Synthesis of (±)-Campherenone, (±)-Epicampherenone, (±)-β-Santalene, (±)-epi-β-Santalene, (±)-α-Santalene, (±)-Ylangocamphor, (±)-Copacamphor, and (±)-Sativene [1]

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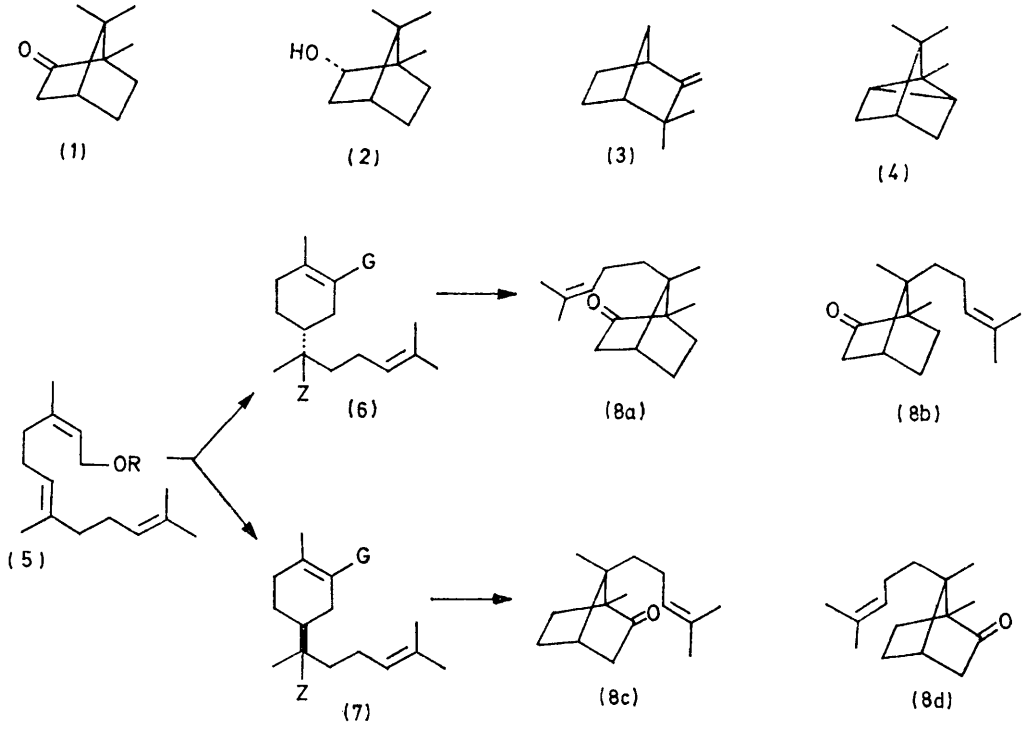
The completion of part of a general synthetic route to sesquiterpene analogues of camphor, bornan-2-ol, camphene and tricyclene is illustrated by an alternative total synthesis of campherenone and epicampherenone [the epimeric 1,7-dimethyl-7-(4-methylpent-3-enyl)norbornan-2-ones], β-santalene and epi-β-santalene [2-methyl-3-methylene-2-(4-methylpent-3-enyl)norbornanes], α-santalene {1,7-dimethyl-7-(4-methylpent-3-enyl)tricyclo-[2.2.1.$0^{2,6}$]heptane}, and the perhydro-1,4-methanoindene derivatives copacamphor, ylangocamphor, and sativene.

As indicated in the preceding paper [2] we have considered an alternative biosynthetic route to bicyclic monoterpenes such as camphor (1), bornan-2-ol (2), camphene (3), and tricyclene (4). The extension of these ideas to the sesquiterpene area leads naturally to a structural analysis in which appropriate sesquiterpenes are conveniently classified in a series of 'structural quartets' (see Schemes 2—4). The members of each quartet have the same structural (and presumably biosynthetic) relationship to each other as camphor, bornan-2-ol, camphene, and tricyclene. The key intermediate between farnesyl pyrophosphate (5; R = $P_2O_6H_3$) and the structural quartets could be an appropriate monocyclic enol ester, enol ether, or enamine (6 or 7; Z = biological leaving group) and its derivation could involve processes similar to those suggested for the analogous monoterpene intermediate.[2] Cyclisation of structures (6) and (7) could produce four possible compounds (8a—d) which may be regarded as sesquiterpene analogues of camphor. In addition, these compounds can also be considered as parent ketones of four structural quartets (Scheme 2) and their conversion into other members of the quartet would involve reduction, dehydration, and rearrangement processes which have analogy in monoterpene chemistry. One of the structural quartets consists entirely of known sesquiterpenes, *i.e.* (—)-campherenone (8c),† (—)-campherenol (9c),†



SCHEME 1

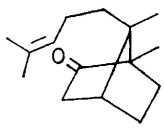
† Campherenone (8c) and campherenol (9c) were originally assigned [3] configurations enantiomeric to those shown. Thus we were compelled to conclude that these compounds and the santalenes (α- and β-) belonged to different structural quartets and that in spite of their co-occurrence a biosynthetic relationship did not exist between them. This anomalous situation and related studies in our laboratory prompted a reinvestigation of the absolute configuration of (—)-campherenone and (—)-campherenol. The result of this study was a reassignment of absolute configuration to these compounds.[4]

[1] Preliminary communications, G. L. Hogdson, D. F. MacSweeney, and T. Money, *Chem. Comm.*, 1971, 766; *Tetrahedron Letters*, 1972, 3683.

[2] J. C. Fairlie, G. L. Hodgson, and T. Money, preceding paper.

[3] H. Hikino, N. Suzuki, and T. Takemoto, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 87.

[4] G. L. Hodgson, D. F. MacSweeney, R. W. Mills, and T. Money, *J.C.S. Chem. Comm.*, 1973, 235.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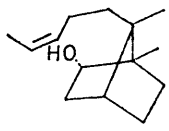
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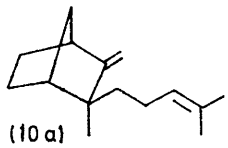
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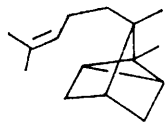
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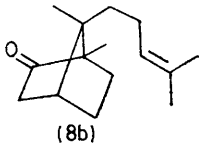
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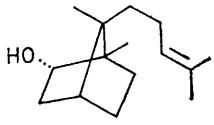
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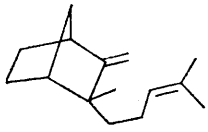
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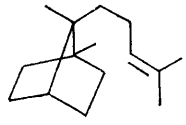
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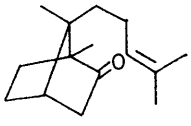
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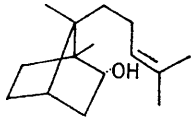
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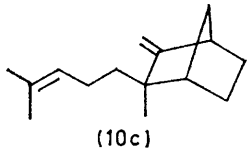
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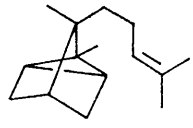
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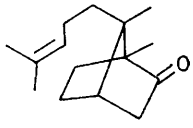
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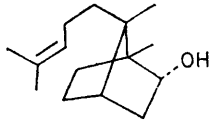
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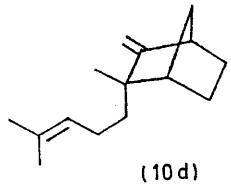
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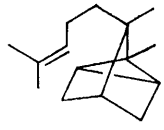
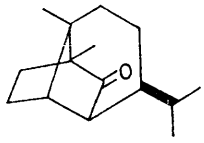

(11d)

SCHEME 2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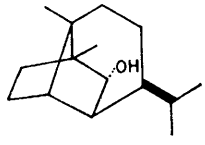
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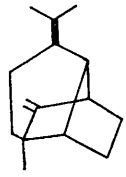
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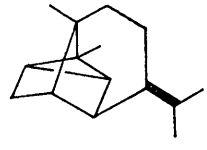
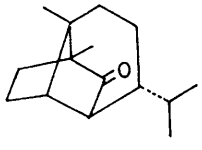

(15a)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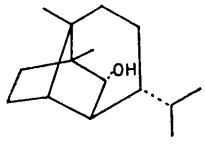
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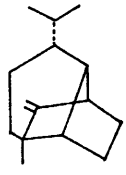
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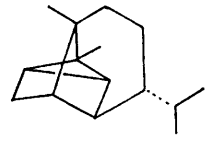
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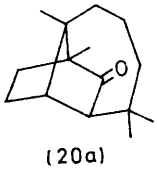
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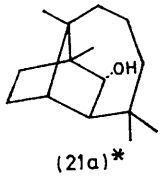
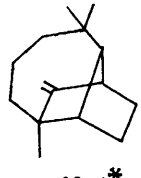
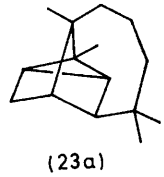
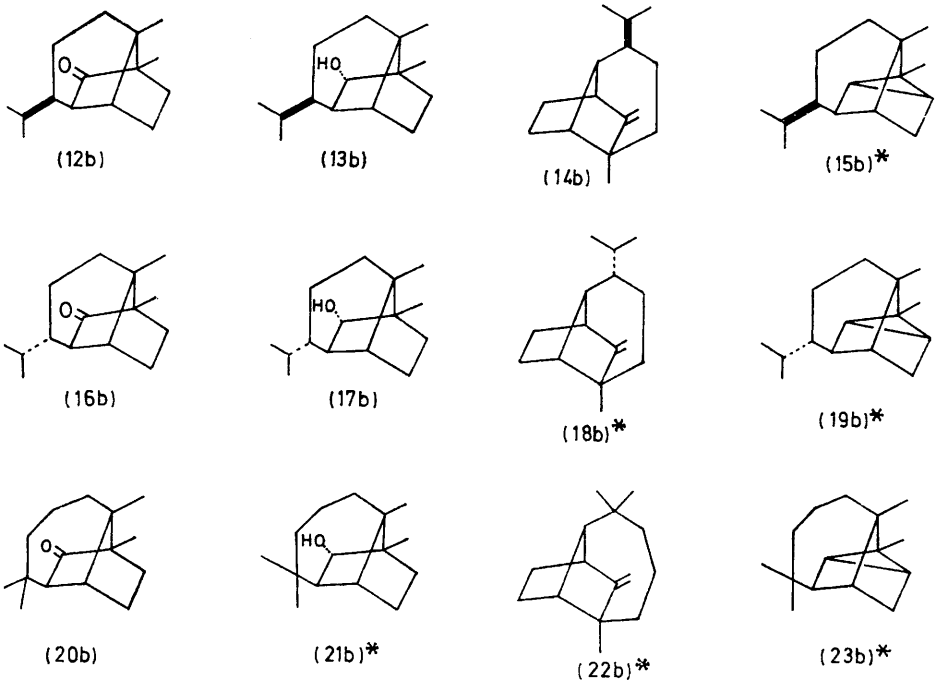

(21a)*

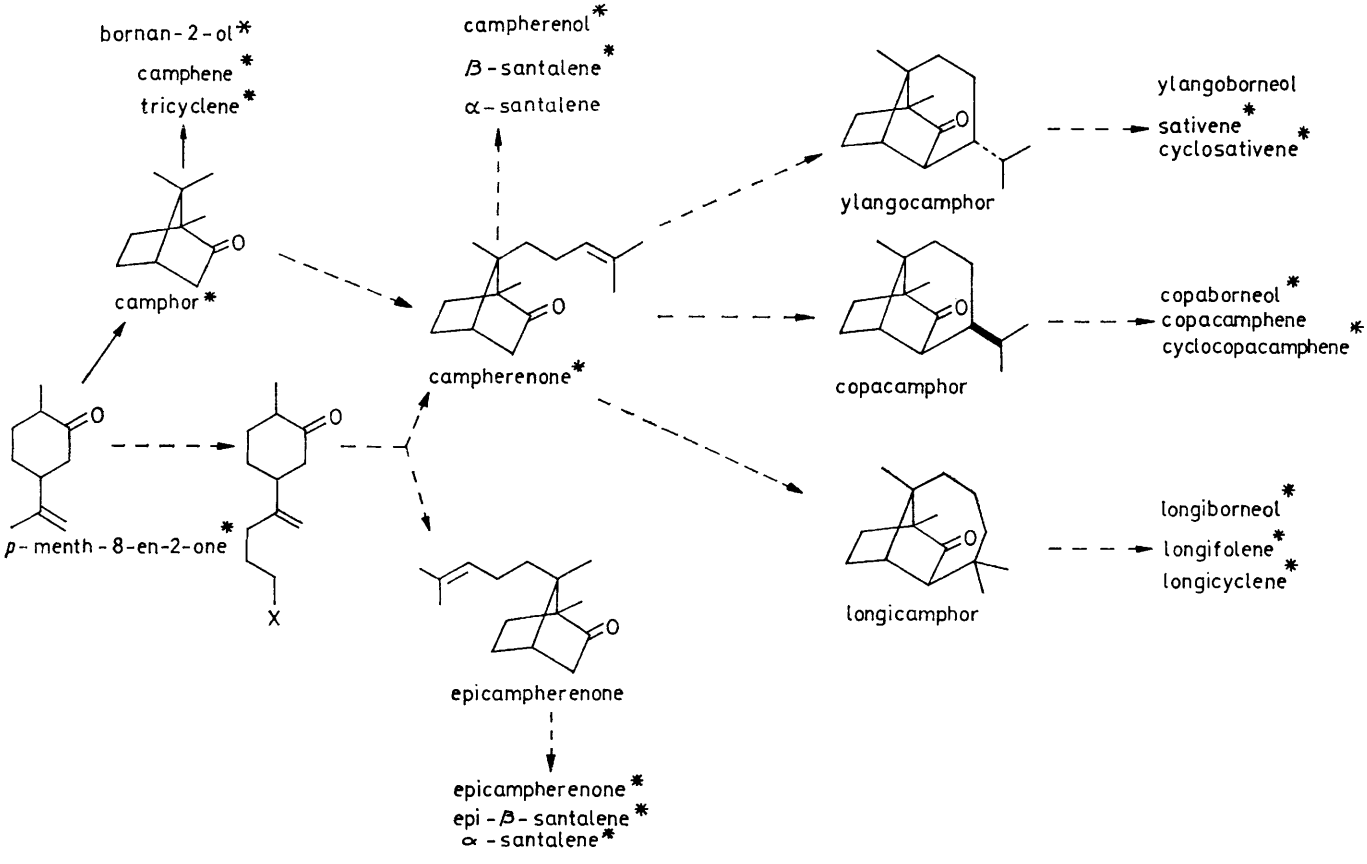

(22a)*


(23a)

SCHEME 3



SCHEME 4



SCHEME 5 (*denotes naturally occurring compound)

(−)-β-santalene (10c), and (+)-α-santalene (11b); these compounds co-occur in *Cinnamomum camphora* Siebold (Lauraceae).[3] (+)-Epi-β-santalene (10b), which co-occurs with (−)-β-santalene and (+)-α-santalene in *Santalum album*,[5] may be placed in a quartet along with (+)-epicampherenone (8b) (unknown in nature), or it could be derived from (+)-α-santalene (11b) by cleavage of the cyclopropane ring. The remainder of the compounds in these sets are at present unknown in nature.*

More complex quartets containing tricyclic and tetracyclic structures can be constructed by extending the basic cyclisation process to an appropriate enol derivative of (−)-campherenone. In this way three tricyclic ketones, (+)-copacamphor (12a), [6] (+)-ylangocamphor (16a),[7] and (−)-longicamphor (20a) [8] could theoretically be produced and these may be regarded as the parent ketones of three structural quartets (Scheme 3) which include the naturally occurring compounds (+)-copaborneol (13a),[9] (−)-sativene (18a),[10] (−)-longiborneol (21a),[11] and (−)-longifolene (22a).[11] Moreover, if one includes the enantiomeric series three additional quartets may be constructed (Scheme 4) which contain naturally occurring sesquiterpenes: (+)-cyclocopacamphene (15b),[6,12] (+)-sativene (18b),[13] (+)-cyclosativene (19b),[13,14] (+)-longiborneol (21b),[15] (+)-longifolene (22b),[13,16] and (+)-longicyclene (23b).[13,17] Thus fifteen of the bicyclic, tricyclic, and tetracyclic structures indicated by asterisks in Schemes 2—4 represent naturally occurring sesquiterpenes; one might expect the discovery of missing members in the natural source from which other members of the same quartet have been derived.†

In any event, and *irrespective of the validity of these biosynthetic ideas*,‡ the structural analysis and presumed biosynthetic relationships just outlined can provide us with a general synthetic strategy for the sesquiterpene structures included within its scope. In essence the synthetic plan (Scheme 5) involves the sequential conversion of monocyclic into bicyclic and tricyclic ketones and the subsequent conversion of each of these 'parent' ketones to sesquiterpene analogues of bornan-2-ol, camphene, and tricyclene. The latter transformations are analogous to the known conversion [29] of camphor (1) into bornan-2-ol (2), camphene (3), and tricyclene (4). Thus, with the exception of epi-β-santalene all the compounds in our general synthetic scheme can be derived, in theory, from campherenone and, appropriately, the total synthesis of this compound was the primary objective of our synthetic investigations. Our initial approaches to campherenone were modelled on our successful synthesis of camphor, and the appropriate monocyclic ketone (30) was synthesised in two ways. The first synthetic route (Scheme 6), although efficient, was superseded by a shorter sequence (Scheme 7) involving alkylation of dihydrocarvone 2,2-dimethyltrimethylene acetal (31) § with 1-chloro-3-methylbut-

* The *exo*-alcohol derived from epicampherenone has been isolated recently from *Verbesina rupestris* (Professor W. R. Chan, University of West Indies, personal communication).

