τ *ca.* 4·6 conclusively demonstrated the *trans*-disposition of the cyclopropane substituents in (40). Catalytic hydrogenation of (40) and (33); significantly the C-1 and C-3 substituents in both isomers were *trans* to one another, and the cyclopropyl methyl group in the isomer (44) was deshielded relative to the same methyl group in (45) (τ 8·75 *vs.* 8·88) as expected from its disposition *cis* to the ethoxycarbonyl substituent. The formation of (44) and (45) was accompanied by production of the corresponding t-butyl esters, and also the positional isomer (46) of ethyl farnesoate; presumably (46) results from basic isomerisation of (39; R = Et). Reduction of the two esters (44) and (45) with lithium aluminium hydride produced the corresponding isomeric alcohols (47) and (48). The alcohols showed closely similar spectral data, but in their n.m.r. spectra the cyclopropyl methyl signal in isomer (48) was at significantly higher field (τ 8·95) than the corresponding resonance in isomer (47) (τ 8·85) [see formulae (47) and (48)]; these

[34] The accuracy of this method can be as good as ±5%. Fuller details are contained in the Ph.D. Thesis of D. A. R. Findley, Nottingham, 1973.

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

data, taken in conjunction with n.m.r. figures for the related alcohols (42) and (43) fully substantiate the stereochemical assignments given to (47) and (48).

matography. The separated isomers each showed one major band (>90%) on g.l.c. analysis, and inspection of n.m.r. data in comparison with those of model



Attention was then turned to synthesis of the ester precursor (21a) of presqualene alcohol. Under the usual conditions, reaction between (37) and (39; R = Et), produced a mixture of the two cyclopropane C-2 epimers of (21a), which were cleanly resolved by chro-

compounds (32), (33), (47), and (48) led to the stereochemical assignments shown in (49) and (50). Added confirmation of these stereochemical assignments was obtained at this stage by studying europium-induced

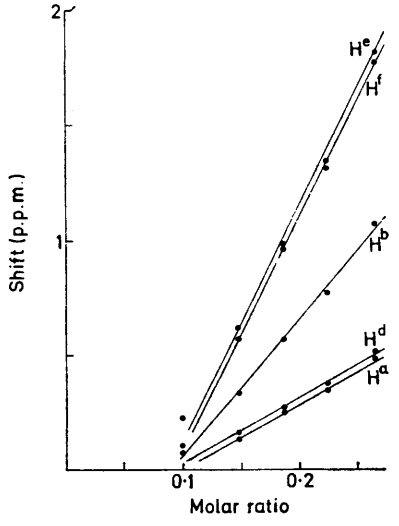


FIGURE 5 Eu(hfod)$_3$-induced shift response of methyl *trans*-chrysanthemate (51) signals in the n.m.r. spectrum (0·38 mmol in 0·32 ml)

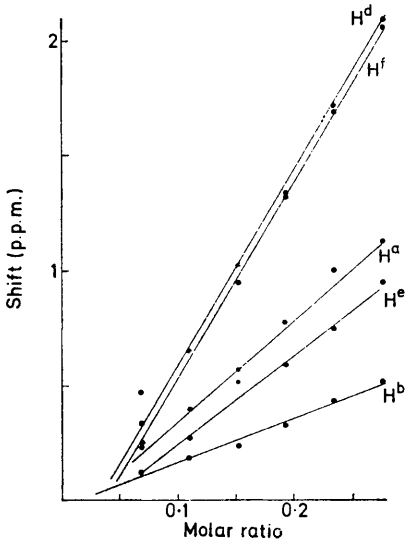
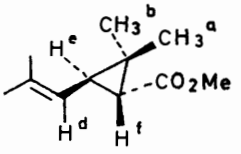


FIGURE 6 Eu(hfod)$_3$-induced shift response of methyl *cis*-chrysanthemate (52) signals in the n.m.r. spectrum (0·35 mmol in 0·32 ml)

n.m.r. shift data for the two isomers and for methyl *cis*- (52) and *trans*- (51) chrysanthemates.[36] Plots of the shift responses against the molar ratios of tris-(1,1,1,2,2,3,3-heptafluoro-7,7,7-trimethyloctane-4,6-dionato)europium(III) [Eu(hfod)$_3$] to ester (Figures 5 and 6) showed that the response of H^f to the shift reagent is similar for both isomers, but that H^e and H^b are more affected in the *trans*-ester (51), and H^d and H^a more affected in the *cis*-compound (52). These effects are consistent with the known *cis*- and *trans*-geometries of the two esters, and provide confirmatory evidence for the stereochemical relationships adduced previously between the C-2 methyl groups and the C-1 methoxycarbonyl substituents in the esters; the 2-Me *cis* to the CO_2Me in (51) (*i.e.* CH_3^b) resonates at lower field (8·75) than the 2-Me oriented *trans* to this group [τ (CH_3^a) 8·89]. The multiplicities of the signals due to H^e and H^f in (51) and (52) are clearly observed when clarified by Eu(hfod)$_3$, and coupling constants of (J_{ef}) of 5·1 and



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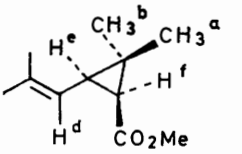
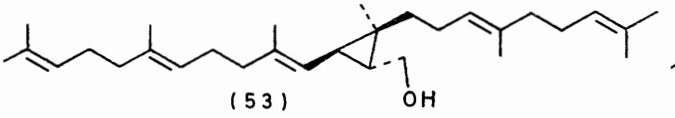


(52)

8·8 Hz for the *trans*- and *cis*-ester, respectively, were obtained. The multiplicities of the signals due to cyclopropyl protons in (49) and (50), corresponding to H^e and H^f in (51) and (52), were also clearly discerned in Eu(hfod)$_3$-shifted spectra and could be further clarified by double resonance. Coupling constants (J_{ef}) of 5·1 Hz were observed for both, which fully confirmed the 1,3-*trans* geometry in each isomer.

Reduction of ester (49) with lithium aluminium hydride gave a (±)-alcohol (53) which displayed identical mass spectral data and t.l.c. behaviour on direct comparison with naturally derived presqualene alcohol. The two alcohols also showed closely similar i.r. and n.m.r. spectra, but direct comparison by g.l.c. was not satisfactory because of extensive decomposition and 'tailing' of bands on all the columns employed. In contrast, reduction of the ester (50) led to an isomeric C_{30}-cyclopropylmethanol (54), which was cleanly resolved from natural presqualene alcohol by t.l.c. and showed n.m.r. and other spectral data different from those of the natural product. Catalytic hydrogenation of synthetic (53) produced a mixture of the saturated alcohol (55) and the hydrocarbon (56). The two compounds were separated by chromatography, and the alcohol (55) showed n.m.r., i.r., and mass spectral data similar to those for the cyclopropylmethanol formed by hydrogenation of natural presqualene alcohol.

Tritium-labelled specimens of the isomeric (±)-alcohols (53) and (54) were obtained by reduction of the corresponding esters with lithium aluminium tritiide. Phosphorylation of these alcohols produced the corresponding pyrophosphates, one of which, assigned the relative geometry shown in (57), co-chromatographed with natural presqualene.* When the two tritium-labelled pyrophosphates were incubated with a yeast microsomal preparation and NADPH, the (±)-isomer (57) gave ^{3}H-labelled squalene (4) in 63% of the expected yield, whereas the pyrophosphate derived from the (±)-stereoisomer (54) afforded squalene in only 0·4% theoretical yield.* Goodwin and his colleagues[37] have similarly demonstrated that the pyrophosphate from our synthetic alcohol (53) is efficiently (*ca.* 10%) converted into squalene in a cell-free preparation from pea seeds (*Pisum sativum*) under conditions where the pyrophosphate from the isomeric alcohol (54) was not incorporated.



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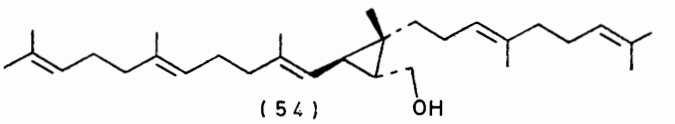

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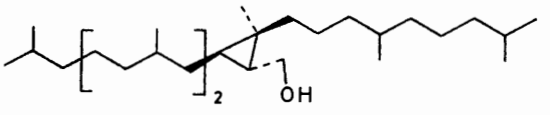

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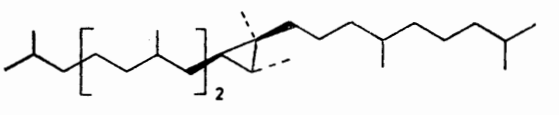
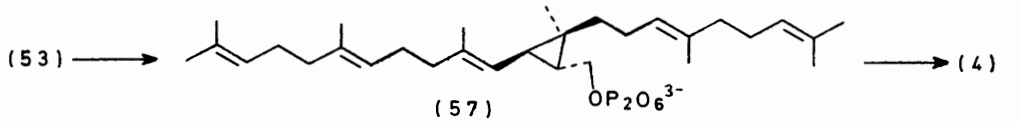


(56)

The foregoing synthesis unambiguously establishes the structure of naturally derived presqualene alcohol as (5b). Furthermore, extrapolation of the extensive



(57)

* We thank Professor Rilling for this comparison and also for the biosynthetic experiments.