† Many derivatives of the structures shown are known natural products and will be considered in later papers in this series. These compounds include (+)-α-santalol,[18-20] (−)-β-santalol,[18] epi-β-santalol,[9] β-santalic acid,[18] tricycloekasantalal,[21] cyclocopacamphenols,[22] cyclocopacamphenic acids,[23] longifol-7(15)-en-5β-ol,[24] longifolan 3α,7α-oxide,[24] culmorin,[25] helminthosporal,[26] and the picrotoxanes.[27]

‡ The biosynthetic scheme described in this paper provides an alternative to previously published proposals [28] which involve cyclisation of farnesyl pyrophosphate to ten- and eleven-membered ring intermediates. The latter are considered to undergo-1,3-hydride shifts before cyclising to the tricyclic and tetracyclic compounds listed in Schemes 2 and 3. Of course the biosynthetic route to the bicyclo[2.2.1]heptane systems represented in Schemes 1—4 could be derived by rearrangement of bicyclo-[3.1.1]heptane derivatives formed directly from farnesyl pyrophosphate.

§ Preliminary investigations indicated that the ethylenedioxy protecting group was labile under these conditions. A similar instability of this group to alkyl-lithium reagents has been reported previously.[30]

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[22] A. Homma, M. Kato, M. Wu, and A. Yoshikoshi, *Tetrahedron Letters*, 1970, 231; N. H. Anderson, *ibid.*, p. 1755.

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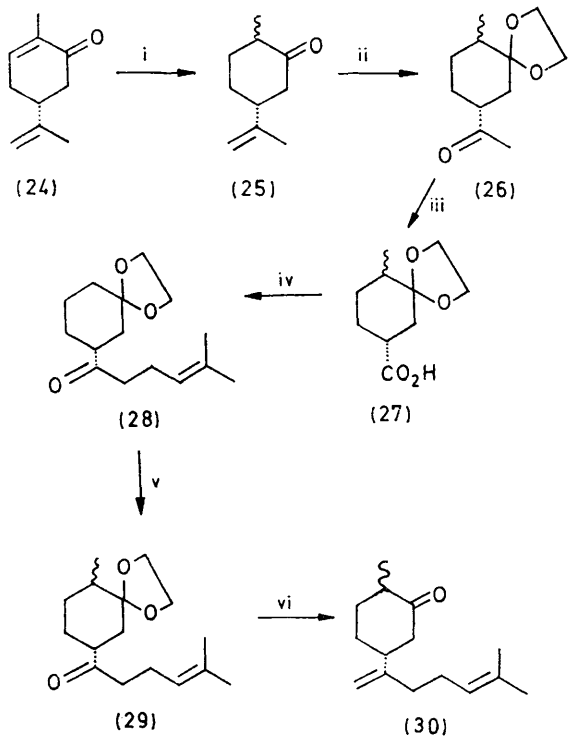
2-ene * in the presence of n-butyl-lithium and tetramethylethylenediamine.† Hydrolysis of the reaction product (32) provided the ketone (30) in 70% overall yield. Reaction of (30) with isopropenyl acetate and toluene-*p*-sulphonic acid provided the isomeric enol acetates (33) and (34) (ratio 4 : 1), which were separated



SCHEME 6 Reagents: i, Zn–KOH; ii, (a) $(CH_2OH)_2$–H^+, (b) O_3, (c) Me_2S; iii, KOCl; iv, (a) $(COCl)_2$, (b) $Me_2C{:}CH{\cdot}[CH_2]_2MgBr$–CuCl; v, $Ph_3P{:}CH_2$; vi, H^+–Me_2CO

by preparative g.l.c. Treatment of (33) in methylene chloride with boron trifluoride [2] yielded a mixture of bicyclic and tricyclic ketones. Three components (A—C) of the reaction mixture were isolated by chromatography (silica) and separated by preparative g.l.c. (relative abundance of A—C was *ca.* 5 : 8 : 1). Compound A was assigned structure (37a) on the basis of its spectral characteristics but was later shown to be a mixture of diastereoisomers (37a and b). These were separated as their enol acetates (40a and b), and compound (37b) was converted into the corresponding crystalline oxime (41) (Scheme 8) whose structure was confirmed by *X*-ray crystallographic analysis.[32] Structural assignments to components B (38) and C (39a and b) are based on spectral characteristics and, in the case of C, must be regarded as highly speculative. The formation of compounds (37a and b)—(39a and b) from the enol acetate (33) can be accounted for in terms of 1,5-diene cyclisation to form an intermediate bicyclic enol acetate (36) (Scheme 7), which can be hydrolysed to the enone B (38) or can cyclise to A (37a and b) or C (39a and b). The formation of the latter can be rationalised by invoking methyl migration in (36) prior to cyclisation. Some support for these speculative mechanistic suggestions comes from the fact that the ketone (30), on treatment with boron trifluoride, is efficiently converted (85% yield) into the bicyclic ketone (35) in 5 min at room temperature. Conversion of (35) into the enol acetate (36) followed by cyclisation with boron trifluoride in wet methylene chloride gave compounds (37a and b), (38), and (39a and b) in the ratio 5 : 1 : 3.

The recognition that the failure of the enol acetate (33) to provide campherenone or epicampherenone was associated with the presence of 1,5-diene functionality in (33) prompted us to devise a variation in our general synthetic approach. A variety of enol acetates (43; R = Me, CO_2Me, $CH_2{\cdot}CH_2{\cdot}CO_2Me$, $[CH_2]_3{\cdot}O{\cdot}CH_2Ph$, $CH_2{\cdot}CH_2Br$, or $CH_2{\cdot}CH_2Cl$) were synthesised and subjected to the usual cyclisation conditions (BF_3–CH_2Cl_2); it was found that our objectives could be most conveniently achieved by using the bicyclic chloro-ketones (48a and b) as synthetic precursors of campherenone and epicampherenone. The chloro-ketones (48a and b), were synthesised by two distinct reaction sequences (Schemes 8 and 9) which are now described.

Conversion of (+)-dihydrocarvone (25) into 5-acetyl-2-methylcyclohexanone ethylene acetal (26) (Scheme 6) followed by treatment with 3-tetrahydropyran-2-yloxypropyltriphenylphosphonium iodide ‡ in the presence of sodium methylsulphonylmethanide yielded compound (45). Treatment of (45) in benzene with ethylene glycol in the presence of oxalic acid gave the hydroxy-acetal (46; X = OH) which was converted into the corresponding chloride (46; X = Cl) in 78% yield by heating with carbon tetrachloride and tri-n-octylphosphine.[33] Subsequent hydrolysis yielded the chloro-ketone (42; R = $CH_2{\cdot}CH_2Cl$), which was converted into a mixture of enol acetates (43; R = $CH_2{\cdot}CH_2Cl$) and (44; R = $CH_2{\cdot}CH_2Cl$) (relative yields 5 : 1) by treatment with isopropenyl acetate and toluene-*p*-sulphonic acid. Separation and purification of (43; R = $CH_2{\cdot}CH_2Cl$) by preparative g.l.c. followed by cyclisation with boron trifluoride in wet methylene chloride gave 8-(2-chloroethyl)camphor (48a) § and 9-(2-chloroethyl)camphor (48b) (55—60% yield) and the monocyclic enone (47) (*ca.* 30—40% yield).

* The original report [31] described the C-10 alkylation of limonene with 1-bromo-3-methylbut-2-ene. This gave the desired product (β-bisabolene) and an isomeric compound in the ratio 4 : 1. We have found, inadvertently, that the use of the corresponding chloro-compound in the alkylation process provides β-bisabolene and no trace of the isomeric compound.

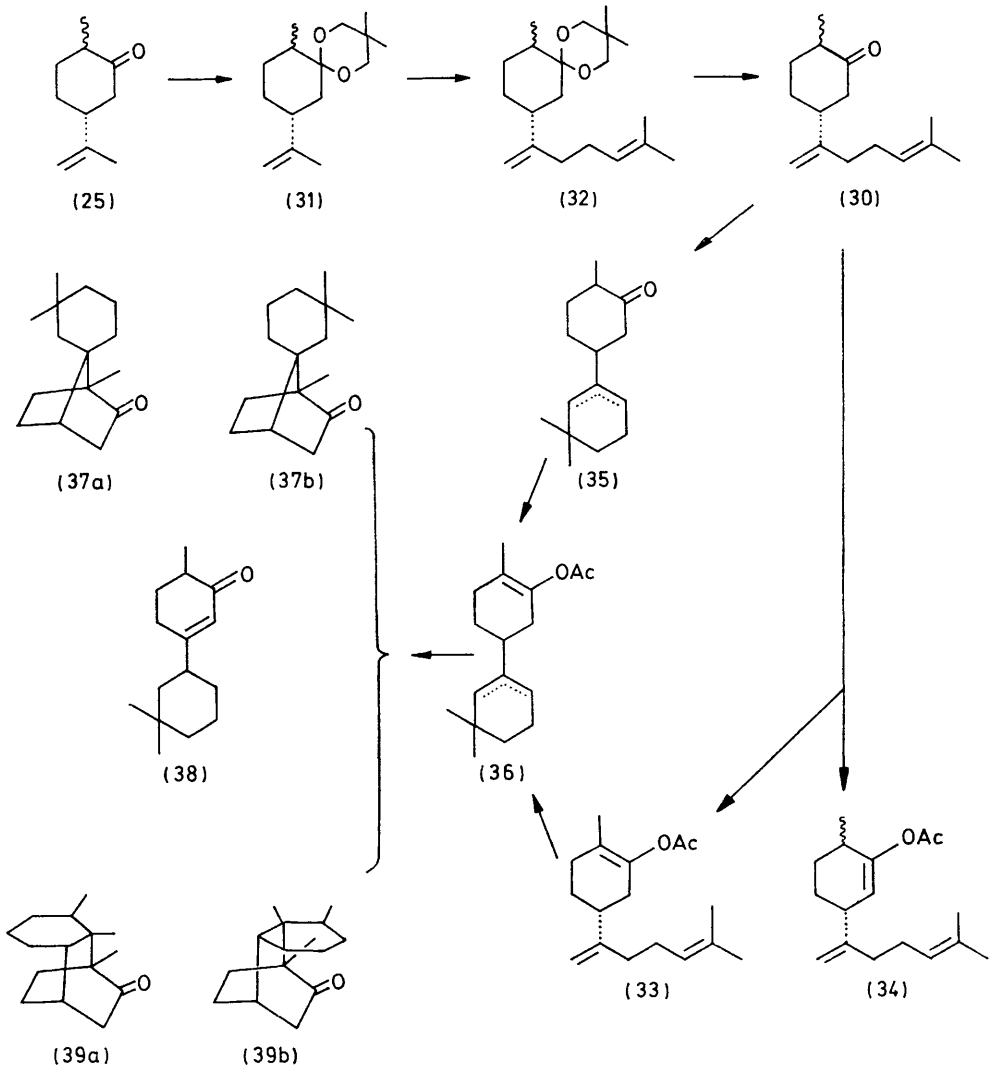
† These conditions were identical with those used for the alkylation of limonene.[31] We thank Dr. Crawford for advice on experimental details prior to publication.

‡ We thank Dr. J. R. Cannon, University of Western Australia, for providing us with experimental details for the synthesis of a similar compound, (4-benzyloxybutyl)triphenylphosphonium iodide.

§ The racemic nature of (48a) and (48b) was expected by analogy with our previous results in the monoterpene series.[2]

[31] R. Crawford, W. F. Erman, and C. D. Broaddus, *J. Amer. Chem. Soc.*, 1972, **94**, 4298.
[32] J. Trotter and S. J. Rettig, to be published.
[33] J. Hooz and S. S. H. Gilani, *Canad. J. Chem.*, 1968, **46**, 86; *cf.* I. M. Downie, J. B. Holmes, and J. B. Lee, *Chem. and Ind.*, 1966, 900.

Later studies (Scheme 9) provided a more efficient route to (48a and b). Treatment of dihydrocarvone 2,2-dimethyltrimethylene acetal (31) with n-butyl-lithium–tetramethylethylenediamine followed by ethylene oxide afforded the alcohol (49; X = OH) in 91% yield. Conversion of (49; X = OH) into the corresponding chloro-derivative (49; X = Cl) was achieved in 84% yield by migration of the acyclic double bond had also occurred. Subsequent treatment of the total reaction product under the usual cyclisation conditions gave the bicyclic chloroketones (48a and b) in 55—60% yield. Conversion of (48a and b) into the corresponding ethylene acetals followed by treatment with sodium iodide in acetone yielded the iodo-acetals (53a and b; X = I). The

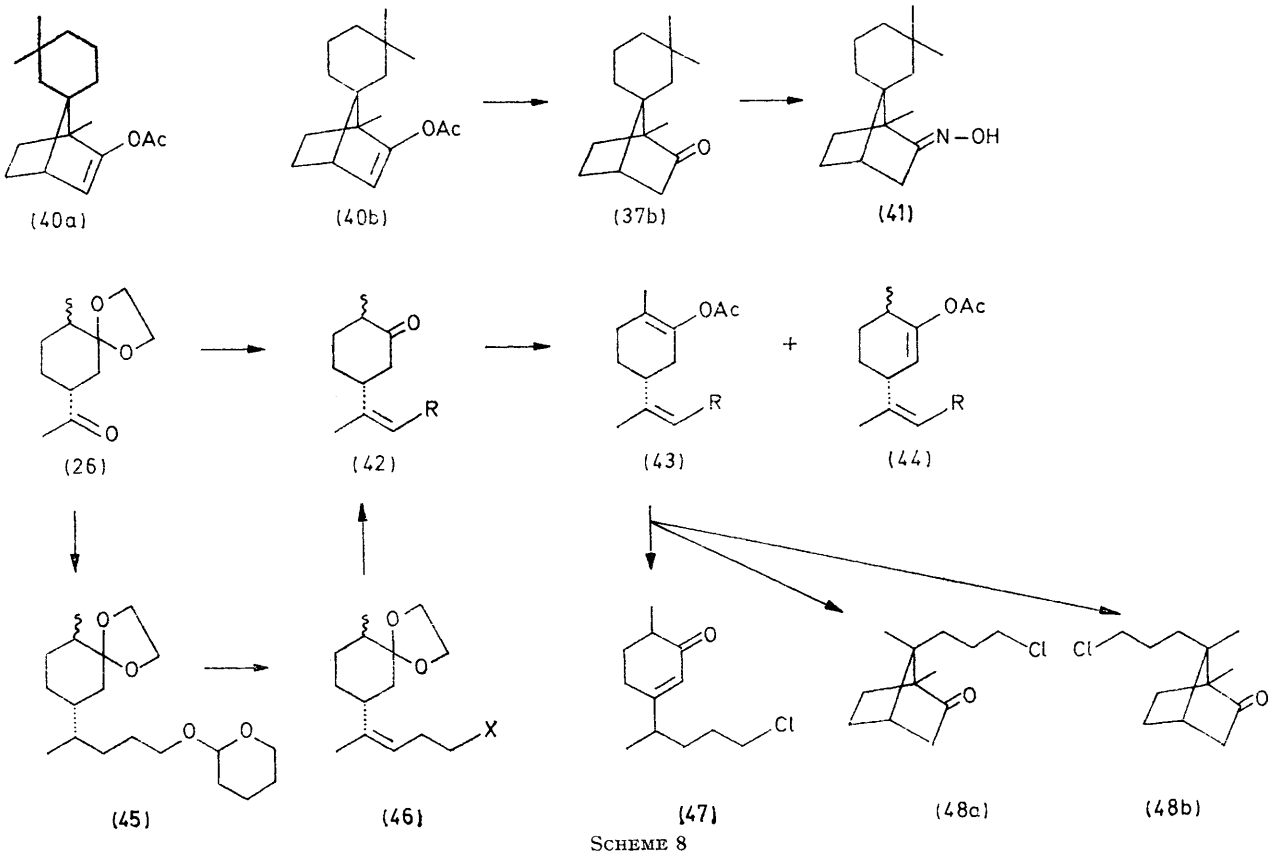


SCHEME 7

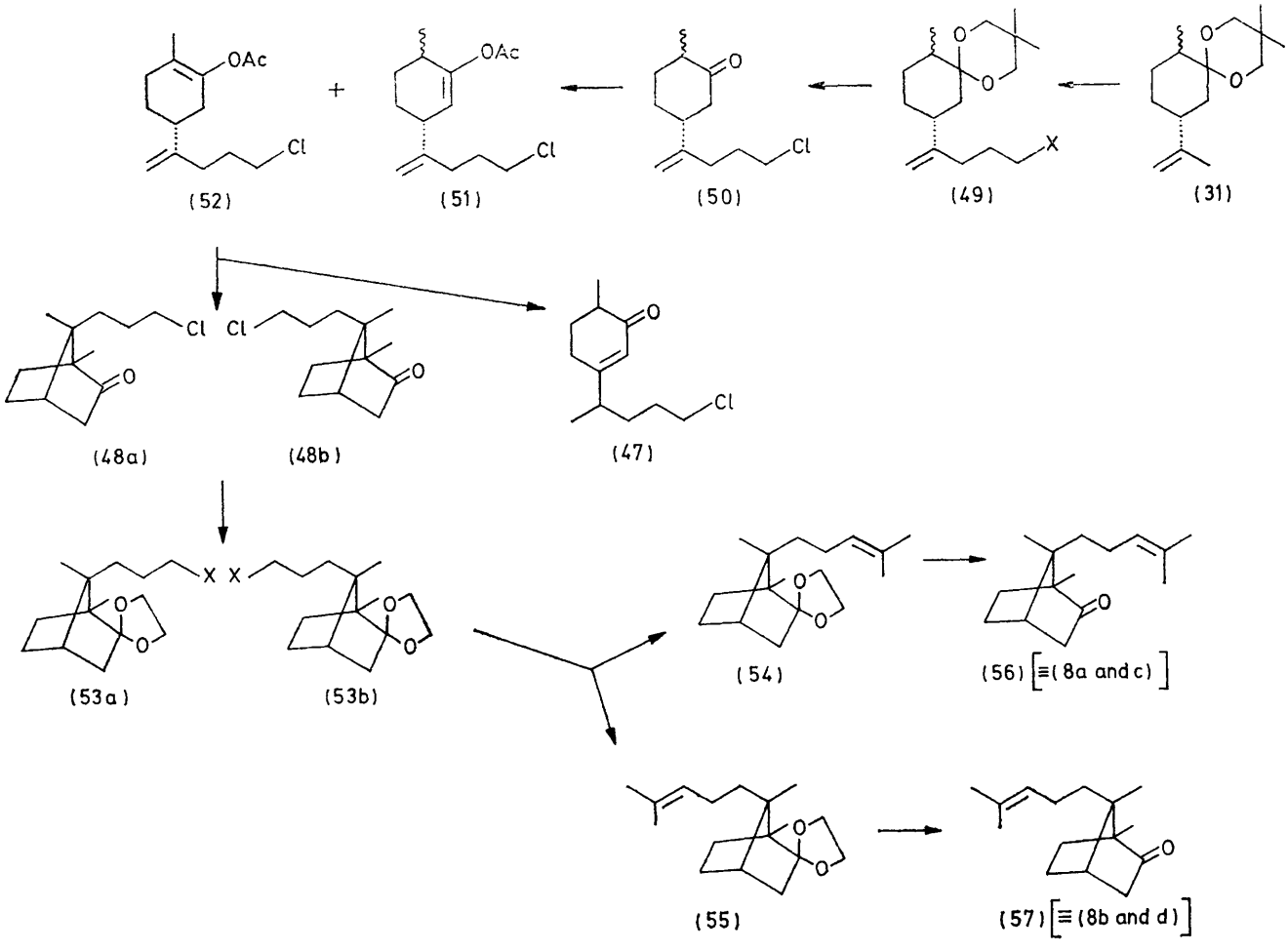
refluxing with tri-n-octylphosphine in carbon tetrachloride,[33] and hydrolysis of (49; X = Cl) provided the chloro-ketone (50). Treatment of (50) with toluene-*p*-sulphonic acid–isopropenyl acetate provided the enol acetates (51) and (52) (relative yields 1 : 3), which were separated and purified by preparative g.l.c.* Cyclisation of (52) as already described provided the bicyclic chloro-ketones (48a and b) (*ca.* 55% yield) and the monocyclic enone (47). It was shown later that enol acetylation of (50) with acetic anhydride–perchloric acid [34] produced a higher proportion (*ca.* 90%) of tetra-substituted enol acetate (52), although there was spectral evidence for the presence of compounds in which triphenylphosphonium salts derived from (53a and b; X = I) reacted with acetone in the presence of sodium methylsulphonylmethanide to provide a mixture of campherenone ethylene acetal (54) and the corresponding epicampherenone derivative (55) in 84% overall yield from the iodo-acetals (53a and b). Subsequent separation of (54) and (55) by preparative g.l.c. followed by hydrolytic removal of acetal groups afforded (±)-campherenone (56) and (±)-epicampherenone (57), with spectral properties, analytical figures, and reactions (see

* In large scale cyclisations it was convenient to use a mixture of enol acetates (51) and (52) (see Experimental section).

[34] B. E. Edwards and P. N. Rao, *J. Org. Chem.*, 1966, **31**, 324.



SCHEME 8



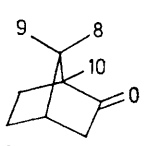
SCHEME 9

later) in agreement with the assigned structures. A distinction between (±)-campherenone (56) and (±)-epicampherenone (57) was made possible by a comparison of their n.m.r. spectra with that of camphor [35] (solutions in carbon tetrachloride and benzene; Table 1). Additional support for the structure of our synthetic product (56) was obtained when reduction with sodium–propan-1-ol [36] and with lithium hydridotrimethoxyaluminate [37] yielded (±)-campherenol (58; $R^1 = H$, $R^2 = OH$) and (±)-isocampherenol (58; $R^1 = OH$, $R^2 = H$),* respectively. In a similar fashion (±)-epicampherenone (57) was converted into the corresponding alcohols (61; $R^1 = H$, $R^2 = OH$) and (61; $R^1 = OH$, $R^2 = H$). Comparative n.m.r. data for compounds (58), (61), and the bornan-2-ols are shown in Table 2.

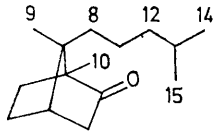
In accordance with our general synthetic scheme (*cf.* Scheme 5) we regarded campherenone and epicampherenone as parent ketones of a series of structural quartets. Two of these sets include α-santalene (63),

TABLE 1

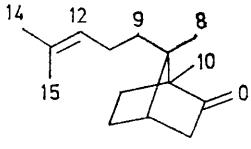
N.m.r. signals of bicyclic ketones *



Camphor



Campherenone



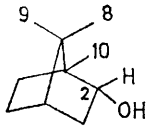
Epicampherenone

	Solvent	8-H	9-H	10-H	12-H	14-, 15-H
Camphor	CCl_4	9·19	9·07	9·18		
	C_6H_6	9·40	9·35	9·11		
Campherenone	CCl_4		9·03(9·04)	9·14(9·15)	4·95(4·97)	8·35(8·36), 8·39(8·41)
	C_6H_6		9·30(9·33)	9·07(9·10)	4·97(5·02)	8·35(8·38), 8·48(8·51)
Epicampherenone	CCl_4	9·13		9·13	4·89	8·32, 8·38
	C_6H_6	9·35		9·06	4·83	8·28, 8·41

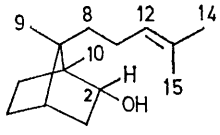
* Literature values [3] for campherenone are shown in parentheses.

TABLE 2

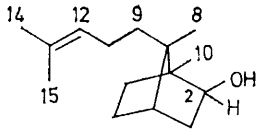
N.m.r. signals of bicyclic alcohols (in CCl_4) *



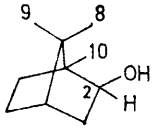
Bornan-2α-ol



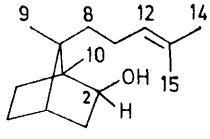
Campherenol



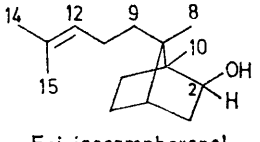
Epicampherenol



Bornan-2β-ol



Isocampherenol



Epi-isocampherenol

	2-H	8-H	9-H	10-H	12-H	14-, 15-H
Bornan-2α-ol	6·08	9·14	9·14	9·17		
Bornan-2β-ol	6·49	8·98	9·17	9·11		
Campherenol	6·00(6·03)		9·11	9·17	4·94	8·34, 8·41
Isocampherenol	6·46(6·94)		9·18	9·12	4·92	8·36, 8·39
Epicampherenol	6·06	9·13		9·18	4·92	8·33, 8·40
Iso-epicampherenol	6·47	8·96		9·12	4·93	8·33, 9·39

* Literature values [3] for campherenol and isocampherenol are shown in parentheses.

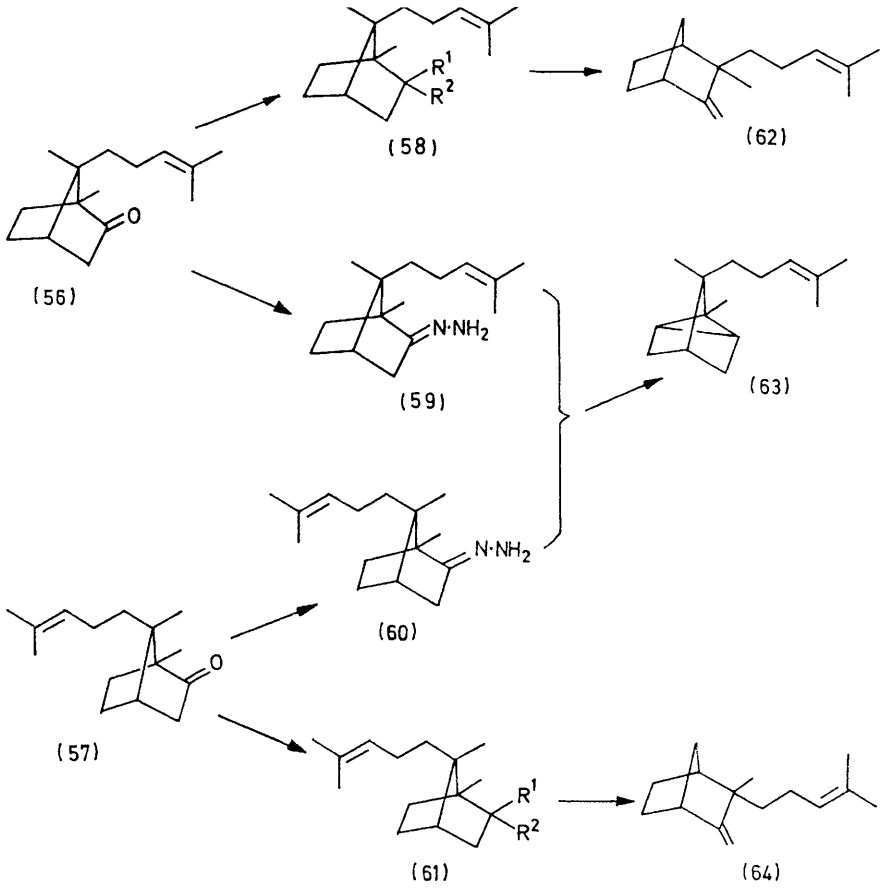
* This compound was originally named 'epicampherenol'.[3] However, in view of the nature of epicampherenone and by anology with monoterpene nomenclature we proposed [1] 'isocampherenol' as a more appropriate name.

[35] J. D. Connolly and R. McCrindle, *Chem. and Ind.*, 1965, 379; *J. Chem. Soc.* (*C*), 1966, 1613.

[36] D. H. R. Barton and N. H. Werstuik, *J. Chem. Soc.* (*C*), 1968, 148.

[37] H. C. Brown and H. R. Deck, *J. Amer. Chem. Soc.*, 1965, **87**, 5620.

β-santalene (62), and epi-β-santalene (64) * and the synthetic results just described enabled us to proceed with alternative synthetic routes to these compounds.† Thus (±)-isocampherenol (58; $R^1 = OH$, $R^2 = H$), on heating with pyridine and toluene-*p*-sulphonyl chloride, provided (±)-β-santalene (62) ‡ in 80% yield. In a similar fashion (±)-isoepicampherenol (61; $R^1 = OH$, $R^2 = H$) yielded (±)-epi-β-santalene (64). The synthesis of (±)-α-santalene (63) was accomplished in 65% overall yield when a methanolic solution of the hydrazones (59) and (60) (Scheme 10) was heated with mercuric oxide.[42,44] The synthetic samples of β-santalene, epi-β-santalene, and α-santalene exhibited the same g.l.c. and spectral characteristics as authentic specimens of these compounds isolated from sandalwood oil.§



SCHEME 10

The successful synthesis of campherenone (56) also enabled us to evaluate its use as a key intermediate in the projected synthesis of the tricyclic and tetracyclic sesquiterpenes included within the scope of our general scheme (Scheme 5). Our initial approach was based on our previous successful use of enol acetate intermediates in cyclisation reactions and the favourable geometric disposition of potentially reactive functional groups in campherenone enol acetate (65) led us to expect that this intermediate would cyclise to ylangocamphor, copacamphor, and longicamphor (Scheme 5) under appropriate conditions. However, in spite of numerous attempts, we were unable to achieve this objective; therefore alternative cyclisation processes were investigated. We eventually achieved an efficient cyclisation of campherenone epoxide in basic solution.

* Synthetic routes to β-santalene,[38-40] epi-β-santalene,[38,39,41] and α-santalene [41-43] have been reported.