[36] L. Crombie, D. A. R. Findley, and D. A. Whiting, *Tetrahedron Letters*, 1972, 4027.

[37] G. H. Beastall, H. H. Rees, and T. W. Goodwin, *Fed. European Biochem. Soc. Letters*, 1972, **28**, 243.

n.m.r. data for the model compounds (18), (19), (28), (29), (32), (33), (40), (44), and (45) has allowed us to

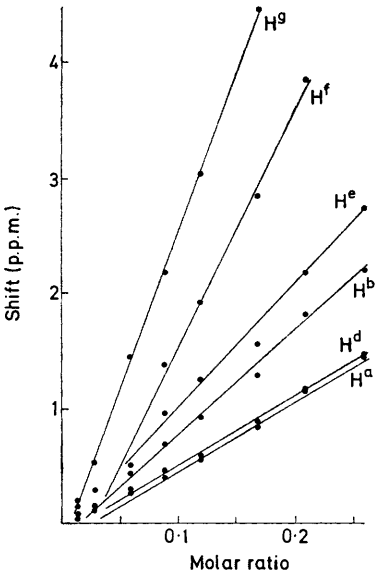


FIGURE 7 Eu(hfod)$_3$-induced shift response of *trans*-chrysanthemyl alcohol (58) signals in the n.m.r. spectrum (0·33 mmol in 0·32 ml)

assign the relative geometry shown in (49) to the ester precursor of presqualene alcohol, and hence the stereochemistry shown in (53) to the alcohol itself. An examination of the europium-induced n.m.r. shift data for the synthetic isomeric alcohols (53) and (54), and comparison with similar data for *cis*- and *trans*-chrysanthemyl alcohols (59) and (58), fully corroborated

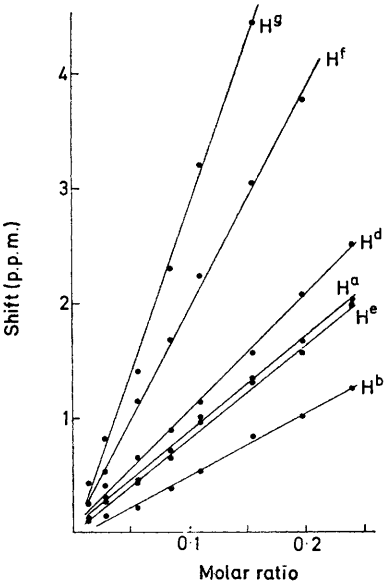


FIGURE 8 Eu(hfod)$_3$-induced shift response of *cis*-chrysanthemyl alcohol (59) signals in the n.m.r. spectrum (0·35 mmol in 0·32 ml)

the stereochemical assignment given to natural presqualene alcohol. Shift data obtained for *cis*- and *trans*-chrysanthemyl alcohols (Figures 7 and 8) were closely similar to those for the corresponding *cis*- and *trans*-chrysanthemates (*cf.* Figures 5—8), except that the shift response, as expected, was greater for the alcohols owing to increased co-ordination. As in the case of the esters, H^e and H^b are more affected by the shift reagent in the *trans*-alcohol (58) whereas H^a and

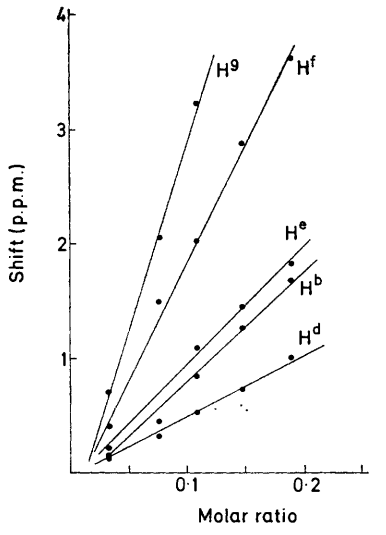


FIGURE 9 Eu(hfod)$_3$-induced shift response of the cyclopropylmethanol (53) signals in the n.m.r. spectrum (0·106 mmol in 0·21 ml)

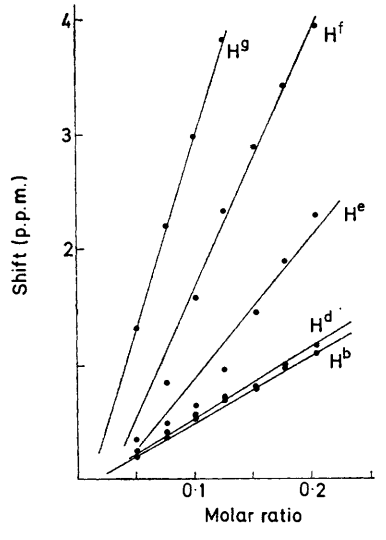
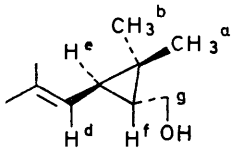


FIGURE 10 Eu(hfod)$_3$-induced shift response of the cyclopropylmethanol (54) signals in the n.m.r. spectrum (0·098 mmol in 0·21 ml)

H^d are more affected in the *cis*-isomer (59). Comparison of the shift data for protons corresponding to H^d and H^e in the isomeric alcohols (53) and (54) (Figures 9 and 10) with those in (58) and (59) fully confirms the 1,3-*trans*-geometry in both (53) and (54). The cyclopropyl methyl group [≡ $CH_3{}^b$ in (58) and $CH_3{}^a$ in (59)] in the synthetic alcohol which was found to be identical with naturally derived presqualene alcohol, was much more

affected by the shift reagent (gradient 9·0) than the same methyl group in the other synthetic alcohol (gradient 5·5). Similar gradients (CH_3^b 9·5; CH_3^a 5·5) for the C-2 methyl groups *cis*- and *trans*- to the hydroxymethyl group were observed for *trans*-chrysanthemyl alcohol (58), and these data then unequivocally confirmed the *cis*-relationship of the cyclopropyl methyl and hydroxymethyl groups in natural presqualene alcohol. These additional n.m.r. data provide further evidence for the stereochemical assignments deduced earlier for naturally derived presqualene alcohol.



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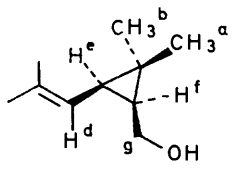
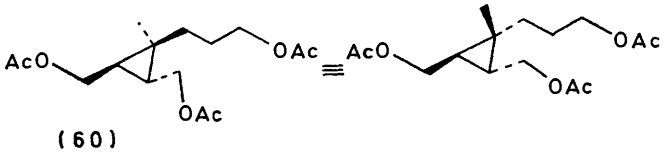


(59)

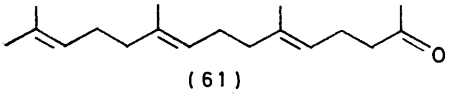
Rilling and his co-workers [18] have examined the stereochemistry of presqualene by synthesis of the degradation product (60) resulting from reductive ozonisation of the



(60)

natural product followed by acetylation. Although establishing the 1,3-*trans*-relationship of the cyclopropane ring substituents in (60) and hence in natural presqualene alcohol, this work in itself did not allow an unambiguous distinction to be made between *cis*- and *trans*-1,2-substituents in (60) or presqualene alcohol. Examination of the optical properties of the benzoates of natural presqualene alcohol (53) and (+)-*trans*-(1*R*,3*R*)-chrysanthemyl alcohol (43), and also of the benzoates of the ozonisation products of (53) and (43), supports the view that presqualene alcohol has the absolute configuration (1*R*,2*R*,3*R*), *viz.* (53).[18,38]

The sulphone addition–elimination approach was applied to prephytoene alcohol (68) *via* the C_{20} ester (65) and the C_{20} sulphone (64), both of which were prepared from (5*E*,9*E*)-farnesylacetone (61). Wadsworth–Emmons condensation between (61) and methyl di-*O*-ethylphosphonoacetate led to a mixture of (2*E*)- and (2*Z*)-isomers of geranylgeranoate (62) from which the all-*E*-ester was separated by chromatography.[39] The all-*E*-isomer showed one major peak (>95%) on g.l.c. analysis, and its n.m.r. spectrum, as suggested by the relative intensities of the vinyl methyl resonances, was consistent with its assigned all-*E*-configuration. Reduction of the ester (62) with lithium aluminium hydride produced the corresponding all-*E*-alcohol (63), which on sequential reaction with phosphorus tribromide and sodium benzenesulphinate led to the C_{20} sulphone (64). Rigorous purification of the sulphone by chromatography gave the all-*E*-isomer, which displayed n.m.r. data closely similar to those of the C_{15} analogue (37). Reaction between (62) and (64), and separation of the resulting cyclopropanecarboxylates gave the C_{40} esters (66) and (67), whose configurations followed from n.m.r. data and comparison with the C_{30} analogues (49) and (50) and the other model compounds. Both isomers showed one major band (>98%) in g.l.c. analysis, and the *E*-configurations assigned to the trisubstituted double bonds in each followed from the relative intensities of the vinyl methyl resonances in their n.m.r. spectra.[34] The positional isomer (65) of geranylgeranoate was also isolated from the products of the reaction between (62) and (64) [*cf.* (46)]. Reduction of the esters with lithium aluminium hydride produced the corresponding alcohols (68) and (69), whose geometries once more followed from comparative n.m.r.