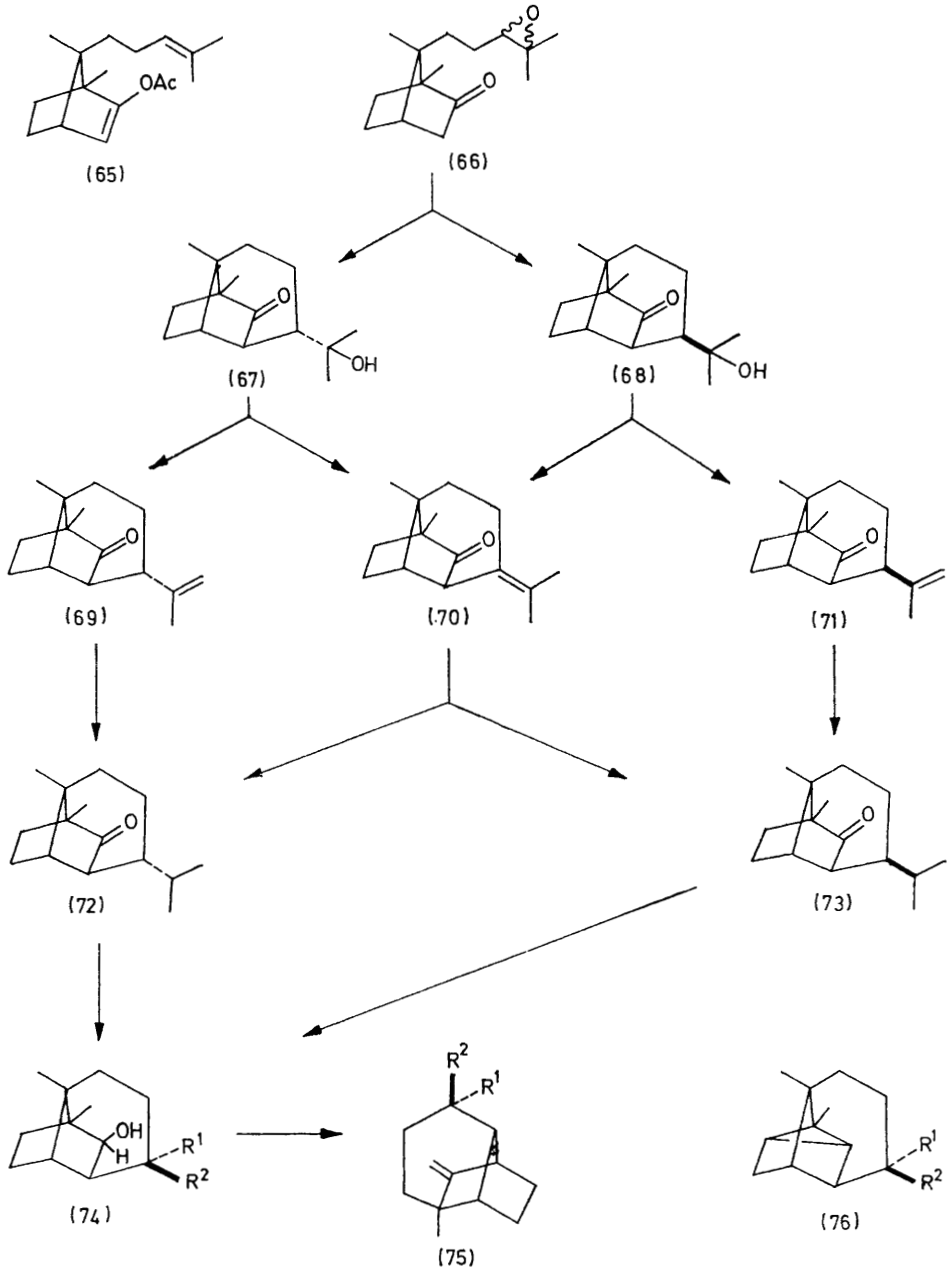
† The structures chosen to represent (±)-campherenone, (±)-campherenol, (±)-α-santalene, (±)-β-santalene, and (±)-epi-β-santalene do not necessarily depict the absolute configuration [4] of the naturally occurring enantiomers (Scheme 2).

‡ The conversion of natural campherenone into β-santalene (specific rotation not recorded) has been described previously.[3]

§ We are grateful to Fritzsche, Dodge, and Olcott, Inc., New York, and Norda Essential Oil and Chemical Co., Inc., New York, for generous samples of Mysore sandalwood oil.

[38] E. J. Corey, R. Hartmann, and P. A. Vatakencherry, *J. Amer. Chem. Soc.*, 1962, **84**, 2611.
[39] G. Brieger, *Tetrahedron Letters*, 1963, 1949.
[40] J. Wolinsky, R. L. Marhenke, and R. Lau, *Synthetic Communications*, 1972, **2**, 165.
[41] E. J. Corey and M. F. Semmelhack, *J. Amer. Chem. Soc.*, 1967, **89**, 2755.
[42] E. J. Corey, S. W. Chow, and R. A. Scherrer, *J. Amer. Chem. Soc.*, 1957, **79**, 5773.
[43] E. Y. Kamat, K. K. Chakravarti, and S. C. Bhattacharyya, *Tetrahedron*, 1967, **23**, 4487.
[44] *Cf.* H. Meerwein and K. Van Emster, *Ber.*, 1920, **53**, 1815; J. W. Powell and M. C. Whiting, *Tetrahedron*, 1959, **7**, 305.

Treatment of (±)-campherenone epoxide (66) with potassium t-butoxide in refluxing t-butyl alcohol provided a mixture (*ca.* 1 : 1) of tricyclic alcohols (67) and (68) (*ca.* 80% yield), which were separated by preparative g.l.c. The structural assignments were initially based on i.r. data since the expected presence of intramolecular hydrogen bonding in (67) could be shown by dilution studies. In contrast the isomeric alcohol (68) exhibited absorption bands at 3620 and 3440 cm^{-1} and, on dilution, a relative increase in the intensity of the bond at 3620 cm^{-1} was noted. These assignments were confirmed by the following chemical transformation. Dehydration of the keto-alcohol (68) with thionyl chloride and pyridine yielded a mixture (7 : 3) of tricyclic alkenes (70) and (71), separated by preparative g.l.c. Catalytic reduction ($Pt–H_2$) * of the terminal olefinic bond in (71) provided (±)-copacamphor (73); reduction of the tetrasubstituted alkene (70) provided a mixture (5 : 1) of (±)-ylangocamphor (72) and (±)-copacamphor (73). In the isomeric series the tricyclic alcohol (67) behaved



SCHEME 11

* When Pd–C was used as catalyst isomerisation of the double bond to the tetrasubstituted position occurred. Subsequent reduction then produced a mixture (5 : 1) of ylangocamphor and copacamphor.

analogously and an identical sequence of reactions provided the terminal alkene (69), which was hydrogenated to (±)-ylangocamphor (72). The g.l.c. and spectral characteristics of synthetic copacamphor (73) were identical with those of the authentic compound,[45,46] and the spectral data for synthetic ylangocamphor (72) were identical with those for ylangocamphor prepared by an alternative synthetic route.[45] Subsequent investigations have shown that it is unnecessary to separate mixtures of isomers at various stages in our synthetic route (Scheme 11) and this has made large-scale synthetic work more convenient. In effect, this simplification in procedure has allowed us to synthesise ylangocamphor (72) and copacamphor (73) from (±)-campherenone (56) * in 84% overall yield and removes the need for preparative g.l.c. or column chromatography until the final mixture of products has been obtained.

In our general synthetic scheme (Scheme 5) copacamphor (73) and ylangocamphor (72) are depicted as key intermediates in the synthesis of related compounds. In the case of copacamphor conversion into copaborneol (74; $R^1 = H$, $R^2 = Pr^i$, OH *endo*), copaisoborneol (74; $R^1 = H$, $R^2 = Pr^i$), and copacamphene (75; $R^1 = H$, $R^2 = Pr^i$) has been described previously [46] and therefore the synthesis of copacamphor constitutes a total synthesis of these compounds. The conversion of copacamphor (73) into cyclocopacamphene (76; $R^1 = H$, $R^2 = Pr^i$) remains to be accomplished in this series and this, together with the related conversion of ylangocamphor (72) into cyclosativene (76; $R^1 = Pr^i$, $R^2 = H$), is being investigated (*cf.* conversion of campherenone into α-santalene already described).

In the ylangocamphor series treatment of the parent ketone (72) with lithium aluminum hydride provided (±)-isoylangoborneol (74; $R^1 = Pr^i$, $R^2 = H$) which, according to our general synthetic plan, was considered to be an ideal synthetic precursor of (±)-sativene. However, isoylangoborneol (74; $R^1 = Pr^i$, $R^2 = H$) proved to be stable to the usual dehydration–rearrangement conditions (toluene-*p*-sulphonyl chloride–pyridine) and, after the event, this was explained in terms of steric hindrance around the hydroxy-function. By using less sterically demanding conditions (methanesulphonyl chloride–pyridine) (±)-isoylangoborneol was converted into (±)-sativene (75; $R^1 = Pr^i$, $R^2 = H$) [47] in 53% yield).

Our strategy has now provided us with a general and reasonably efficient synthetic route to a variety of sesquiterpenes. Part of our present investigation is concerned with placing this scheme on an absolute configurational basis.[4]

* If a mixture of campherenone and epicampherenone is used the alcohol(s) formed from epicampherenone epoxide during the cyclisation reaction can be removed from tricyclic alcohols (67) and (68) by distillation.

[45] We thank Professor E. Piers of this department for providing us with an authentic sample and g.l.c. and spectral characteristics of copacamphor (E. Piers, R. W. Britton, R. J. Keziere, and R. D. Smillie, *Canad. J. Chem.*, 1971, **49**, 2620) and for spectral data for synthetic ylangocamphor prior to publication (E. Piers, M. B. Geraghty, F. Kido, and M. Soucy, *Synth. Comm.*, 1972, **3**, 39).

EXPERIMENTAL

General experimental conditions are described in the preceding paper. The following g.l.c. columns were used

Column	Dimensions	Stationary phase	Support	Mesh
A		3% SE 30	Varoport 30	100—120
B	10 ft × 1/4 in	5% QF 1		60—80
C		10% Carbowax		60—80
D		20% DEGS	Chromosorb W	60—80
E	20 ft × 3/8 in	30% SE 30		45—60
F		30% QF 1		45—60

p-*Menth*-8-*en*-2-*one Ethylene Acetal*.[48]—A mixture of *p*-menth-8-en-2-one (25) [2] (15·0 g, 0·986 mol), ethylene glycol (25 ml), and oxalic acid (500 mg) in benzene (300 ml) was refluxed in a Dean–Stark apparatus for 20 h, with Drierite in the side arm to aid in water removal. The mixture was cooled, the solvent removed under reduced pressure, and the residue extracted with petroleum. Washing of the extract with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride followed by drying (Na_2SO_4) and solvent removal provided an oil. Distillation gave the acetal (18·8 g, 97%), b.p. 52° at 0·25 mmHg; n_D^{25} 1·4749; $[\alpha]_D^{24}$ −7·5° (*c* 10·2 in $CHCl_3$) {lit.,[48] b.p. 69—71° at 1·0 mmHg; n_D^{22} 1·4737; $[\alpha]_D^{24}$ −6·1° (*c* 3·3 in $CHCl_3$)}; $\nu_{max.}$ (neat) 3100, 1650, 1170, 1090, and 889 cm^{-1}; τ (CCl_4) 9·18 (3H, d, *J* 5·5 Hz), 8·30 (3H, m), 6·15 (2H, s), 6·12 (2H, s), and 5·33br (2H, s).

5-*Acetyl*-2-*methylcyclohexanone Ethylene Acetal* (26).—A solution of the foregoing acetal (15 g, 0·076 mol) in methanol (400 ml) was saturated with ozone at −70°. The excess of ozone was removed by passing nitrogen through the solution, and work-up was effected by addition of dimethyl sulphide (15 ml). After 16 h at room temperature the excess of dimethyl sulphide was removed by bubbling nitrogen through the solution and the solvent was removed under reduced pressure. The residue was diluted with petroleum, washed with water and saturated aqueous sodium chloride, and dried (Na_2SO_4). Solvent removal and vacuum distillation afforded the *acetal* (26) (14·7 g, 97%) as an oil, b.p. 78° at 0·2 mmHg; n_D^{25} 1·4708; $[\alpha]_D^{24}$ −18·0° (*c* 12·5 in $CHCl_3$); $\lambda_{max.}$ 280 nm (ε 34); $\nu_{max.}$ (neat) 1710, 1170, and 1090 cm^{-1}; τ (CCl_4) 9·18 (3H, d, *J* 6 Hz), 7·92 (3H, s), and 6·07br (4H, s); *m/e* 198 (3·6%, M^+), 155 (100), 113 (27·2), 99 (16·8), 55 (13·2), and 43 (19·8) (Found: C, 66·75; H, 9·25. $C_{11}H_{18}O_3$ requires C, 66·65; H, 9·15%).

2,2-*Ethylenedioxy*-4-*methylcyclohexanecarboxylic Acid* (27).—Calcium hypochlorite (30 g) (Fisher Certified; 72·7% available chlorine) was dissolved in warm water (120 ml) and a solution of potassium carbonate (21 g) and potassium hydroxide (6 g) in water (60 ml) was added to give a slurry of calcium carbonate in potassium hypochlorite solution. Suction filtration followed by washing of the precipitate with water (25 ml) provided a clear solution of potassium hypochlorite. The acetal (26) (12·0 g, 6·06 mol) was added with vigorous stirring at such a rate as to maintain the reaction temperature between 55 and 60°. Stirring was continued for 3 h at room temperature, after which the

[46] M. Kolbe-Haugwitz and L. Westfelt, *Acta Chem. Scand.*, 1970, **24**, 1623.

[47] Spectral data in agreement with published values: P. de Mayo and R. E. Williams, *J. Amer. Chem. Soc.*, 1965, **87**, 3275.

[48] A. R. Pinder and R. A. Williams, *J. Chem. Soc.*, 1963, 2773.

excess of hypochlorite was destroyed by addition of aqueous 20% sodium disulphite (*ca.* 20 ml) (starch–iodide test). After washing the petroleum layer and cooling to 5° in an ice-bath, the solution of crude acid salt was acidified to pH 5 by dropwise addition of 12N-hydrochloric acid. The precipitated acid was filtered off (7·0 g); crystallisation from petroleum–ether (9 : 1) yielded the *acid* (27) (6·3 g, 52%), m.p. 71—74°. Recrystallisation from petroleum provided pure acid (27), m.p. 73—75·5°; $[\alpha]_D^{25}$ −31·1° (*c* 9·43 in $CHCl_3$); $\lambda_{max.}$ 212 nm (ε 75); $\nu_{max.}$ (CCl_4) 3300, 3000, 2650, 1700, 1170, and 1090 cm^{-1}; τ (CCl_4) 9·08br (3H, d, *J* 6 Hz), 6·05 (4H, s), and −1·09br (1H, s); *m/e* 200 (22·1%, M^+), 155 (100), 113 (77·4), 69 (36·8), 55 (47·9), and 41 (62·9) (Found: C, 60·15; H, 7·9. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·05%).

2-*Methyl*-5-(5-*methylhex*-4-*enoyl*)*cyclohexanone Ethylene Acetal* (28).[49]—The acid (27) (6·00 g, 0·03 mol) in benzene (10 ml) was treated with oxalyl chloride (6 ml; 0·07 mol) and refluxed for 30 min. The excess of oxalyl chloride was removed under reduced pressure and the crude acid chloride was used without further purification; $\nu_{max.}$ (neat) 1790, 1170, and 1090 cm^{-1}. A solution of the Grignard reagent prepared from 5-bromo-2-methylpent-2-ene [50] (5·9 g, 0·036 mol) was added dropwise to a cooled (0—5°) solution of the crude acid chloride in anhydrous ether (25 ml) and in the presence of copper(I) chloride (200 mg). The mixture was stirred for 16 h at room temperature and the organic layer was separated and treated in the usual way. Solvent removal and distillation of the residue (7·7 g) provided the ketone (28) (6·15 g, 77%), b.p. 103—104° at 0·03 mmHg; n_D^{20} 1·4852 (lit.,[49] b.p. 180—185° at 7 mmHg; n_D^{30} 1·4682); $[\alpha]_D^{25}$ −13·9° (*c* 10·6 in $CHCl_3$); $\lambda_{max.}$ 285 nm (ε 58); $\nu_{max.}$ (neat) 1705, 1170, 1090, and 835 cm^{-1}; τ (CCl_4) 9·18 (3H, d, *J* 6 Hz), 8·35 (6H, m), 6·09 (4H, s), and 4·98 (1H, m); *m/e* 266 (42·8%, M^+), 155 (97·4), 69 (84·2), 55 (100), 43 (92·3), and 42 (81·3) (Found: C, 72·2; H, 9·95. Calc. for $C_{16}H_{26}O_3$: C, 72·15; H, 9·85%).