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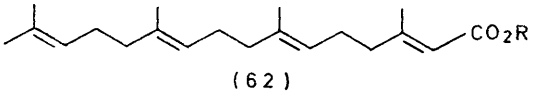

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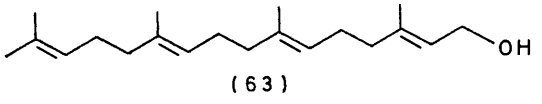

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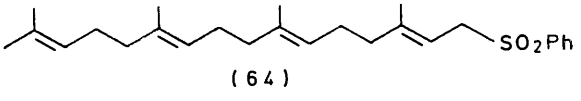
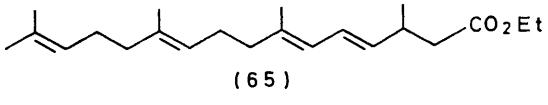
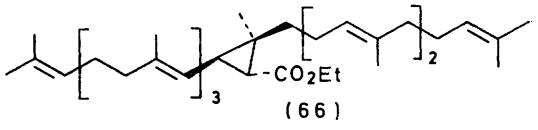


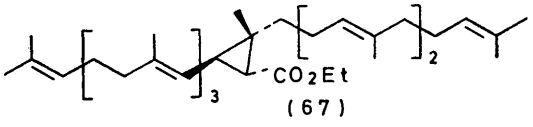
(64)



(65)



(66)



(67)

[38] G. Popják, J. Edmond, and Sih-May Wong, *J. Amer. Chem. Soc.*, 1973, **95**, 2713.

[39] *Cf.* Om. P. Vig, J. C. Kapur, J. Singh, and B. Vig, *Indian J. Chem.*, 1969, **7**, 574.

spectral data. The C_{40} alcohols showed spectral data closely similar to those of the two isomers of synthetic (±)-presqualene alcohol, assigned the stereochemistries shown in (53) and (54), and europium shift data similar to those recorded for (53) and (54) were obtained (see Figures 11 and 12).

The stereochemistry of naturally derived prephytoene alcohol is not known with the same certainty as that of presqualene alcohol, although it would be surprising if the stereochemistry of the substituents on the cyclopropane rings in the two molecules differed. The triacetate (60) has been identified as a degradation product of natural prephytoene alcohol, and this has established the 1,3-*trans*-geometry of the substituents in (68), similar to that found in presqualene alcohol. Rilling and his colleagues have independently synthesised prephytoene alcohol, and, like ourselves, have concluded that the naturally derived alcohol has the stereochemistry shown in (68). The same workers have also been able to demonstrate that synthetic tritium-labelled (±)-prephytoene (8a) is converted into carotenoids by a bacterial extract, from a species of *Mycobacteria*, in 34—45% of theoretical yield. We have prepared tritium-labelled (68) by reduction of the corresponding C_{40} ester with lithium aluminium tritiide, and samples are under biosynthetic examination.

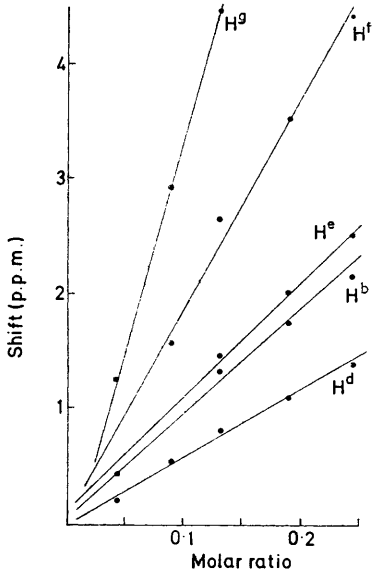


FIGURE 11 Eu(hfod)$_3$-induced shift response of the cyclopropylmethanol (68) signals in the n.m.r. spectrum (0·059 mmol in 0·21 ml)

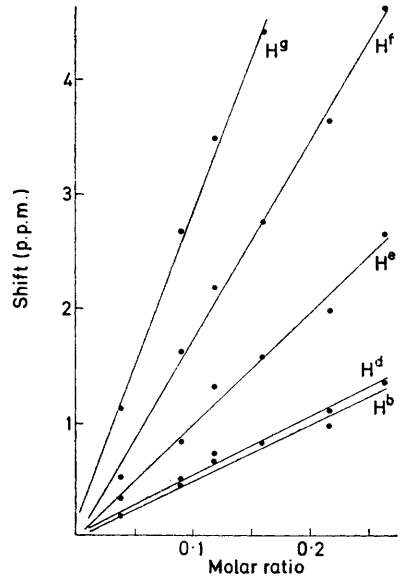
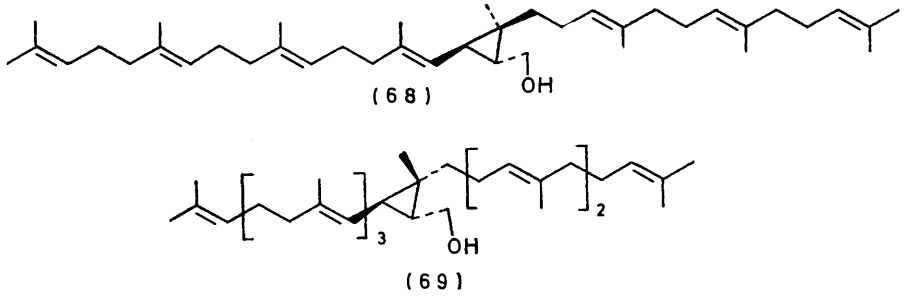


FIGURE 12 Eu(hfod)$_3$-induced shift response of the cyclopropylmethanol (69) signals in the n.m.r. spectrum (0·089 mmol in 0·21 ml)



EXPERIMENTAL

^{1}H N.m.r. spectra were determined with a Perkin-Elmer R10 or a Varian HA-100 spectrometer, with tetramethylsilane as internal standard. Bands were singlets except where stated otherwise; splittings (J) are in Hz. ^{13}C N.m.r. spectra were recorded on a JEOL JNM-PS-100 spectrometer. Molecular weights were determined from mass spectra, measured with an A.E.I. MS 902 spectrometer. Radioactivity data were measured with a Nuclear Enterprises 8310B counter, for solutions in dioxan.

Analytical g.l.c. was performed on a Pye 104 instrument by using 50 ft SCOT capillary columns at the temperatures specified. For preparative layer chromatography, layers of fluorescent silica gel HF_{254} on 20 × 20 cm or 18 × 18 in plates were employed. All solvents for chromatography were carefully redistilled. Unless stated otherwise all organic solutions were dried over anhydrous magnesium sulphate.

The αβ-Unsaturated Esters.—(Z)- *and* (E)-*Methyl 3,7-dimethylocta-2,6-dienoate* [(30) *and* (31)]. A 1 : 2 mixture

of *Z*- and *E*-isomers of citral (15 g) was added during 1 h to a stirred suspension of freshly precipitated silver oxide (from 34 g $AgNO_3$ and 8 g NaOH) in water (100 ml). The mixture was stirred at 25° for 18 h, then filtered, and the filtrate was acidified with hydrochloric acid and then extracted with ether. The combined extracts were washed (H_2O), dried, and evaporated to leave a mixture of isomers of 3,7-dimethylocta-2,6-dienoic acid (13·2 g, 80%) as a pale yellow oil. A mixture of the acid (11 g) and anhydrous potassium carbonate (9·7 g) in acetone (100 ml) was stirred and heated to gentle reflux, and then treated dropwise during 0·5 h with dimethyl sulphate (8 g). The mixture was heated for a further 2 h, then cooled and filtered. Evaporation of the filtrate and distillation of the residue produced a mixture of isomers of the ester (12 g) as an almost colourless oil, b.p. 63° at 0·3 mmHg. Preparative layer chromatography on silica [5% ether–light petroleum (b.p. 40—60°) as eluant] gave (a) *Z*-methyl 3,7-dimethylocta-2,6-dienoate (eluted first), n_D^{19} 1·4695, $\nu_{max.}$ 1722, 1652, and 850 cm^{-1}, τ 4·35 (m, :CH·CO), 4·85 (m, :CH), 6·38 (OMe), 7·2—7·5 (2H), 7·6—7·9 (2H), 8·15 (d, *J* 2, :CMe), 8·3 (Me), and 8·4 (Me) [g.l.c. (OV-225; 140°) showed one major peak (>98%)]; and (b) the *E*-isomer (eluted second), n_D 1·4710, $\nu_{max.}$ 1722, 1652, 866, and 732 cm^{-1}, τ 4·31 (m, :CHCO), 4·85 (m, :CH), 6·37 (OMe), 7·85 (d, *J* 2, :CMe), *ca.* 7·9 (obscured, 4H), 8·31 (Me), and 8·41 (Me) [g.l.c. showed one major peak (>98%), cleanly resolved from the *Z*-isomer].