2-*Methyl*-5-(5-*methyl*-1-*methylenehex*-4-*enyl*)*cyclohexanone Ethylene Acetal* (29).—Sodium hydride (50% oil dispersion; 0·806 g, 0·0168 mol) in a flame-dried flask (dry nitrogen atmosphere) was washed with a small portion of anhydrous ether and then heated with dry dimethyl sulphoxide (5 ml) in an oil-bath (70°) until liberation of hydrogen ceased. The resulting solution of sodium methylsulphonylmethanide was cooled in an ice-bath and methyltriphenylphosphonium bromide (6·00 g, 0·0168 mol) in dimethyl sulphoxide (10 ml) was added slowly. After warming to room temperature the keto-acetal (28) (3·01 g, 0·0113 mol) in dry tetrahydrofuran (10 ml) was added, and the solution was stirred for 24 h. The mixture was extracted with petroleum (3 × 70 ml) and the dimethyl sulphoxide layers were combined, diluted with water, and extracted with more petroleum (70 ml). The combined extracts were dried, concentrated, and chromatographed over alumina (20 g). Elution with petroleum provided the diene acetal (29) (2·45 g, 82%), homogeneous by g.l.c. (column A; 200°); $\nu_{max.}$ (neat) 3090, 1645, 1170, 1090, 890, and 830 cm^{-1}; τ (CCl_4) 9·17br (3H, d, *J* 6 Hz), 8·38—8·32 (6H), 4·10 (4H, s), 5·33br (2H, s), and 4·94 (1H, m).

2-*Methyl*-5-(5-*methyl*-1-*methylenehex*-4-*enyl*)*cyclohexanone* (30).—The acetal (29) (2·16 g) was dissolved in acetone (100 ml) and treated with 6N-hydrochloric acid (3 ml). The reaction was quenched after 4 h by addition of saturated aqueous sodium hydrogen carbonate, solvent was removed, and the residue was dissolved in petroleum and washed with water. Evaporation provided an oil (2·14 g) which, on distillation, provided the ketone (30) [1·82 g; 82% overall yield from (28)], b.p. 80—82° at 0·04 mmHg (lit.,[49] 135—138° at 5 mmHg); $\nu_{max.}$ (neat) 1710, 1650, 892, and 835 cm^{-1}; τ (CCl_4) 9·03 (3H, d, *J* 6·0 Hz), 8·40 and 8·32 (6H, two singlets), 5·23 (2H, s), and 4·94 (1H, m).

p-*Menth*-8-*en*-2-*one* 2,2-*Dimethyltrimethylene Acetal* (31).—(+)-*p*-Menth-8-en-2-one (25) [2] {120 g, 0·79 mol; $[\alpha]_D^{29}$ +18·3° ($CHCl_3$)} was refluxed with a mixture of 2,2-dimethylpropane-1,3-diol (90 g) and oxalic acid (3 g) in benzene (150 ml) in a Dean–Stark apparatus for 4 days. G.l.c. analysis (column A; 160°) of the mixture indicated 93% product and 7% starting material; longer reaction times did not improve the yield of product. The mixture was washed with saturated aqueous sodium hydrogen carbonate and twice with saturated aqueous sodium chloride and dried (Na_2SO_4). Solvent removal and distillation afforded the *acetal* (31) (155 g, 82%) and a mixture (22 g) of starting material and product which, on redistillation, provided a further amount (16 g) of (31) (overall yield 91%), b.p. 50° at 0·025 mmHg; n_D^{20} 1·4748; $[\alpha]_D^{24}$ −9·4° (*c* 10·3 in $CHCl_3$); $\nu_{max.}$ (neat) 3100, 1650, 1150, 1100, and 88 cm^{-1} (Found: C, 75·6; H, 11·15. $C_{15}H_{26}O_2$ requires C, 75·6; H, 11·0%).

The n.m.r. spectrum of the acetal (31) was complex; [51] analysis by g.l.c. (column D; 100°) indicated the presence of two components of relative retention times (t_R) 70 and 79 min (ratio 3 : 1). Samples of each component were collected and the component of t_R 70 min was assigned the *trans*-structure (31; β-Me), $[\alpha]_D^{25}$ −20° (*c* 4·05 in $CHCl_3$); τ (CCl_4; 100 MHz) 9·33 (3H, s), 9·05 (3H, m), 8·88 (3H, s), 8·33 (3H, m), 7·32 (1H, m, major coupling *J* 13 Hz), 6·79 (2H, m, major coupling *J* 11 Hz), 6·46 and 6·30 (2H, two doublets, *J* 11 Hz), and 5·38 (2H, m); *m/e* 238 (24·7%, M^+), 155 (69·2), 95 (69·4), 69 (100), 56 (85·3), 55 (89·2), 43 (83·9), and 41 (83·3).

The component having t_R 79 min was assigned the *cis*-structure (31; α-Me), $[\alpha]_D^{25}$ +23° (*c* 0·90 in $CHCl_3$); τ (CCl_4; 100 MHz) 9·12 (3H, s), 9·10 (3H, d, *J* 7 Hz), 9·09 (3H, s), 8·31 (3H, m), 6·63 (4H, m, $W_{\frac{1}{2}}$ 4 Hz), and 5·37 (2H, m); *m/e* 238 (3·4%, M^+), 181 (53·5), 155 (50·4), 69 (100), 55 51·6), and 41 (67·5).

Alternative Synthesis of the Ketone (30).—A solution of n-butyl-lithium–tetramethylethylenediamine (1 : 1 complex) was prepared by slow addition of the diamine (15 ml, 0·1 mol) to n-butyl-lithium (2·35M; 43 ml, 0·1 mol) in hexane under dry nitrogen. To the resultant yellow solution was added the acetal (31) (19·5 g, 0·082 mol). After stirring for 18 h the deep red solution was cooled to −50° and treated slowly with 1-chloro-3-methylbut-2-ene (10·5 g, 0·1 mol). After warming to room temperature, water was added cautiously and the mixture was extracted with ether and washed with 3N-hydrochloric acid. Removal of the acetal function (3N-HCl–Me_2CO) followed by distillation afforded *p*-menth-8-en-2-one (3 g, 40%) and dihydrocryptomerion (30) (9·5 g, 85% based on consumed starting material), $[\alpha]_D^{19}$ +8·26 (*c* 4·7 in $CHCl_3$), b.p. 100—103° at 0·04 mmHg, identical (g.l.c., i.r., n.m.r.) with material prepared by the former route.

[49] O. P. Vig, J. M. Sehgal, M. M. Mahajan, and S. D. Sharma, *J. Indian Chem. Soc.*, 1969, **46**, 887.

[50] M. Julia, S. Julia, and R. Guegan, *Bull. Soc. chim. France*, 1960, **26**, 1072.

[51] *Cf.* K. Pihlaja, G. M. Kellie, and F. G. Riddell, *J.C.S. Perkin II*, 1972, 252.

2-Acetoxy-1-methyl-4-(5-methyl-1-methylenehex-4-enyl)-cyclohexene (33).—A mixture of the ketone (30) (1·2 g, 5·5 mmol) and toluene-*p*-sulphonic acid monohydrate (60 mg) in isopropenyl acetate (20 ml) was heated for 24 h with slow distillation of volatile materials. After washing with saturated aqueous sodium hydrogen carbonate and drying (Na_2SO_4) the crude product was chromatographed over alumina (35 g) affording a mixture (1·3 g) of two compounds. Pure samples of each were obtained by preparative g.l.c. (column E; 250°; t_R 58 and 66 min, respectively; ratio 1 : 3) followed by distillation.

1-Acetoxy-3-(5-methyl-1-methylenehex-4-enyl)-6-methylcyclohexene (34), t_R 58 min, showed $\nu_{max.}$ (neat) 2950, 1755, 1680, 1645, 1210, 915, and 895 cm^{-1}; τ (CCl_4) 9·10 (3H, d, J 7 Hz), 8·46 and 8·39 (6H, two singlets), 7·96 (3H, s), 5·23br (2H, d), and 4·90 (2H, m); *m/e* 262 (0·6%, M^+), 220 (96·9), 151 (99·9), 109 (61·4), 107 (6·13), and 69 (100).

The *triene* (33), t_R 66 min, showed $\nu_{max.}$ (neat) 2950, 1750, 1710, 1645, 1220, 1210, 890, and 830 cm^{-1}; τ (CCl_4) 8·55, 8·44, and 8·34 (9H, three singlets), 7·96 (3H, s), 5·26br (2H, d), and 4·93 (1H, m); *m/e* 262 (20·1%, M^+), 220 (100), 202 (68·8), 151 (70·7), 135 (65·0), and 109 (69·4) (Found: C, 78·0; H, 10·1. $C_{17}H_{26}O_2$ requires C, 77·8; H, 10·0%).

Cyclisation of the Acetoxy-triene (33).—To wet methylene chloride (1500 ml) saturated with boron trifluoride gas was added a solution of the enol acetate (33) (5·4 g, 0·02 mol) in methylene chloride (500 ml) during 30 min. The mixture was stirred vigorously and a slow stream of boron trifluoride was maintained for 2 h. Neutralisation with saturated aqueous sodium hydrogen carbonate and work-up in the usual way afforded the crude product (4·4 g), which was chromatographed over silica gel and distilled. G.l.c. analysis (column B; 155°) indicated that the distillate contained three main components (A—C), t_R 3·8, 5·6, and 7·5 min, respectively. Preparative g.l.c. (column E; 240°) afforded pure samples.

Component A (37a and b) (25—30%) showed $\nu_{max.}$ (neat) 1740 and 1410 cm^{-1}; τ (CCl_4) 9·21 (3H, s), and 9·10, 9·05, 9·00, and 8·94 (6H, four singlets); *m/e* 220 (22·5%), 105 (68·4), 77 (100), 69 (31·6), 53 (34·9), and 43 (34·6); component B (39a and b) (5%) showed $\nu_{max.}$ (neat) 1715 and 1404 cm^{-1}; τ (CCl_4) 9·22 (3H, d, J 5 Hz), 9·07 (3H, s), 9·03 (3H, s), and 8·55br (6 or 7H, s, $W_{\frac{1}{2}}$ 7 Hz); *m/e* 220 (22·5%), 111 (68·9), 110 (100), 109 (94·1), 69 (81·3), and 43 (67·3); and component C (38) (40—45%) showed $\lambda_{max.}$ 237 nm (ε 15,000); $\nu_{max.}$ (neat), 1670, 1625, 1210, and 880 cm^{-1}; τ (CCl_4) 9·03 (6H, s), 8·93 (3H, d, J 6·5 Hz), and 4·25 (1H, s); *m/e* 220 (64·6%, M^+), 178 (59·8), 163 (66·6), 95 (93·5), 79 (58·0), and 41 (100) (Found: C, 81·85; H, 10·95. Calc. for $C_{15}H_{24}O$: C, 81·75; H, 11·0%).

5-(3,3-Dimethylcyclohexenyl)-2-methylcyclohexanone (35).—The ketone (30) (500 mg) in methylene chloride (100 ml) was added rapidly to wet methylene chloride (350 ml) presaturated with boron trifluoride. During the addition boron trifluoride gas was passed through the solution and after 5 min the mixture was worked up by adding saturated aqueous sodium hydrogen carbonate, removing the excess of boron trifluoride with a stream of nitrogen, and washing the methylene chloride extracts with water. Removal of the solvent provided an oil which was shown by g.l.c. (column C; 200°) to consist of starting material (12%) and product (88%). Preparative g.l.c. of the product yielded the *cyclohexenylcyclohexanone* (35) as an oil, $\nu_{max.}$ 1710 cm^{-1}; τ (CCl_4) 9·08 (9H, s), and 4·60 (1H, m), M^+ 220 (Found: C, 81·9; H, 11·2. $C_{15}H_{24}O$ requires C, 81·75; H, 11·0%).

Cyclisation of 2-Acetoxy-4-(3,3-dimethylcyclohexenyl)-1-methylcyclohexene (36).—A mixture of 5-(3,3-dimethylcyclohexenyl)-2-methylcyclohexanone (35) (240 mg), isopropenyl acetate (15 ml), and toluene-*p*-sulphonic acid (20 mg) was heated for 2 days with slow removal of volatile material by distillation. The residue was worked up in the usual way and the product (240 mg, 84%) was shown by n.m.r. and g.l.c. (column A; 160°) to be a mixture of enol acetates from which the major *component* (36) (80%) was isolated by preparative g.l.c. (column E); $\nu_{max.}$ 1760, 1710, 1220, and 1210 cm^{-1}; τ (CCl_4) 9·13 (6H, s), 8·56 (3H, s), 7·98 (3H, s), and 4·64br (1H, s); M^+ 262 (Found: C, 78·05; H, 10·0. $C_{17}H_{26}O_2$ requires C, 77·8; H, 10·0%).

Treatment of compound (36) with boron trifluoride for 20 min as already described provided a mixture with three major components. These were shown by g.l.c. (column B; 155°) and spectral comparison to be (37a and b), (38), and (39a and b) (ratio 5 : 1 : 3).

Separation of the Tricyclic Ketones (37a *and* b) *and Formation of 7-(3,3-Dimethylcyclohexyl)-1-methylnorbornan-2-one Oxime* (41).—To a solution of the tricyclic ketones (37a and b) (350 mg) in dry tetrahydrofuran (3 ml) containing a trace of triphenylmethane as indicator was added sufficient butyl-lithium to give the red colour of triphenylmethanide anion. The solution was cooled to −50° and pure acetic anhydride (0·35 ml) was added. After warming to room temperature the mixture was extracted with ether and the extracts were washed with saturated aqueous sodium hydrogen carbonate and water. Removal of the solvent provided an oil which, on column chromatography over silica (petroleum–benzene, 1 : 1), gave a mixture of enol acetates (40a and b) (280 mg, 77%), separated by preparative g.l.c. (column A; 225°). The enol acetate (40b) (25 mg) [τ (CCl_4) 9·20, 9·17, and 9·10 (9H, three singlets), 7·98 (3H, s), and 4·50 (1H, d, J 4 Hz)] with shorter retention time was dissolved in acetone (3 ml) and treated with N-hydrochloric acid (3 drops). After 24 h at room temperature the ether was removed and the residue was extracted with ether. Work-up in the usual way provided a low-melting solid which on sublimation gave the tricyclic ketone (37b), m.p. 62—65°; $\nu_{max.}$ (Nujol) 1740 and 1410 cm^{-1}; τ (CCl_4) 9·24, 9·12, 9·10, and 9·03 (9H, four singlets). Treatment of (37b) (15 mg) with hydroxylamine hydrochloride (25 mg), pyridine (1 ml), and ethanol–water (10 : 1; 1 ml) provided a product which, after column chromatography over silica (elution with ethyl acetate–benzene, 1 : 9), provided the oxime (41) as a white crystalline solid, m.p. 165—168°. The *X*-ray crystallographic analysis which confirmed the structure of this compound was carried out by Drs. J. Trotter and S. J. Rettig of this department and will be published in the near future.

3-(Tetrahydropyran-2-yloxy)propyltriphenylphosphonium Iodide.—Sodium iodide (100 g, 0·667 mol) was added to 3-chloropropan-1-ol (30·0 g, 0·317 mol) in acetone (500 ml) and the solution was refluxed under nitrogen for 48 h. The solvent was removed and the residue was dissolved in ether and washed with aqueous sodium disulphite and water. Evaporation provided an oil (57·6 g) which, on distillation, yielded 3-iodopropan-1-ol (55·2 g, 93%), b.p. 97—99 at 15 mmHg; n_D^{15} 1·5520; $\nu_{max.}$ (neat) 3350 and 1040 cm^{-1}; τ (CCl_4) 7·93 (2H, quintet, J 6 Hz), 6·67 (2H, t, J 6 Hz), 6·29 (2H, t, J 6 Hz), and 5·97 (1H, s).

Treatment of 3-iodopropan-1-ol (37·2 g, 0·2 mol) with dihydropyran (50 ml) and 12N-hydrochloric acid (1 drop) at room temperature for 16 h followed by removal of excess of

dihydropyran under reduced pressure provided 1-iodo-3-(tetrahydropyran-2-yloxy)propane. A mixture of the crude iodide and triphenylphosphine (53 g, 0·2 mol) in dry benzene (240 ml) was refluxed for 85 h and after filtration the solvent was removed to yield 3-(tetrahydropyran-2-yloxy)propyltriphenylphosphonium iodide, m.p. 162—164 (98 g, 92%) which was dried over P_2O_5 for 8 h before further use.