Ethyl (2E,6E)-3,7,11-*trimethyldodeca*-2,6,10-*trienoate* [*ethyl* (2E,6E)-*farnesoate*] (39; R = Et). A sample containing a mixture of geometrical isomers of ethyl farnesoate was chromatographed in ether–light petroleum (b.p. 40—60°) (5 : 95) on alumina (t.l.c. control) to separate the (2*E*,6*E*)-isomer (eluted last). Distillation gave isomerically homogenous ester (g.l.c. on SCOT 50 ft OV-225 and DEGS; 160°), b.p. 118—120° at 0·01 mmHg, $\nu_{max.}$ 1715 and 1645 cm^{-1}, τ 4·40 (:C*H*·CO_2Et), 4·92br (2 × :CH), 5·92 (q, *J* 8, CH_2·CH_3), 7·85 (:CMe), 7·85—8·05 (8H), 8·32 (:CMe), 8·40 (2 × *CMe*), and 8·75 (t, *J* 8, CH_2·CH_3) (Found: C, 77·7; H, 10·4. Calc. for $C_{17}H_{28}O_2$: C, 77·45; H, 10·65%).

A mixture of isomers of methyl farnesoate was obtained from commercial farnesol according to the procedure of Corey *et al.*[35] (MnO_2–MeOH–NaCN–HOAc). Extensive chromatography gave: (i) methyl (2*Z*,6*E*)-farnesoate (eluted first), n_D^{22} 1·4815, $\nu_{max.}$ (film) 1723 and 1651 cm^{-1}, τ 4·38 (:C*H*·CO_2Me), 4·9br (2 × CH), 6·38 (OMe), 7·2—8·2 (8H), 8·11 (:CMe), 8·33 (:CMe), and 8·4 (2 × :CMe); and (ii) the (2*E*,6*E*)-isomer (eluted second), n_D^{20} 1·4841 (lit.,[32] n_D^{22} 1·4840), τ 6·37 (OMe).

all-E-*Methyl* 3,7,11,15-*tetramethylhexadeca*-2,6,10,14-*tetraenoate* (62; R = Me). A mixture of isomers of commercial farnesylacetone was purified prior to use by spinning-band distillation to separate the (5*E*,9*E*)-isomer, b.p. 98—100° at 0·05 mmHg, n_D^{23} 1·4795 (lit.,[32] n_D^{20} 1·4815), $\nu_{max.}$ 1715 and 1155 cm^{-1}, τ 4·90br (3 × :CH), 7·45—7·8 (CH_2), 7·89 (COMe), 7·9—8·1 (10H), 8·3 (Me), and 8·41 (3 × Me) (Found: C, 82·5; H, 11·5%; *m/e*, 262·2301. Calc. for $C_{10}H_{30}O$: C, 82·4; H, 11·5%; *M*, 262·2296).

A solution of methyl di-*O*-ethylphosphonoacetate (20 g) in 1,2-dimethoxyethane (25 ml) was added to a stirred suspension of sodium hydride (3·0 g) in 1,2-dimethoxyethane (200 ml) and the mixture was stirred under nitrogen at 25° until hydrogen evolution ceased (*ca.* 1 h). (5*E*,9*E*)-Farnesylacetone (16·2 g) in 1,2-dimethoxyethane (200 ml) was added during 0·7 h, and the mixture was stirred at 65° for 1 h, and then at 25° for 18 h.[39] The mixture was poured onto water and then extracted with ether. Evaporation of the washed (H_2O) and dried extracts left a residue (21 g) which was chromatographed in 5% ether–light petroleum (b.p. 40—60°) to give (a) the (2Z,7E,11E)-*tetraenoate* (3 g) (eluted first), $\nu_{max.}$ 1710 cm^{-1}, τ 4·32 (:C*H*·COMe), 4·94br (3 × :CH), 6·38 (OMe), 7·8—8·1 (12H), 8·15 (d, *J ca.* 2, :CMe), 8·34 (Me), and 8·41 (3 × Me) (Found: *m/e*, 318·2557. $C_{21}H_{34}O_2$ requires *M*, 318·2557), and (b) the (2E,7E,11E)-*tetraenoate* (7 g) (eluted second), $\nu_{max.}$ 1710 and 1642 cm^{-1}, τ 4·36 (:C*H*·CO_2Me), 4·94br (3 × CH), 6·38 (OMe), 7·85 (d, *J ca.* 2, :CMe), 7·9—8·05 (12H), 8·34 (Me), and 8·41 (3 × Me) (Found: C, 79·2; H, 10·8%; *m/e*, 318·2557. $C_{21}H_{34}O_2$ requires C, 79·5; H, 10·65%).

Geraniol and Nerol.—The alcohols, obtained from Fluka Chemical Co., were shown to be isomerically homogenous in g.l.c. analysis (OV-225 at 112°).

Farnesol.—Various commercial samples of farnesol were examined for geometrical isomers by g.l.c. (50 ft OV-225 SCOT capillary; 132°). A sample rich (>60%) in the (2*E*,6*E*)-isomer and containing *ca.* 30% (2*Z*,6*E*)- and *ca.* 5% (2*Z*,6*Z*)-isomers was used in the present studies.

all-E-3,7,11,15-*Tetramethylhexadeca*-2,6,10,14-*tetraen*-1-*ol.* (63).—A solution of all-*E*-methyl 3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenoate (15·3 g) in dry ether (20 ml) was added to a stirred suspension of lithium aluminium hydride (4 g) in ether (50 ml) at such a rate as to maintain gentle reflux. The mixture was heated under reflux for 0·75 h, then cooled to 25°, and treated, cautiously at first, with saturated ammonium chloride solution. The ethereal solution was separated, then washed (H_2O), dried, and evaporated to leave the alcohol as an oil. Distillation gave a sample, b.p. 114—119° at 0·05 mmHg, n_D^{24} 1·4920 (lit.,[39] n_D^{18} 1·4962), $\nu_{max.}$ 3400, 1660, 1100, 1005, and 835 cm^{-1}, τ 4·6 (t, *J* 7, :C*H*·CH_2·OH), 4·9br (3 × :CH), 5·91 (d, *J* 7, CH_2·OH), 7·51 (OH, disappears on treatment with D_2O), 7·8—8·15 (6 × CH_2), and 8·32 and 8·39 (5 × :CMe) (Found: *m/e*, 290·2620. Calc. for $C_{20}H_{34}O$: *M*, 290·2609), homogenous in g.l.c. (OV-229; 180°).

Preparation of Phenyl Sulphones; General Procedure.—Phosphorus tribromide (0·38 mol. equiv.) was added dropwise during 1·5 h to a cooled (0 ± 1°) and stirred solution of the alcohol (1 mol. equiv.) and dry pyridine (*ca.* 2 mol. equiv.) in ether, and with rigorous exclusion of light. The mixture was warmed to 25° during 1 h, and was then poured onto iced water and extracted with ether. The combined extracts were washed successively with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water and then dried. Evaporation, and distillation of the residue gave the corresponding bromides, as pale yellow liquids.

The bromide (1 mol. equiv.) was added dropwise during 2 h to a stirred solution of sodium benzenesulphinate (1 mol. equiv.) in dry methanol, and the mixture was stirred at 25° for 1 h. The methanol was then distilled off as water was slowly added to maintain a constant volume. The mixture was extracted with methylene chloride, and the extracts were washed with water, dried, and evaporated to leave the sulphone, which was either used directly in the next stage or purified by preparative t.l.c. [silica gel HF 254; 5% ether–light petroleum (b.p. 40—60°) as eluant].

3-*Methylbut*-2-*enyl phenyl sulphone* (14). By the general procedure, 3-methylbut-2-en-1-ol was converted into the corresponding bromide (50%), b.p. 86—96° at 150 mmHg

(lit., 64—68° at 70 mmHg), $n_D^{22.5}$ 1·4856, $\nu_{max.}$ (film) 1665, 1453, 1380, and 1205 cm^{-1}, τ 4·49 (m, *J* 9, :CH), 6·08 (d, *J* 9, :CH·C*H*$_2$), 8·22 (Me), and 8·27 (Me), which gave the sulphone as needles [from light petroleum (b.p. 60—80°)], m.p. 50—52° (lit.,[30] 54—56°), $\nu_{max.}$ (KBr) 1585, 1452, 1305, 1250, 1154, 1135, 1085, 1030, 780, 745, and 690 cm^{-1}, τ 2·0—2·4 (m, 5 × aryl :CH), 4·83 (t, *J* 9, :C*H*·CH$_2$), 6·31 (d, *J* 9, :CH·C*H*$_2$), 8·29 (Me), and 8·66 (Me).

(2E)-3,7-*Dimethylocta*-2,6-*dienyl phenyl sulphone* (*geranyl phenyl sulphone*) (27). By the general procedure, geraniol was converted into the corresponding bromide (82%), b.p. 73—75° at 1·5 mmHg (lit.,[40] 87—89° at 0·05 mmHg), $\nu_{max.}$ (film) 3900, 1653, 1450, 1380, 1195, 1100, and 835 cm^{-1}, τ 4·48 (t, *J ca.* 9, :C*H*·CH$_2$Br), 4·93br (:C*H*), 6·02 (d, *J* 9, CH$_2$Br), 7·8—8·0 (m, 4H), 8·3 (2 × Me), and 8·4 (Me). This gave the sulphone as a pale yellow *liquid*, which after purification by chromatography showed $\nu_{max.}$ 1145, 1080, and 895 cm^{-1}, τ 2·0—3·0 (m, 5 × aryl :CH), 4·82 (t, *J* 9, :C*H*·CH$_2$S), 4·98br (partly obscured, :C*H*), 6·2 (d, *J* 9, :CH·C*H*$_2$·S), 7·9—8·1 (m, 4H), 8·32 (Me), 8·41 (Me), and 8·69 (Me) (Found: *m/e*, 278·1326. $C_{16}H_{22}O_2S$ requires *M*, 278·1340). G.l.c. analysis (OV-225; 200°) showed one major peak (>98%).

(2Z)-3,7-*Dimethylocta*-2,6-*dienyl phenyl sulphone* (*neryl phenyl sulphone*) (26). By the general procedure, nerol was converted into the corresponding bromide (72%), b.p. 63—64° at 0·6 mmHg (lit.,[40] 73—75° at 0·05 mmHg), $\nu_{max.}$ (film) 2900, 1650, 1450, 1380, 1200, and 850 cm^{-1}, τ 4·5 (t, *J* 9, :C*H*·CH$_2$Br), 4·9br (:CH), 6·07 (d, *J* 9, CH$_2$Br), 7·8—8·0 (m, 4H), 8·25 (Me), 8·33 (Me), and 8·41 (Me). Reaction of the bromide with sodium benzenesulphinate in tetrahydrofuran gave the *sulphone*, which was purified by chromatography and showed $\nu_{max.}$ 1145, 1130, and 970 cm^{-1}, τ 2·0—2·8 (m, 5 × aryl :CH), 4·83 (t, *J* 9, :C*H*·CH$_2$S), *ca.* 5·0br (partly obscured, :CH), 6·2 (d, *J* 9, :CH·C*H*$_2$S), 8·1—8·3 (m, 4H), 8·35 (Me), 8·4 (Me), and 8·5 (Me) (Found: *m/e*, 278·1326. $C_{16}H_{22}O_2S$ requires *M*, 278·1340). G.l.c. analysis (OV-225; 200°) showed one major peak (>93%); a minor less volatile constituent co-chromatographed with the isomeric geranyl phenyl sulphone.

3,7,11-*Trimethyldodeca*-2,6,10-*trienyl phenyl sulphone* (*farnesyl phenyl sulphone*) (37). By the general procedure, farnesol [containing a mixture of the (2*E*,6*E*)-, (2*Z*,6*E*)-, and (2*Z*,6*Z*)-isomers in the approximate proportions 20 : 11 : 1] was converted into the corresponding bromide (85%), b.p. 100—110° at 0·15 mmHg, n_D^{20} 1·5010 (lit., b.p. 122—132° at 10 mmHg, n_D^{20} 1·5055), $\nu_{max.}$ 1105, 990, and 900 cm^{-1}, τ 4·48 (t, *J* 9, :C*H*·CH$_2$Br), *ca.* 4·91br (2 × :CH), 6·05 (d, *J* 9, CH$_2$Br), 7·8—8·03 (m, 8H), and 8·31 and 8·39 (4 × :CMe).

Reaction of the bromide with sodium benzenesulphinate gave (*ca.* 55%) a mixture of isomeric sulphones as a pale yellow oil. Purification by elution chromatography gave (a) (2E,6E)-3,7,11-*trimethyldodeca*-2,6,10-*trienyl phenyl sulphone* (eluted second), an oil, $\nu_{max.}$ 1660, 1450, 1380, 1320, 1140, and 1080 cm^{-1}, τ 2·0—3·0 (m, 5 × aryl :CH), 4·83 (t, *J* 8, :C*H*·CH$_2$S), *ca.* 5·00br (2 × CH), 6·3 (d, *J* 8, :CH·C*H*$_2$S), 7·9—8·1 (8H), 8·32 (Me), 8·40 (2 × Me), and 8·65 (*Me*C:CHCH$_2$S) (Found: C, 72·85; H, 8·85%; *m/e*, 346. $C_{21}H_{30}O_2S$ requires C, 72·8; H, 8·7%; *M*, 346); and (b) the (2Z,6E)-*isomer* (eluted first), $\nu_{max.}$ 1655, 1585, 1455, 1383, 1320, 1310, 1240, 1150, and 1080 cm^{-1}, τ 2·0—2·9 (m, 5 × aryl :CH), 4·7—5·1br (3 × CH), 6·36 (d, *J* 8, :C*H*·CH$_2$S), 8·0—8·2 (8H), and 8·28, 8·35, 8·43, and 8·47 (4 × :CMe) (Found: *m/e*, 346).

3,7,11,15-*Tetramethylhexadeca*-2,6,10,14-*tetraenyl phenyl sulphone* (*geranylgeranyl phenyl sulphone*) (64). By the general procedure, the all-*E*-alcohol (63) was converted into the corresponding bromide (84%), $\nu_{max.}$ 1650, 1010, 840, and 805 cm^{-1}, τ 4·44 (t, *J* 8, :C*H*·CH$_2$Br), 4·90br (3 × :CH), 5·99 (d, *J* 8, CH$_2$Br), 7·8—8·10 (12H), and 8·30 and 8·39 (5 × :CMe) (Found: C, 67·3; H, 10·25%; M^+, 352·1742/354·1759. Calc. for $C_{20}H_{33}Br$: C, 67·9; H, 9·35%; *M*, 352·1746/354·1766). Reaction of the bromide with sodium benzenesulphinate gave a mixture of (2*Z*)- and (2*E*)-isomers of the sulphone (*ca.* 65%) as a viscous oil. Purification by elution chromatography gave: (a) the all-E-*sulphone* (eluted second) n_D^{23} 1·5220, $\nu_{max.}$ 1660, 1145, 1080, 840, 770, 737, and 685 cm^{-1}, τ 1·95—2·5 (5 × aryl :CH), 4·8br (:C*H*·CH$_2$S), 4·92br (3 × :C*H*), 6·21 (d, *J* 8, CH$_2$S), 7·8—8·1 (12H), 8·3 and 8·39 (5 × :CMe), and 8·67 (*Me*C:CH·CH$_2$S) (Found: C, 74·9; H, 9·1%; *m/e*, 414·2591. $C_{26}H_{38}O_2$ requires C, 75·3; H, 9·2%; *M*, 414·2591); (b) the (2*Z*,6*E*,10*E*)-sulphone (eluted first).

Preparation of Cyclopropanecarboxylates; General Procedure.—A solution of the sulphone (0·006 mol) in dry DMF (5 ml) was added to a stirred solution of potassium t-butoxide (0·018 mol: freshly prepared) in DMF (30 ml) at 25° under nitrogen. The mixture was stirred for 0·25 h and then treated during 10 min with a solution of the unsaturated ester (0·012 mol) in DMF (5 ml). After being stirred at 25° for 3 h the mixture was poured onto ice–dilute hydrochloric acid, and then extracted with ether. The combined extracts were washed successively with sodium hydrogen carbonate solution and water, then dried and evaporated. Isomerically homogeneous samples of the cyclopropanecarboxylates were then obtained by preparative layer chromatography on silica gel [5% ether–light petroleum (b.p. 40—60°) as eluant].

Ethyl (±)-trans-*Chrysanthemate* (18; R = Et). By the general procedure, methylbutenyl phenyl sulphone and ethyl 3-methylbut-2-enoate produced a mixture of cyclopropanecarboxylates which was purified by chromatography and gave (a) ethyl (±)-*trans*-chrysanthemate (eluted second), $\nu_{max.}$ 1721 cm^{-1}, τ see ref. 31 (Found: C, 73·35; H, 10·1%; *m/e*, 196·1462. Calc. for $C_{12}H_{20}O_2$: C, 73·4; H, 10·3%; *M*, 196·1463); and (b) t-butyl (±)-*trans*-chrysanthemate (eluted first), $\nu_{max.}$ 1720 cm^{-1}, τ 8·8 (CMe_3) and as in ref. 31 (Found: C, 75·5; H, 10·4%; *m/e*, 224·1776. Calc. for $C_{14}H_{24}O_2$: C, 74·95; H, 10·8%; *M*, 224·1772).