5-(4-Hydroxy-1-methylbut-1-enyl)-2-methylcyclohexanone Ethylene Acetal (46; X = OH).—A solution of sodium methylsulphonylmethanide [from sodium hydride (50% oil dispersion; 8·00 g, 0·167 mol) and dimethyl sulphoxide (50 ml)] was cooled in an ice-bath and mixed with a solution of 3-(tetrahydropyran-2-yloxy)propyltriphenylphosphonium iodide (88 g, 0·165 mol) in dimethyl sulphoxide (150 ml). After 10 min, 5-acetyl-2-methylcyclohexanone ethylene acetal (26) (25·0 g, 0·126 mol) was added to the deep red solution and the mixture was stirred for 43 h at room temperature. Work-up was effected by several extractions with petroleum and washing each extract with dimethyl sulphoxide and then water. The extracts were concentrated and dried by sequential addition and evaporation of several portions of benzene. The crude product (*ca.* 50 g) exhibited i.r. peaks at 1160, 1080, and 835 cm^{-1} and no hydroxyl or carbonyl absorption. Without further purification selective removal of the tetrahydropyranyl group was performed by refluxing the crude product with ethylene glycol (106 ml), oxalic acid (1 g), and benzene (200 ml) for 48 h in a Dean–Stark apparatus. The cooled mixture was washed with saturated aqueous sodium hydrogen carbonate and water, the solvent was removed, and the residue was distilled to provide the *hydroxy-acetal* (46; X = OH), b.p. 100—102 at 0·02 mmHg (17·3 g, 57%). Hydrolysis of the residues under the conditions already described followed by distillation afforded a further amount (4 g) of (46; X = OH), b.p. 100—102° at 0·02 mmHg; $[\alpha]_D^{24}$ +20·4° (*c* 10·9 in $CHCl_3$); $\nu_{max.}$ (neat) 3450, 1165, 1080, and 835 cm^{-1}; τ (CCl_4) 9·18 (3H, d, *J* 5·5 Hz), 8·41 (3H, d, *J* 1·5 Hz), 7·00 (1H, s), 6·52 (2H, t, *J* 7 Hz), 6·11 (4H, s), and 4·95 (1H, t, *J* 7 Hz); *m/e* 240 (65·3%, M^+), 183 (100), 113 (100), 87 (72·6), 86 (62·1), and 41 (81·0) (Found: C, 70·15; H, 9·9. $C_{14}H_{24}O_3$ requires C, 69·95; H, 10·05%).

5-(4-Chloro-1-methylbut-1-enyl)-2-methylcyclohexanone Ethylene Acetal (46; X = Cl).—A solution of the hydroxy-acetal (46; X = OH) (21·5 g, 0·0892 mol) in carbon tetrachloride (150 ml) (dried over $CaCl_2$) was treated with tri-n-octylphosphine (37·0 g, 0·0997 mol). The mildly exothermic reaction was moderated during the addition with a cold water bath and rapid stirring. Stirring was continued for 1 h at room temperature and the solvent was removed under reduced pressure. Distillation of the residue afforded the *chloro-acetal* (46; X = Cl) (17·8 g, 78%), b.p. 109—111° at 0·02 mmHg; n_D^{20} 1·4960; $[\alpha]_D^{24}$ +17·8° (*c* 10·8 in $CHCl_3$); $\nu_{max.}$ (neat) 1168, 1090, and 835 cm^{-1}; τ (CCl_4) 9·18 (3H, d, *J* 5·5 Hz), 8·38 (3H, m), 7·48 (2H, m), 6·57 (2H, t, *J* 7 Hz), 6·10 (2H, s), and 4·92 (1H, sextet, *J* 7 and 1·5 Hz); *m/e* 260 (25·7%, M^+), 258 (63·2, M^+), 203 (86·2), 292 (54·0), 201 (100), 113 (76·4), and 86 (62·6) (Found: C, 64·8; H, 8·85; Cl, 13·55. $C_{14}H_{23}ClO_2$ requires C, 65·0; H, 8·95; Cl, 13·7%).

5-(4-Chloro-1-methylbut-1-enyl)-2-methylcyclohexanone (42; R = $CH_2{\cdot}CH_2Cl$).—The chloro-acetal (46; X = Cl) (12·0 g, 0·463 mol) in acetone (125 ml) was treated with 6N-hydrochloric acid (0·5 ml) and after 16 h the reaction was quenched with saturated aqueous sodium hydrogen carbonate (15 ml). The crude product (10 g) was distilled to yield the chloro-ketone (42; R = $CH_2{\cdot}CH_2Cl$) (8·48 g, 85%), b.p. 80—85° at 0·02 mmHg); $\nu_{max.}$ (neat) 1710, 1660, 850, and 835 cm^{-1}; τ (CCl_4) 8·97 (3H, d, *J* 6 Hz), 8·23 (3H, d, *J* 1·5 Hz), 6·51 (2H, t, *J* 7 Hz), and 4·86 (1H, m).

2-Acetoxy-4-(4-chloro-1-methylbut-1-enyl)-1-methylcyclohexene (43; R = $CH_2{\cdot}CH_2Cl$).—The chloro-ketone (42; R = $CH_2{\cdot}CH_2Cl$) (8·90 g, 0·414 mol) was treated with isopropenyl acetate (15 ml) and toluene-*p*-sulphonic acid monohydrate (100 mg) for 48 h under slow distillation conditions (head temperature 50—70°). The mixture was cooled to room temperature, diluted with petroleum, washed with saturated aqueous sodium hydrogen carbonate and then water, and dried (Na_2SO_4). Solvent removal provided a crude mixture which was distilled at reduced pressure yielding a mixture of isomeric enol acetates (9·61 g, 90%), b.p. 89—92° at 0·02 mmHg; two main components by g.l.c. analysis (column A, 175°) in the ratio 5·5 : 1·0 for (43; R = $CH_2{\cdot}CH_2Cl$) and its isomer (44; R = $CH_2{\cdot}CH_2Cl$) respectively (t_R 5·1 and 4·2 min). Pure enol acetate (43; R = $CH_2{\cdot}CH_2Cl$) was obtained by preparative g.l.c. (column E; 225°); $\nu_{max.}$ (neat) 1750, 1710, 1210, and 850 cm^{-1}; τ (CCl_4) 8·50 (3H, s), 8·34 (3H, d, *J* 1·5 Hz), 7·95 (3H, s), 6·58 (2H, t, *J* 7 Hz), and 4·87 (1H, m).

5-(4-Hydroxy-1-methylbut-1-enyl)-2-methylcyclohexanone 2,2-Dimethyltrimethylene Acetal (49; X = OH).—To n-butyl-lithium (135 ml, 0·322 mol; 2·38M in hexane) in a dry nitrogen atmosphere was added tetramethylethylenediamine (48·0 ml, 0·414 mol) followed by *p*-menth-8-en-2-one 2,2-dimethyltrimethylene acetal (31) (75·7 g, 0·317 mol). The mixture was kept under nitrogen at room temperature for 32 h during which time a deep red colour developed. Ethylene oxide gas in a carrier stream of nitrogen was passed rapidly through the solution (cooled in an ice-bath) until the red colour had disappeared (*ca.* 15 min). Residual traces of ethylene oxide were removed by passing nitrogen through the solution at room temperature. Crushed ice was added carefully until the initially formed inorganic precipitate had redissolved, and the organic phase was separated, washed twice with water, and then neutralised by shaking with dilute sodium hydrogen sulphate. After drying (Na_2SO_4) the combined organic extracts were concentrated and distilled under reduced pressure to provide starting material (36·2 g, 48%) and the *hydroxy-acetal* (49; X = OH) (42·6 g, 48%) (91% yield based on consumed starting material) as a viscous liquid, b.p. 120° at 0·02 mmHg; n_D^{20} 1·4901; $[\alpha]_D^{24}$ −16·5° (*c* 6·05 in $CHCl_3$); $\nu_{max.}$ (neat) 3420, 1645, 1148, 1098, and 890 cm^{-1}; τ (CCl_4) 9·0 (9H, m), 8·22br (1H), 6·5 (6H, m), and 5·27 (2H, s); *m/e* 282 (16·6%, M^+), 225 (41·9), 155 (73·2), 69 (100), 55 (36·5), and 41 (43·4) (Found: C, 72·0; H, 10·55. $C_{17}H_{30}O_3$ requires C, 72·3; H, 10·7%).

5-(4-Chloro-1-methylbut-1-enyl)-2-methylcyclohexanone 2,2-Dimethyltrimethylene Acetal (49; X = Cl).—Tri-n-octylphosphine (113 g, 0·305 mol) was carefully added to a stirred, cooled solution of the hydroxy-acetal (49; X = OH) (81·3 g, 0·288 mol) in carbon tetrachloride (50 ml). The mixture was stirred for 1 h at room temperature, the solvent was removed, and the residue was distilled under reduced pressure to provide the *chloro-acetal* (49; X = Cl) (72·2 g, 84%), b.p. 110—112° at 0·07 mmHg; n_D^{20} 1·4910; $[\alpha]_D^{25}$ −10·6° (*c* 10·7 in $CHCl_3$); $\nu_{max.}$ (neat) 1145, 1098, and 892 cm^{-1}; τ (CCl_4) 9·0 (9H, m), 6·5 (6H, m), and 5·21 (2H, m); *m/e* 302 (9·4%, M^+), 300 (26·0, M^+), 265 (43·1), 243 (69·9), 155 (100), 69 (60·2), and 55 (48·8) (Found: C, 68·15; H, 9·7; Cl, 11·6. $C_{17}H_{29}ClO_2$ requires C, 67·85; H, 9·7; Cl, 11·8%).

5-(4-*Chloro*-1-*methylbut*-1-*enyl*)-2-*methylcyclohexanone* (50).—The chloro-acetal (49; X = Cl) (55·2 g, 0·185 mol) was dissolved in acetone and treated with 6N-hydrochloric acid (5 ml) at room temperature. After 16 h the mixture was worked up in the usual way to provide an oil (52 g), which on distillation yielded the *chloro-ketone* (50) (36·0 g, 91%), b.p. 82° at 0·03 mmHg; $[\alpha]_D^{34}$ +6·9° (*c* 2·31 in $CHCl_3$); n_D^{20} 1·4946; $\lambda_{max.}$ 284 nm (ε 32); $\nu_{max.}$ (neat) 1710, 1645, 895, and 730 cm^{-1}; τ (CCl_4) 9·05 and 8·98 (3H, 2 doublets, *J* 7 and 6 Hz), 6·08 (2H, t, *J* 6 Hz), and 5·15 (2H, m); *m/e* 216 (19·2%, M^+), 214 (86·0, M^+), 137 (90·0), 109 (86·6), 95 (86·6), 81 (96·6), 68 (86·6), and 55 (100) (Found: C, 67·05; H, 9·05; Cl, 16·3. $C_{12}H_{19}ClO$ requires C, 67·1; H, 8·9; Cl, 16·5%).

2-*Acetoxy*-4-(4-*chloro*-1-*methylbut*-1-*enyl*)-1-*methylcyclohexene* (52).—A mixture of the chloro-ketone (50) (30·7 g, 0·143 mol), isopropenyl acetate (76 ml), and toluene-*p*-sulphonic acid monohydrate (500 mg) was heated for 4 days with slow removal of volatile materials by distillation. The mixture was cooled, diluted with petroleum, and washed with saturated aqueous sodium hydrogen carbonate, water, and saturated aqueous sodium chloride. After drying (Na_2SO_4) the solvent was removed and the residue was distilled under reduced pressure through a 12 cm Vigreux column to provide a mixture of the enol acetate (52) and its isomer (51) in the ratio 72 : 28 as judged by g.l.c. analysis (column A; 175°; t_R 5·2 and 4·2 min, respectively). Pure *enol acetate* (52) obtained by redistillation had b.p. 95° at 0·03 mmHg; n_D^{20} 1·4948; $[\alpha]_D^{25}$ +56·2° (*c* 10·6 in $CHCl_3$); $\nu_{max.}$ (film) 3100, 1745, 1710, 1645, 1210, and 895 cm^{-1}; τ (CCl_4) 8·50 (3H, s), 7·93 (3H, s), 6·51 (2H, t, *J* 6 Hz), and 5·17 (2H, m); *m/e* 258 (5·5%, M^+), 256 (11·4, M^+), 211 (67·7), 132·5 (59·9), 104 (68·9), and 89 (100) (Found: C, 65·35; H, 8·4; Cl, 13·55. $C_{14}H_{21}ClO_2$ requires C, 65·5; H, 8·25; Cl, 13·8%).

8- *and* 9-(2-*Chloroethyl*)*camphor* (48a *and* b).—(*a*) Cyclisation conditions and results were identical for the enol acetates (43; R = $CH_2{\cdot}CH_2Cl$) and (52). A three-necked flask (2 l) was fitted with two addition funnels, a gas inlet tube extending to the bottom of the flask, and a magnetic stirrer. A solution of the enol acetate (43; R = $CH_2{\cdot}CH_2Cl$) or (52) (5·0 g, 0·0195 mol) in methylene chloride (1000 ml) was added in 200 ml portions at 20 min intervals to a vigorously stirred mixture of methylene chloride (800 ml) and water (2 ml) (mixture was presaturated with boron trifluoride gas and a moderate flow of the gas was maintained throughout the addition process). Water was added in 2 ml portions 5 min before each addition of enol acetate. The mixture was stirred for 2 h and then transferred to a separating funnel (2 l). The organic phase was washed with water, dilute aqueous sodium hydrogen carbonate, and saturated aqueous sodium chloride. Solvent removal afforded a pale yellow oil which was dissolved in petroleum and filtered through Celite (5 g). Removal of solvent afforded an oil (4 g, 95%) which was shown by g.l.c. (column A; 160°) to consist of 8-(2-chloroethyl)camphor (48a) and 9-(2-chloroethyl)camphor (48b) (55—60%), and the enone (47) (35—40%) (t_R 4·6 and 6·5 min, respectively). Two minor components (t_R 3·1 and 3·6 min) were present to the extent of *ca.* 2 and 4%, respectively.

The difficulty involved in separating large quantities of isomeric enol acetates [*e.g.* (52) and (51)] led to the use of the mixture of isomers in the cyclisation step. Cyclisation of a mixture (23 g) of enol acetates (52) and (51) (76 : 24), under the conditions already described, provided an oil (18·4 g) which was distilled twice under reduced pressure to yield 8-(2-chloroethyl)camphor (48a) and 9-(2-chloroethyl)camphor (48b) (6·7 g, 46%), {b.p. 64—65° at 0·03 mmHg; $[\alpha]_D^{25}$ 0° (*c* 10·0 in $CHCl_3$); n_D^{20} 1·4980; $\lambda_{max.}$ 285 nm (ε 44); $\nu_{max.}$ (film) 1740 and 1410 cm^{-1}; τ (CCl_4) 9·11 (3H, s), 9·16 and 9·03 (3H, two singlets), and 6·55 and 6·48 (2H, two overlapping triplets, *J* 6 Hz); τ (C_6H_6) 9·52 and 9·45 (3H, two singlets), 9·12 (3H, s), and 7·04 and 6·92 (2H, two overlapping triplets, *J* 7 Hz); *m/e* 216 (33·6%, M^+), 214 (97·3, M^+), 157 (92·6), 109 (100), 81 (93·3), and 69 (85·2)} and 3-(4-*chloro*-1-*methylbutyl*)-6-*methylcyclohex*-2-*enone* (47), b.p. 76° at 0·05 mmHg; n_D^{20} 1·5032; $[\alpha]_D^{25}$ +0·2° (*c* 10·0 in $CHCl_3$); $\lambda_{max.}$ 234 (ε 15,000) and 339 nm (ε 58); $\nu_{max.}$ (film) 1670, 1210, and 883 cm^{-1}; τ (CCl_4) 8·91 (3H, d, *J* 6·5 Hz), 8·87 (3H, d, *J* 6·5 Hz), 6·52br (2H, t, *J* 6 Hz), and 4·30 (1H, s); *m/e* 216 (33·0%, M^+), 214 (73·5, M^+), 172 (63·0), 137 (45·9), 109 (65·3), 96 (100), and 95 (67·0) (Found: C, 67·4; H, 8·85; Cl, 16·3. $C_{12}H_{19}ClO$ requires C, 67·1; H, 8·9; Cl, 16·5%).