Condensation between equimolar quantities of the sulphone and the unsaturated ester in THF, in the presence of 2 equiv. of potassium t-butoxide at 0° for 40 h, produced, after chromatography in 5 ⟶ 40% ether in light petroleum (b.p. 40—60°) (a) ethyl (±)-*trans*-chrysanthemate (eluted first), unresolved from ethyl 3-methylbut-2-enoate; (b) 2,7-dimethyl-5-phenylsulphonylocta-2,6-dien-4-one (16),[29] m.p. 104—105°, $\nu_{max.}$ (KBr) 1682 cm^{-1}, τ 2·0—2·4 (m, 5H), 3·49br (:CH·CO), 4·54 (d, *J* 10, :C*H*·CH), 5·19 (d, *J* 10, :CH·C*H*), 7·85 (Me), 8·03 (Me), 8·22 (Me), and 8·54 (Me) (Found: C, 65·6; H, 6·9%; *m/e*, 292. Calc. for $C_{16}H_{20}O_3S$: C, 65·7; H, 6·9%; *M*, 292); and (c) ethyl 3,3,6-trimethyl-4-phenylsulphonylhept-5-enoate (20; R = Et), characterised as the corresponding acid, m.p. 100—105° (lit.,[29] 108°), $\nu_{max.}$ (KBr) 1693 cm^{-1}, τ 2·0—2·4 (m, 5H), 4·65 (d, *J* 12, :C*H*·CH), 5·51 (d, *J* 12, :CH·C*H*), 6·64 (d, *J* 17, C*H*H), 7·53 (d, *J* 17, CH*H*), 8·39 (Me), 8·55 (Me),

[40] N. F. Blau, T. T. S. Wang, and C. M. Buess, *J. Chem. Eng. Data*, 1970, **15**, 206.

8·85 (Me), and 9·14 (Me) (Found: *m/e*, 310. Calc. for $C_{16}H_{22}O_4S$: *M*, 310).

Ethyl trans-3-[(1E)-2,6-*dimethylhepta*-1,5-*dienyl*]-2,2-*dimethylcyclopropanecarboxylate* (29). By the general procedure, geranyl phenyl sulphone and ethyl 3-methylbut-2-enoate produced the *ester* (*ca.* 50%), which was purified by chromatography and showed $\nu_{max.}$ 1720, 1110, and 860 cm^{-1}, τ 4·92br (partly obscured, :CH), 5·1 (d, *J ca.* 8, :CH), 5·86 (q, *J* 7, $CH_2{\cdot}CH_3$), 7·8—8·1 (m, 4H), 8·32 (2 × :CMe), 8·41 (:CMe), 8·64 (d, *J ca.* 6, $CH{\cdot}CH$), *ca.* 8·75 (t, *J* 7, $CH_3{\cdot}CH_2$), 8·75 (Me), and 8·88 (Me) (Found: *m/e*, 264·2088. $C_{17}H_{28}O_2$ requires *M*, 264·2089). G.l.c. analysis showed one peak only (OV-225; 160°).

Ethyl trans-3-[(1Z)-2,6-*dimethylhepta*-1,5-*dienyl*]-2,2-*dimethylcyclopropanecarboxylate* (28). By the general procedure, neryl phenyl sulphone and ethyl 3-methylbut-2-enoate produced the *ester* (*ca.* 45%), which was purified by chromatography and showed $\nu_{max.}$ 1720, 1110, and 860 cm^{-1}, τ 4·92br (partly obscured, :CH), 5·1 (d, *J* 8, :CH), 5·88 (q, *J* 7, $CH_2{\cdot}CH_3$), 7·7—8·0 (m, 4H), 8·31 (2 × :CMe), 8·41 (:CMe), 8·64 (d, *J ca.* 6, $CH{\cdot}CH$), 8·76 (t, *J* 7, $CH_2{\cdot}CH_3$), 8·76 (Me), and 8·88 (Me) (Found: *m/e*, 264·2087. $C_{17}H_{28}O_2$ requires *M*, 264·2088). G.l.c. analysis showed one major peak (>95%) which was completely resolved from the ester obtained from geranyl phenyl sulphone.

C-2 *Epimers of methyl* 2-*methyl*-2-(4-*methylpent*-3-*enyl*)-trans-3-(2-*methylprop*-1-*enyl*)*cyclopropanecarboxylate* [(32) *and* (33)]. By the general procedure, methyl (2*E*)-3,7-dimethylocta-2,6-dienoate and methylbutenyl phenyl sulphone produced a mixture of C-2 epimers of the cyclopropane esters (*ca.* 60%). Chromatography separated (a) the t-2-*methyl*-2-(4-*methylpent*-3-*enyl*)-t-3-(2-*methylprop*-1-*enyl*)*cyclopropane*-r-1-*carboxylate* (eluted first), an oil, n_D^{19} 1·4810, $\nu_{max.}$ 1720 cm^{-1}, τ 4·9br (:CH), 5·1 (d, *J* 8, :CH), 6·37 (OMe), 7·8—8·2 (m, 5H), 8·31 (3 × :CMe), 8·40 (:CMe), 8·7 (d, *J ca.* 6, $CH{\cdot}CH$), and 8·89 (Me) (Found: *m/e*, 250·1936. $C_{16}H_{26}O_2$ requires *M*, 250·1933); (b) the c-2-*methyl*-2-(4-*methylpent*-3-*enyl*)-t-3-(2-*methylprop*-1-*enyl*)-*cyclopropane*-r-1-*carboxylate* (eluted second), an oil, n_D^{19} 1·4795, $\nu_{max.}$ 1720 cm^{-1}, τ 4·9br (:CH), 5·1 (d, *J* 8, :CH), 6·36 (OMe), 7·7—8·1 (m, 5H), 8·3 (3 × :CMe), 8·4 (:CMe), *ca.* 8·7 (1H), and 8·75 (Me) (Found: *m/e*, 250·1948).

Ethyl 2,2-*dimethyl*-trans-3-[(1E,5E)-2,6,10-*trimethylundeca*-1,5,9-*trienyl*]*cyclopropanecarboxylate* (40). By the general procedure, farnesyl phenyl sulphone and ethyl 3-methylbut-2-enoate produced the ester (*ca.* 45%), which was purified by chromatography and showed $\nu_{max.}$ 1722, 1026, and 850 cm^{-1}, τ 4·95br (d, 2 × :CH), 5·15 (d, *J* 8, :CH), 5·95 (q, *J* 7, $CH_2{\cdot}CH_3$), 7·75—8·1 (m, 4H), 8·32 (3 × :CMe), 8·42 (:CMe), 8·76 (Me), 8·76 (t, *J* 7, $CH_2{\cdot}CH_3$), and 8·88 (Me) (Found: *m/e*, 332·2719. $C_{22}H_{36}O_2$ requires *M*, 332·2715). G.l.c. analysis (OV-225; 170°) showed one major constituent (>98%). In some experiments, the corresponding *t-butyl ester* (eluted first in t.l.c.), $\nu_{max.}$ 1720 and 850 cm^{-1}, τ 4·95br (d, 2 × :CH), 5·15 (d, *J* 8, :CH), 7·8—8·1 (m, 4H), 8·32 (3 × :CMe), 8·42 (:CMe), 8·58 (CMe_3), 8·78 (Me), and 8·89 (Me) (Found: *m/e*, 360·3048. $C_{24}H_{40}O_2$ requires *M*, 360·3028), was concurrently produced (⩾5%).

C-2 *Epimers of ethyl* 2-[(E)-4,8-*dimethylnona*-3,7-*dienyl*]-2-*methyl*-trans-3-(2-*methylprop*-1-*enyl*)*cyclopropanecarboxylate* [(44) *and* (45)]. By the general procedure, methylbutenyl phenyl sulphone and ethyl (2*E*,6*E*)-farnesoate produced (*ca.* 50%) a mixture of C-2 epimers of the cyclopropane esters. Chromatography gave (a) the c-2-[(E)-4,8-*dimethylnona*-3,7-*dienyl*]-2-*methyl*-t-3-(2-*methylprop*-1-*enyl*)-*cyclopropane*-r-1-*carboxylate* (eluted first), an oil, $\nu_{max.}$ 1719 and 856 cm^{-1}, τ 4·9br (4 × :CH), 5·1 (d, *J* 8, :CH), 5·9 (q, *J* 7, $CH_2{\cdot}CH_3$), 7·9—8·1 (m, 8H), 8·31 (:CMe), 8·42 (2 × :CMe), 8·75 (t, *J* 7, $CH_2{\cdot}CH_3$), and 8·88 (Me) (Found: *m/e*, 332·2684. $C_{22}H_{36}O_2$ requires *M*, 332·2715) [g.l.c. analysis (OV-225; 175°) showed one major peak (>95%)]; and (b) the t-2-[(E)-4,8-*dimethylnona*-3,7-*dienyl*]-2-*methyl*-t-3-(2-*methylprop*-1-*enyl*)*cyclopropane*-r-1-*carboxylate*, an oil, $\nu_{max.}$ 1719 and 856 cm^{-1}, τ 4·9br (4 × :CH), 5·1 (d, *J* 8, :CH), 5·9 (q, *J* 7, $CH_2{\cdot}CH_3$), 7·8—8·1 (m, 8H), 8·31 (:CMe), 8·42 (2 × :CMe), 8·75 (Me), and 8·75 (t, *J* 7, $CH_2{\cdot}CH_3$) (Found: *m/e*, 332·2714) (g.l.c. showed one major peak).

Also separated by chromatography were: (a) a partially resolved fraction (eluted before the ethyl esters) containing the corresponding t-butyl ester, τ 8·58 (CMe_3), and (b) ethyl (4E,6E)-3,7,11-*trimethyldodeca*-4,6,10-*trienoate* (eluted last) (*ca.* 30%), $\lambda_{max.}$ 236 (log ε 4·24) and 240 nm (4·27), $\nu_{max.}$ 1732 and 965 cm^{-1}, τ 3·84 (dd, *J* 11 and 15, :CH·CH:CH), 4·33 (d, *J* 11, :CH·CH), 4·61 (dd, *J* 15 and 8, HC:CH·CH), 4·97br (:CH), 5·96 (q, *J* 7, $CH_2{\cdot}CH_3$), 8·0 (4H), 8·3 (:CMe), 8·36 (:CMe), 8·43 (:CMe), 8·79 (t, *J* 7, $CH_2{\cdot}CH_3$), and 8·95 (d, *J* 6, CH*Me*) (Found: *m/e*, 264·2079. $C_{17}H_{28}O_2$ requires *M*, 264·2089).

C-2 *Epimers of ethyl* 2-[(E)-4,8-*dimethylnona*-3,7-*dienyl*]-2-*methyl*-trans-3-[(1E,5E)-2,6,10-*trimethylundeca*-1,5,9-*trienyl*]*cyclopropanecarboxylate* [(49) *and* (50)]. By the general procedure, the (2*E*,6*E*)-farnesyl sulphone and ethyl (2*E*,6*E*)-farnesoate produced a mixture of C-2 epimers of the cyclopropane ester (*ca.* 45%). Chromatography separated (a) the c-2-(4,8-*dimethylnonadienyl*)-2-*methyl*-t-3-(2,6,10-*trimethylundecatrienyl*)*cyclopropane*-r-1-*carboxylate* (*ca.* 13%) (eluted first), $\nu_{max.}$ 1720 and 975 cm^{-1}, τ 4·85br (4 × :CH), 5·06 (d, *J* 8, :CH), 5·86 (q, *J* 7, $CH_2{\cdot}CH_3$), 7·9—8·1 (16H), 8·32 (3 × :CMe), 8·4 (4 × :CMe), 8·6 (d, *J* 5, $CH{\cdot}CH$), 8·74 (t, *J* 8, $CH_2{\cdot}CH_3$), and 8·87 (Me) (Found: *m/e*, 468·3959. $C_{32}H_{52}O_2$ requires *M*, 468·3967) [G.l.c. (50 ft DEGS and OV-210 SCOT columns) showed one major peak (>98%)]; (b) the t-2-(4,8-*dimethylnona*-3,7-*dienyl*)-2-*methyl*-t-3-(2,6,10-*trimethylundecatrienyl*)*cyclopropane*-r-1-*carboxylate* (*ca.* 30%) (eluted second), $\nu_{max.}$ 1720 and 975 cm^{-1}, τ 4·85br (4 × :CH), 5·03 (d, *J* 8, :CH), 5·83 (q, *J* 7, $CH_2{\cdot}CH_3$), 7·9—8·1 (16H), 8·32 (3 × :CMe), 8·40 (4 × :CMe), 8·55 (d, *J* 5·2, $CH{\cdot}CH$), 8·73 (t, *J* 7, $CH_2{\cdot}CH_3$), and 8·73 (Me) (Found: *m/e*, 468·3958) [g.l.c. (as above) showed one major peak (>90%)]; and (c) ethyl (4*E*,6*E*)-3,7,11-trimethyldodeca-4,6,10-trienoate (eluted last) (33%), spectrally identical with that obtained previously.

C-2 *Epimers of ethyl* 2-*methyl*-trans-3-[(1E,5E,9E)-2,6,10,14-*tetramethylpentadeca*-1,5,9,13-*tetraenyl*]-2-[(3E,7E)-4,8,12-*trimethyltrideca*-3,7,11-*trienyl*]*cyclopropanecarboxylate* [(66) *and* (67)]. By the general procedure, (2*E*,6*E*,10*E*)-geranylgeranyl sulphone and ethyl (2*E*,6*E*,10*E*)-geranylgeranoate produced a mixture of C-2 epimers of the cyclopropane ester (*ca.* 45%). Chromatography separated (a) the t-2-*methyl*-t-3-(*tetramethylpentadecatetraenyl*)-2-(*trimethyltridecatrienyl*)*cyclopropane*-r-1-*carboxylate* (*ca.* 22%) (eluted first), $\nu_{max.}$ 1715 cm^{-1}, τ 4·91br (6 × :CH), 5·10 (d, *J* 8, :CH), 5·9 (q, *J* 7, $CH_2{\cdot}CH_3$), 7·85—8·1 (24H), 8·32 and 8·41 (9 × :CMe), 8·61 (d, *J* 5, $CH{\cdot}CH$), 8·78 (t, *J* 7, $CH_2{\cdot}CH_3$), and 8·88 (Me) (Found: *m/e*, 604·5214. $C_{42}H_{68}O_2$ requires *M*, 604·5219) [g.l.c. (50 ft OV-17 SCOT; 190°) showed one major peak (>98%)]; (b) the c-2-*methyl*-t-3-(*tetramethylpentadecatetraenyl*)*trimethyltridecatrienyl*)*cyclopropane*-r-1-*carboxylate* (*ca.* 22%) (eluted second), $\nu_{max.}$ 1715 cm^{-1}, τ 4·88br (6 × :CH), 5·06 (d, *J* 8, :CH), 5·87 (q,

J 7, CH_2·CH_3), 7·85—8·1 (24H), 8·33 and 8·41 (9 × :CMe), 8·59 (d, *J* 5, *CH*·CH), 8·75 (Me), and 8·76 (t, *J* 7, CH_2·CH_3) (Found: *m/e*, 604·5252) [g.l.c. (50 ft OV-17, OV-225, OV-1 DEGS SCOT columns; 170—190°) showed one major peak (>98%)]; and (c) ethyl (4*E*,6*E*,10*E*)-3,7,11,15-tetramethylhexadeca-4,6,10,14-tetraenoate (40%) (eluted last), $\nu_{max.}$ 1730, 1010, and 960 cm^{-1}, τ 3·82 (dd, *J* 11 and 15, :CH·C*H*:CH), 4·31 (d, *J* 11, :C*H*·CH), 4·58 (dd, *J* 8 and 15, HC:C*H*·CH), 4·95br (2 × :C*H*), 5·94 (q, *J* 7, CH_2·CH_3), 7·9—8·05 (8H), 8·28, 8·34, and 8·41 (4 × :CMe), 8·77 (t, *J* 7, CH_2·CH_3), and 8·93 (d, *J* 6, CH*Me*), *m/e* 332 ($C_{22}H_{36}O_2$).

Preparation of Cyclopropylmethanols; General Procedure.—A solution of the cyclopropanecarboxylate (*ca.* 0·2 g) in dry ether (2 ml) was added to a suspension of lithium aluminium hydride (LAH) (*ca.* 0·04 g) in dry ether (2 ml). The mixture was heated under reflux for 0·5 h, and cooled to *ca.* 10°; then a saturated solution of ammonium chloride was added to give two clear liquid phases. The ethereal layer was separated, washed (H_2O), dried, and evaporated. Preparative layer chromatography on silica gel [25% ether–light petroleum (b.p. 40—60°)] as eluant gave the pure alcohols.

2,2-*Dimethyl*-trans-3-[(1E,5E)-2,6,10-*trimethylundeca*-1,5,9-*trienyl*]*cyclopropylmethanol* (42).—By the general procedure, the corresponding ester (0·2 g) with LAH (0·04 g) gave the *alcohol* (0·16 g) as an oil, $\nu_{max.}$ 3400 cm^{-1}, τ 4·95br (2 × :CH), 5·19 (d, *J* 8, :CH), 6·3 (dd, *J* 6 and 11, C*H*H·OH), 6·58 (dd, *J* 8 and 11, CH*H*·OH), 7·9—8·1 (8H), 8·34 and 8·42 (4 × :CMe), 8·86 and 8·96 (2 × ·CMe), and 9·2 (m, C*H*·CH_2·OH) (Found: *m/e*, 290·2589. $C_{20}H_{34}O$ requires *M*, 290·2610).

t-2-[(3E)-4,8-*Dimethylnona*-3,7-*dienyl*]-2-*methyl*-t-3-(2-*methylprop*-1-*enyl*)*cyclopropan*-r-1-*ylmethanol* (47). By the general procedure, the corresponding ester (0·2 g) with LAH (0·04 g) gave the *alcohol* (0·16 g) as an oil, $\nu_{max.}$ 3400 cm^{-1}, τ 4·9br (4 × :CH), 5·1 (d, *J* 8, :CH), 6·3 (overlapping dd, *J* 6, 8, and 11·5, CH_2·OH), 8·31 and 8·41 (5 × :CMe), 8·85 (·CMe), and 9·2 (m, C*H*·CH_2·OH) (Found: *m/e*, 290·2574. $C_{20}H_{34}O$ requires *M*, 290·2610).