Samples of the two minor components from the cyclisation were isolated by preparative g.l.c. (column E). The component with t_R 3·1 min showed $\lambda_{max.}$ 299 nm (ε 48); $\nu_{max.}$ (film) 1760 cm^{-1}; τ (CCl_4) 8·96 (3H, s), 8·77 (3H, s), 7·37 (2H, s), and 6·54 (2H, m). That with t_R 3·6 min showed $\nu_{max.}$ (film) 1760 cm^{-1}; τ (CCl_4) 8·96 (3H, s), 8·78 (3H, s), 7·51 and 7·37 (2H, two singlets), and 6·53 (2H, m).

(*b*) The chloro-ketone (50) (10 g) in anhydrous ethyl acetate (100 ml) was treated at room temperature for 6 min with an ethyl acetate solution 1·06M in acetic anhydride and 0·023M in perchloric acid prepared by adding acetic anhydride (50 ml) and perchloric acid (1 ml) to anhydrous ethyl acetate (300 ml) and making the volume up to 500 ml. Vigorous stirring was maintained throughout and the reaction was terminated by adding solid sodium hydrogen carbonate (10 g). Removal of solvent and acetic anhydride at 40° and 1 mmHg provided an oil which on distillation yielded a mixture of enol acetates (7·1 g, 59%), b.p. 94—97° at 0·05 mmHg, and a fraction (3·1 g) containing starting material. Re-treatment of the latter with acetic anhydride–perchloric acid afforded a further quantity (2·5 g) of the enol acetate mixture. The overall yield of enol acetate product was 80% and g.l.c. analysis (column A; 160°) indicated that tetrasubstituted and trisubstituted enol acetates [(52) and (51)] were present in the ratio 93 : 7. However, analysis of the n.m.r. spectrum (see before) demonstrated that migration of the acyclic double bond had occurred to some extent. In any event treatment of the *total* enol acetate mixture under the cyclisation conditions described provided bicyclic chloro-ketones (48a and b) in 55% yield.

8- *and* 9-(2-*Chloroethyl*)*camphor Ethylene Acetals* (53a *and* b; X = Cl).—A mixture of 8- and 9-(2-chloroethyl)-camphor (48a and b) (6·50 g, 0·0303 mol) was refluxed with ethylene glycol (17 ml), toluene-*p*-sulphonic acid monohydrate (600 mg), and benzene (30 ml) in a Dean–Stark apparatus for 4 days. The cooled mixture was washed with saturated aqueous sodium hydrogen carbonate, water, and saturated aqueous sodium chloride. After drying (Na_2SO_4) the solvent was removed and the residue distilled under reduced pressure yielding 8- and 9-(2-chloroethyl)-camphor ethylene acetals (53a and b; X = Cl) (7·43 g, 95%), b.p. 73° at 0·04 mmHg; n_D^{20} 1·5010; $[\alpha]_D^{25}$ 0° (*c* 10·4 in $CHCl_3$); $\nu_{max.}$ (film) 1120 and 1044 cm^{-1}; τ (CCl_4) 9·23 (3H, s), 9·16 and 9·00 (3H, s, diastereoisomeric tertiary Me), 6·57 and 6·53 (2H, overlapping triplets, *J* 6 Hz), and 6·23

(4H, m); *m/e* 260 (41·3%, M^+), 258 (55·5, M^+), 69 (79·2), 55 (93·0), 43 (100), and 42 (90·4) (Found: C, 65·03; H, 8·8; Cl, 13·5. Calc. for $C_{14}H_{23}ClO_2$: C, 64·95; H, 8·95; Cl, 13·7%).

8- *and* 9-(2-*Iodoethyl*)*camphor Ethylene Acetals* (53a *and* b; X = I).—A mixture of 8- and 9-(2-chloroethyl)camphor ethylene acetals (53a and b; X = Cl) (5·15 g, 0·02 mol), sodium iodide (7·50 g, 0·05 mol), anhydrous calcium carbonate (700 mg), and dry acetone (10 ml) was refluxed in a dry nitrogen atmosphere for 48 h. After cooling, the mixture was transferred under nitrogen to dry pentane (100 ml) and immediately filtered over Celite (10 g; oven-dried at 100° for 24 h). Removal of the solvent and distillation of the residue afforded 8- and 9-(2-iodoethyl)-camphor ethylene acetals (53a and b; X = I) (6·75 g, 97%), b.p. 89—90° at 0·02 mmHg; n_D^{20} 1·5409; $[\alpha]_D^{25}$ 0° (*c* 2·09 in $CHCl_3$); $\nu_{max.}$ (film) 1116 and 1045 cm^{-1}; τ (CCl_4) 9·22 (3H, s), 9·15 and 8·98 (3H, two singlets, diastereoisomeric tertiary Me), 6·84 (2H, t, *J* 6 Hz), and 6·20 (4H, m); *m/e* 350 (10·0%, M^+), 223 (81·8), 125 (34·7), 113 (30·6), 95 (100), and 87 (32·7) (Found: C, 48·0; H, 6·5; I, 36·1. Calc. for $C_{14}H_{23}IO_2$: C, 48·05; H, 6·6; I, 36·35%).

(±)-*Campherenone* [1,7-*Dimethyl*-7-(4-*methylpent*-3-*enyl*)-*norbornan*-2-*one*] *and* (±)-*Epicampherenone Ethylene Acetals* [(54) *and* (55)].—A mixture of the iodo-acetals (53a and b; X = I) (6·00 g, 0·017 mol) was added to a solution of triphenylphosphine (4·6 g, 0·0176 mol) in dry benzene (10 ml) and the resulting mixture was refluxed for 38 h under nitrogen. The solvent was removed and the crude triphenylphosphonium salt was dissolved in dry dimethyl sulphoxide (5 ml) and added dropwise to a cooled (ice-bath) solution of sodium methylsulphonylmethanide [from sodium hydride (0·864 g, 0·018 mol)] in dimethyl sulphoxide (5 ml). The deep red solution was allowed to warm to room temperature and after 5 min dry acetone (1·5 ml, 0·02 mol) was added. The mixture was stirred for 70 h and then extracted with petroleum (3 × 70 ml). The extracts were washed with dimethyl sulphoxide, water, and saturated brine, solvent was removed, and the residue was distilled to provide a mixture of ethylene acetals of campherenone and epicampherenone, b.p. 75—76° at 0·03 mmHg (3·83 g, 84%). Separation by preparative g.l.c. (column E; 240°) afforded two components, t_R 42 and 47 min which were further purified by short-path distillation. The component with t_R 42 min was *campherenone ethylene acetal* (54), n_D^{20} 1·4956; $[\alpha]_D^{25}$ 0° (*c* 1·31 in $CHCl_3$); $\nu_{max.}$ (film) 1120 and 1050 cm^{-1}; τ (CCl_4) 9·23 (3H, s), 9·13 (3H, s), 8·40 and 8·33 (6H, two singlets), 6·22 (4H, m), and 4·90 (1H, m); *m/e* 264 (59·7%, M^+), 125 (100), 95 (81·6), 87 (61·4), 69 (75·7), and 41 (74·0) (Found: C, 76·95; H, 10·65. $C_{17}H_{28}O_2$ requires C, 77·2; H, 10·65%). The component with t_R 47 min was *epicampherenone ethylene acetal* (55), n_D^{20} 1·4965; $[\alpha]_D^{25}$ 0° (*c* 1·03 in $CHCl_3$); $\nu_{max.}$ (film) 1115 and 1045 cm^{-1}; τ (CCl_4) 9·23 (3H, s), 8·97 (3H, s), 8·40 and 8·33 (6H, two singlets), 6·22 (4H, m), and 4·92 (1H, m); *m/e* 264 (9·7%, M^+), 109 (35·5), 95 (100), 69 (51·6), 55 (32·2), and 41 (64·5) (Found: C, 77·0; H, 10·85%).

(±)-*Campherenone* (56) [≡ (8a *and* c)].—Campherenone ethylene acetal (54) (491 mg, 1·86 mmol) in acetone (50 ml) was treated with 6N-hydrochloric acid (10 drops) for 24 h. Saturated aqueous sodium hydrogen carbonate was added (*ca.* 2 ml) and work-up in the usual way provided crude product which on distillation afforded (±)-campherenone (56) (404 mg, 99%). The purity of the campherenone at this stage was dependent on the care taken earlier in the fractionation of chloro-ketones (48a and b) from the more volatile minor components of the cyclisation mixture. Typically, a small percentage of impurity was detectable by g.l.c. (column B; 175°) with t_R 2·0 min; *cf.* 2·8 min for campherenone (56). Pure *campherenone*, obtained by preparative g.l.c. (column E; 220°) followed by short-path distillation (60° oil-bath; 0·05 mmHg), or chromatography over neutral alumina (elution with petroleum–ether, 95 : 5), exhibited n_D^{25} 1·4888; $[\alpha]_D$ 0° (*c* 1·02 in $CHCl_3$); $\nu_{max.}$ (film) 1738, 1415, and 830 cm^{-1}; τ (CCl_4) 9·14 (3H, s), 9·03 (3H, s), 8·39 and 8·35 (6H, two broad singlets), and 4·95 (1H, m); τ (C_6H_6) 9·30 (3H, s), 9·07 (3H, s), 8·48 and 8·35 (6H, two broad singlets), and 4·97 (1H, m); *m/e* 220 (82·2%, M^+), 135 (44·6), 109 (93·8), 95 (46·4), 81 (33·9), 69 (99·0), 55 (47·2), and 41 (100) (Found: C, 82·0; H, 10·85. $C_{15}H_{24}O$ requires C, 81·75; H, 11·0%).

(±)-*Epicampherenone* (57) [≡ (8b *and* d)].—Removal of the acetal function of (55) (934 mg, 3·54 mmol) as described for campherenone ethylene acetal (54) afforded *epicampherenone* (57) (746 mg, 96%), n_D^{25} 1·4887; homogeneous by g.l.c. analysis (column B; 185°; t_R 2·8 min); $[\alpha]_D^{20}$ 0° (*c* 2·81 in $CHCl_3$); $\nu_{max.}$ (film) 1738, 1415, and 835 cm^{-1}; τ (CCl_4) 9·13 (6H, s), 8·38 and 8·32 (6H, broad singlets), and 4·89 (1H, m); τ (C_6H_6) 9·35 (3H, s), 9·06 (3H, s), 8·41 and 8·28 (3H, two broad singlets), and 4·83 (1H, m); *m/e* 220 (46·4%, M^+), 135 (45·5), 109 (100), 95 (92·7), 81 (52·7), 69 (98·3), 67 (46·4), and 41 (87·3) (Found: C, 82·0; H, 10·95%).

(±)-*Campherenol* (58; R^1 = H, R^2 = OH).—Sodium (0·6 g) was added in portions to a solution of (±)-campherenone (56) (35 mg) in dry propan-1-ol (12 ml). The mixture was refluxed for 2 h, the solvent was removed, and the residue was diluted with water and extracted with ether. Removal of ether provided a product (35 mg, 95%) whose spectral characteristics [$\nu_{max.}$ (film) 3400 and 835 cm^{-1}; τ (CCl_4) 9·17 (3H, s), 9·11 (3H, s), 8·41 and 8·34 (6H, two broad singlets), 6·46 and 6·00 (1H, relative integrals 1 : 7), and 4·94 (1H, m); τ (C_5H_5N) 9·06 (3H, s), 8·98 (3H, s), 6·13 and 5·65 (1H, relative integrals 1 : 7)] indicated that it consisted of a mixture of (±)-campherenol (58; R^1 = H, R^2 = OH) and (±)-isocampherenol (58; R^1 = OH, R^2 = H) in relative yields of 7 : 1. Column chromatography over silica and elution with petroleum–benzene (5 : 1) provided pure (±)-campherenol.

(±)-*Isocampherenol* (58; R^1 = OH, R^2 = H).—A mixture of (±)-campherenone (56) (100 mg) and lithium hydridotrimethoxyaluminate [37] (230 mg) in dry tetrahydrofuran was stirred under nitrogen for 16 h. Addition of water and extraction with ether followed by solvent removal yielded a product which on chromatography over silica (5 g) provided (±)-isocampherenol (96 mg, 95%), $\nu_{max.}$ (film) 3400 and 835 cm^{-1}; τ (CCl_4) 9·18 (3H, s), 9·12 (3H, s), 8·39 and 8·36 (6H, two doublets, *J* 1·5 and 2·0 Hz), 6·46 (1H, t, *J* 6 Hz), and 4·92 (1H, m); τ (C_5H_5N) 9·10 (3H, s), 8·88 (3H, s), and 6·13 (1H, m).

(±)-β-*Santalene* [2-*Methyl*-3-*methylene*-2-(4-*methylpent*-3-*enyl*)*norbornane*] (62).—A mixture of (±)-isocampherenol (58; R^1 = OH, R^2 = H) (45 mg), toluene-*p*-sulphonyl chloride (100 mg) and dry pyridine (4 ml) was heated at 95° for 22 h. Dilution with water, extraction with pentane, and work-up in the usual way provided a product which was chromatographed over silica. Elution with petroleum (b.p. 40—60°) provided (±)-β-santalene (62) (32 mg, 80%), homogeneous by g.l.c. (column A; 110°; t_R 17 min); $\nu_{max.}$ (film) 3060, 1655, 880, and 835 cm^{-1}; τ (CCl_4) 8·95 (3H, s), 8·42 and 8·35 (6H, two broad singlets), 7·36br (1H,

s), 5·57 and 5·31 (2H, two singlets), and 4·96 (1H, m). These g.l.c. and spectral characteristics were identical with those of (−)-β-santalene {$[\alpha]_D^{20}$ −102° (*c* 5·01 in $CHCl_3$)} isolated from Mysore sandalwood oil by fractional distillation and column chromatography (silica; elution with petroleum) followed by preparative g.l.c. (column E; 170°) and distillation.

(±)-*Epicampherenol* (61; R^1 = H, R^2 = OH).—(±)-Epicampherenone (57) (40 mg) was reduced with sodium (0·7 g) in propan-1-ol (15 ml) according to the procedure already described. The product was a mixture (3 : 2) of (±)-epicampherenol (61; R^1 = H, R^2 = OH) and (±)-isocampherenol (61; R^1 = OH, R^2 = H), $\nu_{max.}$ (film) 3400 and 825 cm^{-1}; τ (CCl_4) 9·18 (3H, s), 9·13 (3H, s), 8·40 and 8·33 (6H, two singlets), 6·47 and 6·06 (1H, t and d, relative integrals 2 : 3), and 4·92 (1H, m); τ (C_5H_5N) 9·07 (3H, s), 8·97 (3H, s), and 6·18 and 5·73 (1H, relative integrals 2 : 3). Preparative t.l.c. [developing solvent petroleum–ethyl acetate (95 : 5)] of the mixture afforded pure (±)-epicampherenol.

(±)-*Isoepicampherenol* (61; R^1 = OH, R^2 = H).—Reduction of (±)-epicampherenone (57) with lithium hydridotrimethoxyaluminate as already described provided (±)-isoepicampherenol (61; R^1 = OH, R^2 = H), $\nu_{max.}$ (film) 3440 and 838 cm^{-1}; τ (CCl_4) 9·12 (3H, s), 8·96 (3H, s), 8·39 and 8·33 (6H, two broad singlets), 6·47 (1H, t, *J* 5 Hz), and 4·93 (1H, m); τ (C_5H_5N) 8·88 (3H, s), 8·65 (3H, s), and 6·18 (1H, t, *J* 5 Hz).

(±)-*Epi*-β-*Santalene* (64).—Treatment of (±)-isoepicampherenol (61; R^1 = OH, R^2 = H) (140 mg) with toluene-*p*-sulphonyl chloride (500 mg) in dry pyridine (10 ml) for 19 h at 90—92° and work-up as described for the synthesis of (±)-β-santalene provided a product which on chromatography over silica (elution with petroleum) and/or preparative g.l.c. (column E; 160°) provided (±)-epi-β-santalene (95 mg), homogeneous by g.l.c. (column A; 110°; t_R 16 min); $\nu_{max.}$ (film) 3060, 1655, and 880 cm^{-1}; τ (CCl_4) 9·00 (3H, s), 8·40 and 8·35 (6H, broad singlets), 7·35 (1H, s), 5·57 and 5·34 (2H, singlets), and 4·93 (1H, m); *m/e* 204 (9·6%, M^+), 122 (55·9), 94 (100), 93 (24·3), 79 (19·2), and 41 (39·0). These g.l.c. and spectral characteristics were identical with those of authentic (+)-epi-β-santalene {$[\alpha]_D^{29}$ +23·3° (*c* 4·12 in $CHCl_3$)} isolated from Mysore sandalwood oil by fractional distillation, column chromatography (silica; elution with petroleum), preparative g.l.c. (column E; 170°), and distillation.

(±)-α-*Santalene* {1,7-*Dimethyl*-7-(4-*methylpent*-3-*enyl*)-*tricyclo*[2.2.1.$0^{2,6}$]*heptane*} (63).—A mixture (*ca.* 1 : 1) of (±)-campherenone (56) and (±)-epicampherenone (57) (35 mg, 0·16 mmol) was refluxed in a solution of hydrazine (60 mg) and acetic acid (0·1 ml) in absolute ethanol (2 ml) for 4 h. The solvent was removed and the residue was diluted with water and extracted with ether. The crude hydrazone obtained after solvent removal was dissolved in dry methanol (3 ml) and heated under reflux with red mercuric oxide (100 mg) for 16 h. The solution was filtered, the solid washed with pentane, and the filtrate evaporated to provide a product (30 mg) which was chromatographed over silica gel. Elution with petroleum afforded (+)-α-santalene (10 mg) (31%) and starting material (18 mg) (51%) (overall yield 65% based on consumed starting material). The product was homogeneous by g.l.c. analysis (column A; 140° and column C; 150°; t_R 4·2 and 3·5 min, respectively); $\nu_{max.}$ (film) 3050, 855, and 840 cm^{-1}; τ (CCl_4) 9·20 (s), 9·18 (3H, s), 9·00 (3H, s), 8·41 and 8·34 (6H, broad singlets), and 4·92 (1H, m). The g.l.c. and spectral characteristics were identical with those of authentic (±)-α-santalene {$[\alpha]_D^{30}$ +6·2° (*c* 1·3 in $CHCl_3$)} isolated from Mysore sandalwood oil by column chromatography (silica; elution with petroleum), fractional distillation, preparative g.l.c. (column E; 170°), and distillation.

Campherenone Enol Acetate (65).—(±)-Campherenone (56) (120 mg, 0·55 mmol) in dry tetrahydrofuran (2 ml) was treated at room temperature with n-butyl-lithium (0·28 ml, 0·65 mmol; 2·38M-solution in hexane) for 15 min. The enolate anion thus generated was cooled to −50° and treated with pure acetic anhydride (0·11 ml, 1·1 mmol).[52] The mixture was allowed to warm slowly to room temperature and after 30 min the excess of acetic anhydride was destroyed by stirring with saturated aqueous sodium hydrogen carbonate. Dilution with petroleum and work-up in the usual way provided a crude product which was shown by g.l.c. analysis (column A; 165°) to contain the enol acetate (85%; t_R 3·4 min) and campherenone (t_R 2·8 min). Purified enol acetate (65) exhibited $\nu_{max.}$ (film) 1755, 1205, 835, and 810 cm^{-1}; τ (CCl_4) 9·24 (3H, s), 9·10 (3H, s), 8·44 and 8·36 (6H, two broad singlets), 7·90 (3H, s), 7·57 (1H, t, *J* 1·5 Hz), 4·93 (1H, m), and 4·85 (1H, d).

Attempted Cyclisation of Campherenone Enol Acetate (65).—Campherenone enol acetate (65) was treated under the previously stated optimum cyclisation conditions [1] [BF_3–CH_2Cl_2–0·1% (v/v) enol acetate]. G.l.c. analysis (columns A, C, and D; 160°) indicated a very small percentage of volatile products. Peaks were present on all three g.l.c. traces which corresponded to authentic longicamphor [53] and copacamphor.[45] Analysis on column B (160°) however, failed to indicate a similar correspondence. In view of the large percentage of involatile material encountered in this reaction (even when the reaction was performed at a concentration of 0·06 mg ml^{-1}) other means were sought to obtain cyclisation of campherenone. However the range of acids used in these cyclisation attempts [*i.e.* tin(IV) chloride, boron trifluoride–ether, perchloric acid, hydrochloric acid, silica gel, or phosphate buffer] led to partial or complete regeneration of starting ketone.

Cyclisation of Campherenone Epoxides (66).—Campherenone (500 mg, 2·27 mmol) in dry benzene (5 ml) (cooled in an ice-bath) was treated with 85% *m*-chloroperbenzoic acid (450 mg, 2·36 mmol) in dry benzene (15 ml) over a period of 1 h and the mixture was stirred for an additional 2 h. The organic layer was washed with saturated aqueous sodium hydrogen carbonate, sodium hydrogen sulphite, and saturated sodium chloride solution. Solvent removal provided a mixture of campherenone epoxides (66) (508 mg, 95%) which was used without purification: $\nu_{max.}$ (film) 1240, 870, and 800 cm^{-1}. The crude mixture (495 mg) was added directly to a solution of potassium t-butoxide [prepared by refluxing a mixture of potassium metal (390 mg) and dry t-butyl alcohol (8 ml)] and refluxed for 36 h under dry nitrogen. The mixture was poured into water and extracted with several portions of petroleum. Work-up in the usual way provided a product (488 mg) which was shown by g.l.c. analysis (column A; 175°) to consist of two main components (in the ratio

[52] *Cf.* G. C. Joshi, W. D. Chambers, and E. W. Warnhoff, *Tetrahedron Letters*, 1967, 3613.

[53] We thank Professor Sir Derek Barton for an authentic sample of culmorin diketone dithioacetal, a convenient precursor of (−)-longicamphor [D. H. R. Barton and N. H. Werstiuk, *J. Chem. Soc.* (*C*), 1968, 148].

45 : 55) with t_R 5·4 and 6·6 min, respectively. Preparative g.l.c. (column E; 230°) afforded pure samples of each component (t_R 53 and 60 min).

5-(1-*Hydroxy*-1-*methylethyl*)-1,7a-*dimethylperhydro*-1,4-*methanoinden*-8-*one* (67) (t_R 53 min) exhibited $\nu_{max.}$ (CCl_4) 3620w, 3490s, 1734w, and 1728s cm^{-1} (relative strengths of bands at 3620 and 3490 cm^{-1} did not change upon dilution from 0·08M- to 0·01M-solution); τ (CCl_4; 100 MHz) 9·10 (3H, s), 9·08 (3H, s), 8·95 and 8·94 (3H, two overlapping singlets), 8·76 (3H, s), 7·57br (1H, s), and 7·26 (1H, $W_{\frac{1}{2}}$ 12 Hz); *m/e* 236 (11·6%, M^+), 178 (60·5), 163 (54·2), 95 (100), 51 (60·0), and 41 (81·5) (Found: M^+, 236·1782. $C_{15}H_{24}O_2$ requires *M*, 236·1775). Its *epimer* (68) (t_R 60 min) exhibited $\nu_{max.}$ (CCl_4) 3620, 3440, and 1740 cm^{-1} (dilution from 0·064M to 0·01M increased the intensity of the band at 3620 relative to the 3440 cm^{-1} absorption); τ (CCl_4; 100 MHz) 9·12 (3H, s), 9·07 (3H, s), 8·87br (3H, s), 8·80br (3H, s), 7·80br (1H, s), 7·70br (1H, d), and 7·43br (1H, s, $W_{\frac{1}{2}}$ 2 Hz); *m/e* 236 (13·6%, M^+), 95 (52·9), 93 (39·9), 59 (100), 51 (35·6), and 41 (44·8) (Found: M^+, 236·1793).

5β-*Isopropenyl*-1,7a-*dimethylperhydro*-1,4-*methanoinden*-8-*one* (71) *and its* 5-*Isopropylidene Isomer* (70).—The tricyclic alcohol (68) (44 mg, 0·19 mmol) in dry pyridine (1 ml) was treated with thionyl chloride (0·05 ml) for 30 min. The mixture was diluted with petroleum and worked up in the usual way. Solvent removal provided a crude product (37 mg) which was shown by g.l.c. analysis (column B; 150°) to consist of a mixture (7 : 3) of olefins (71) and (70) (t_R 9·0 and 11·5 min, respectively). Preparative g.l.c. (column F; 150°) afforded pure samples. The 5-isopropenyl compound (71) exhibited $\nu_{max.}$ (film) 3100, 1740, 1650, and 890 cm^{-1}; τ (CCl_4) 9·12 (3H, s), 9·08 (3H, s), 8·27 (3H, s), and 5·15 (2H, m); *m/e* 218 (51·5%, M^+), 95 (99·5), 79 (48·6), 69 (60·6), 55 (48·1), 43 (89·4), and 41 (100); the isomeric alkene (70) showed $\nu_{max.}$ (film) 1740 cm^{-1}; τ (CCl_4) 9·07 (6H, s), 8·37 and 8·28 (6H, two singlets), and 7·06 (1H, s).

(±)-*Copacamphor* (5-*Isopropyl*-1,7a-*dimethylperhydro*-1,4-*methanoinden*-8-*one*) (73).—Hydrogenation of the tricyclic alkenone (71) over platinum oxide in ethyl acetate–acetic acid (19 : 1) with sodium borohydride afforded (±)-copacamphor (73). A sample purified by preparative g.l.c. (column F; 220°) followed by evaporative distillation exhibited n_D^{25} 1·4898 and was homogeneous by g.l.c. analysis with retention times (co-injection) identical with those of authentic (+)-copacamphor [45] on four columns (A, 150°; B, 150°; C, 150°; D, 175°); $\nu_{max.}$ (film) 1735 cm^{-1}; τ ($CDCl_3$) 9·11 (3H, d, *J* 6·5 Hz), 9·10 (3H, s), 9·09 (3H, d, *J* 6·5 Hz), 9·06 (3H, s), and 7·84 (1H, m); *m/e* 220 (82·2%, M^+), 149 (36·6), 135 (40·5), 124 (100), 95 (55·5), and 41 (42·8) (Found: C, 81·65; H, 11·05. $C_{15}H_{24}O$ requires C, 81·5; H, 11·0%).

5α-*Isopropenyl*-1,7a-*dimethylperhydro*-1,4-*methanoinden*-8-*one* (69).—The ketol (67) (39 mg, 0·17 mmol) was dehydrated as for (68) [pyridine (1 ml), thionyl chloride (0·05 ml), 30 min]. Work-up provided a 5 : 1 mixture (26 mg; 72%) of the 5-isopropenyl ketone (69) and the isomeric alkene (70) [t_R 9·0 and 11·5 min, respectively (column B; 150°)]. Preparative g.l.c. (column F; 150°) provided pure samples. The component with t_R 11·5 min exhibited spectral characteristics (g.l.c., infrared, n.m.r.) identical with those of (70) (see before). The isopropenyl compound (69) showed $\nu_{max.}$ (film) 3100, 1740, 1650, and 890 cm^{-1}; τ (CCl_4) 9·12 (3H, s), 9·08 (3H, s), 8·26 (3H, s), and 5·23br (2H, s); *m/e* 218 (96·5%, M^+), 124 (40·0), 123 (49·4), 107 (47·1), 95 (100), and 55 (37·4).

(±)-*Ylangocamphor* (72).—Hydrogenation of the alkenone (69) as for the preparation of copacamphor (73) afforded (±)-*ylangocamphor* (72),[45] n_D^{25} 1·4909, homogeneous by g.l.c. analysis on four columns (A, 150°; B, 150°; C, 150°; D, 150°); $\nu_{max.}$ (film) 1730 cm^{-1}; τ ($CDCl_3$) 9·20 (3H, d, *J* 6·5 Hz), 9·11 (3H, s), 9·10 (3H, s), 9·03 (3H, d, *J* 6·5 Hz), and 7·77 (1H, s); *m/e* 220 (100%, M^+), 124 (73·1), 110 (72·3), 95 (69·8), 93 (62·5), and 41 (78·0) (Found: C, 81·9; H, 10·85. $C_{15}H_{24}O$ requires C, 81·75; H, 11·0%).

Hydrogenation of the Isopropylidene Ketone (70).—The ketone (70) was hydrogenated in glacial acetic acid over platinum for 24 h at atmospheric pressure. The product was a mixture (5 : 1) of ylangocamphor (72) and copacamphor (73) (g.l.c. analysis; column B, 150°; t_R 6·5 and 8·5 min, respectively). I.r. and n.m.r. spectra were in accord with this assignment.

Large-scale Synthesis of (±)-*Copacamphor* (73) *and* (±)-*Ylangocamphor* (72).—For large-scale preparations of (±)-copacamphor (73) and (±)-ylangocamphor (72) it was found more convenient to employ a mixture of (±)-campherenone (56) and (±)-epicampherenone (57) as starting material. Epoxidation of a mixture (1 : 1; 4·8 g) of (56) and (57) as previously described followed by cyclisation in potassium t-butoxide [from potassium (4 g) and dry t-butyl alcohol (100 ml)] afforded a crude product (5·0 g) which on dehydration with thionyl chloride in pyridine, followed by distillation, afforded a mixture (2·03 g) of alkenones (69), (70), and (71). Hydrogenation of the alkenone mixture over platinum (700 mg) in ethyl acetate–acetic acid (9 : 1) provided a quantitative yield of (±)-copacamphor (73) and (±)-ylangocamphor (72) (*ca.* 84% overall based on campherenone) in the approximate ratio 45 : 55, respectively. Preparative g.l.c. (column F; 220°) or column chromatography (grade 4 neutral alumina; eluted with pentane) followed by distillation afforded pure (±)-copacamphor (73) and (±)-ylangocamphor (72).

(±)-*Sativene* (7-*Isopropyl*-4-*methyl*-8-*methyleneperhydro*-1,4-*methanoindene*) (75; $R^1 = Pr^i$, $R^2 = H$).—(±)-Ylangocamphor (72) (200 mg) was treated with lithium aluminum hydride (35 mg) in dry tetrahydrofuran for 16 h. Careful addition of water followed by extraction with ether and work-up in the usual way afforded impure alcohol which, on chromatography over silica gel, provided (±)-isoylangoborneol (74; $R^1 = Pr^i$, $R^2 = H$), m.p. 41—42° (180 mg, 89%); $\nu_{max.}$ (film) 3500 and 1095 cm^{-1}; τ (CCl_4) 9·21 (3H, s), 9·16 (3H, s), 9·08 (6H, d, *J* 7 Hz), and 6·30 (1H, d, *J* 8 Hz); τ (C_5H_5N) 9·13 (3H, s), 8·94 (3H, s), 8·94 (6H, d), and 5·97 (1H, m).

Treatment of (±)-isoylangoborneol (150 mg) with methanesulphonyl chloride (0·1 ml) in dry pyridine (1 ml) at 105° for 16 h followed by the usual work-up [*cf.* synthesis of (±)-β-santalene] and column chromatography over silica provided (±)-sativene [47] (73 mg, 53%), $\nu_{max.}$ (film) 3080, 1660, and 875 cm^{-1}; τ (CCl_4) 9·15 (3H, d, *J* 3·5 Hz), 9·09 (3H, d, *J* 3·5 Hz), 8·98 (3H, s), 7·40br (1H, s), and 5·59 and 5·27 (2H, two singlets); *m/e* 204 (52·3%, M^+), 161 (57·5), 108 (100), 105 (41·8), 91 (43·8), and 41 (44·4).

We thank the National Research Council of Canada for financial support.

[3/155 *Received*, 23*rd January*, 1973]