c-2-[(3E)-4,8-*Dimethylnona*-3,7-*dienyl*]-2-*methyl*-t-3-(2-*methylprop*-1-*enyl*)*cyclopropan*-r-1-*ylmethanol* (48). By the general procedure, the corresponding ester (0·2 g) with LAH (0·4 g) gave the alcohol (0·15 g) as an oil, $\nu_{max.}$ 3400 cm^{-1}, τ 4·9br (4 × :CH), 5·1 (d, *J* 8, :CH), 6·3 (m, CH_2·OH), 8·31 and 8·41 (5 × :CMe), 8·95 (·CMe), and 9·2 (m, ·C*H*·CH_2·OH) (Found: *m/e*, 290·2620. $C_{20}H_{34}O$ requires *M*, 290·2610).

c-2-[(3E)-4,8-*Dimethylnona*-3,7-*dienyl*]-2-*methyl*-t-3-[(1E,5E)-2,6,10-*trimethylundeca*-1,5,9-*trienyl*]*cyclopropan*-r-1-*ylmethanol* (54). By the general procedure, the corresponding ester (0·25 g), with LAH (0·05 g) gave the *alcohol* (0·18 g), $\nu_{max.}$ 3400 cm^{-1}, τ 4·85br (4 × :CH), 5·05 (d, *J* 8, :CH), 6·25 (m, CH_2·OH), 7·95br (16H), 8·31 (3 × :CMe), 8·4 (4 × :CMe), 8·69 (m, C*H*·CH), 8·95 (·CMe), and 9·08 (m, C*H*·CH_2·OH) (Found: *m/e*, 426·3858. $C_{30}H_{50}O$ requires *M*, 426·3861).

t-2-[(E)-4,8-*Dimethylnona*-3,7-*dienyl*]-2-*methyl*-t-3-[(1E,5E)-2,6,10-*trimethylundeca*-1,5,9-*trienyl*]*cyclopropan*-r-1-*ylmethanol* (*presqualene alcohol*) (53). By the general procedure, the corresponding ester (0·2 g) with LAH (0·04 g) gave the alcohol (0·15 g) as an oil, $\nu_{max.}$ 3400 cm^{-1}, τ 4·9br (4 × :CH), 5·05 (d, *J* 8, :CH), 6·16 (dd, *J* 6 and 11, C*H*H·OH), 6·45 (dd, *J* 8 and 11, CH*H*·OH), 7·98br (16H), 8·32 (3 × :CMe), 8·40 (4 × :C*Me*), 8·65 (m, C*H*·CH), 8·85 (·CMe), and 9·05 (m, C*H*·CH_2·OH) (Found: *m/e*, 426·3858). The alcohol did not separate in mixed t.l.c. [silica gel; 3 : 1 light petroleum (b.p. 60—80°)–ether] from naturally derived presqualene alcohol, and their mass spectral data were closely similar.

t-2-*Methyl*-t-3-(*tetramethylpentadecatetraenyl*)-2-(*trimethyltridecatrienyl*)*cyclopropan*-r-1-*ylmethanol* (69). By the general procedure, the corresponding ester (0·15 g) with LAH (0·04 g) gave the *alcohol* (0·11 g) as an oil, $\nu_{max.}$ 3350 cm^{-1}, τ 4·9br (6 × :CH), 5·09 (d, *J* 8, :CH), 6·34 (m, CH_2·OH), 7·99br (24H), 8·32 and 8·40 (9 × :CMe), 8·6 (m, C*H*·CH), 8·96 (·CMe), and 9·14 (m, C*H*·CH_2·OH) (Found: *m/e*, 562·5122. $C_{40}H_{66}O$ requires *M*, 562·5113).

c-2-*Methyl*-t-3-(*tetramethylpentadecatetraenyl*)-2-(*trimethyltridecatrienyl*)*cyclopropan*-r-1-*ylmethanol* (*prephytoene alcohol*) (68). By the general procedure, the corresponding ester (0·14 g) with LAH (0·04 g) gave the *alcohol* (0·09 g), as an oil, $\nu_{max.}$ 3350 cm^{-1}, τ 4·91br (6 × :CH), 5·07 (d, *J* 8, :CH), 6·18 (dd, *J* 6 and 11, C*H*H·OH), 6·47 (dd, *J* 8 and 11, CH*H*·OH), 7·99br (24H), 8·32 and 8·40 (9 × :CMe), 8·65 (m, C*H*·CH), 8·89 (·CMe), and 9·02 (m, C*H*·CH_2·OH) (Found: *m/e*, 562·5108. $C_{40}H_{66}O$ requires *M*, 562·5113).

Ethyl 2,2-*Dimethyl*-trans-3-(2,6,10-*trimethylundecyl*)*cyclopropanecarboxylate* (41).—A solution of ethyl 2,2-dimethyl-*trans*-3-[(1*E*,5*E*)-2,6,10-trimethylundeca-1,5,9-trienyl]cyclopropane-1-carboxylate (0·05 g) in ethyl acetate (3 ml) was hydrogenated (Brown micro-hydrogenator) at 25° over platinum black (20 mg) (uptake 3 mol. equiv.). Filtration and evaporation left the *ester* (31 mg), τ 5·95 (q, *J* 7, CH_2·CH_3) and 8·6—9·2m (*ca.* 40H) (Found: *m/e*, 338·3182. $C_{22}H_{42}O_2$ requires *M*, 338·3184). G.l.c. analysis (OV-225, DEGS; 160°) showed one major peak (>90%).

Ethyl c-2-*Methyl*-t-3-(2,6,10,14-*tetramethylpentadecyl*)-2-(4,8,12-*trimethyltridecyl*)*cyclopropane*-r-1-*carboxylate*.—A solution of the polyunsaturated ester (66) (0·024 g) in ethyl acetate (1·2 ml) was hydrogenated (Brown micro-hydrogenator) at 25° over platinum black (*ca.* 2 mg) [uptake 6·75 mol. equiv. (average of 4 experiments)]. Filtration and evaporation left the *ester* (0·025 g) as an oil, τ 5·87 (q, *J* 7, CH_2·CH_3), 8·74—8·81 (48H), and 9·1—9·2 (27H) (Found: *m/e*, 618·6302. $C_{42}H_{82}O_2$ requires *M*, 618·6314).

c-2-*Methyl*-t-3-(2,6,10,14-*tetramethylpentadecyl*)-2-(4,8,12-*trimethyltridecyl*)*cyclopropan*-r-1-*ylmethanol* (*tetradecahydroprephytoene alcohol*).—A solution of synthetic prephytoene alcohol (0·028 g) in ethyl acetate (1·2 ml) was hydrogenated (Brown micro-hydrogenator) over platinum black (uptake 6·5 ± 0·25 mol. equiv.). Filtration and evaporation left the alcohol (0·025 g) as an oil, τ 6·50 (m, CH_2·OH), 8·75—8·85 (m, 48H), and 9·1—9·2 (m, 27H), *m/e* 576 ($C_{40}H_{80}O$).

t-2-(4,8-*Dimethylnonyl*)-2-*methyl*-3-(2,6,10-*trimethylundecyl*)*cyclopropan*-r-1-*ylmethanol* (*decahydropresqualene alcohol*) (55).—A solution of synthetic presqualene alcohol (0·03 g) in ethyl acetate (3 ml) was hydrogenated over platinum black until *ca.* 5 mol. equiv. had been absorbed. Filtration, evaporation, and chromatography of the residue on silica gel (benzene as eluant) gave (a) r-1-(4,8-*dimethylnonyl*)-t-1,t-2-*dimethyl*-c-3-(2,6,10-*trimethylundecyl*)*cyclopropane* (56) (eluted first), τ 8·86—9·17 (complex) (Found: *m/e*, 420·4672. $C_{30}H_{60}$ requires *M*, 420·4695); and (b) the *alcohol* (55) (eluted second) τ 6·58 (m, CH_2·OH), 7·24 (OH), 8·8—8·95 (36H), and 9·1—9·2 (21H) (Found: *m/e*, 436·4632. $C_{30}H_{60}O$ requires *M*, 436·4644).

Tritium-labelled Presqualene Alcohol (53) *and its Isomer* (54).—The esters (49) and (50) (25 mg) in ether (1 ml) were separately reduced with a solution of lithium aluminium tritiide (0·9 mg; activity 100 mCi $mmol^{-1}$) and

LAH (4 mg) in ether (1 ml). Chromatography of the resulting alcohols to constant activity gave ^{3}H-labelled presqualene alcohol (53) (activity 89 mCi mmol^{-1}) and ^{3}H-labelled isomer (54) (71 mCi mmol^{-1}).

Tritium-labelled Prephytoene Alcohol (68).—The ester (66) (25 mg) in ether (1 ml) was reduced with lithium aluminium tritiide (activity *ca.* 90 mCi mmol^{-1}) and LAH (5 mg) in ether (1 ml). Chromatography gave the ^{3}H-labelled alcohol (12·5 mCi mmol^{-1}).

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