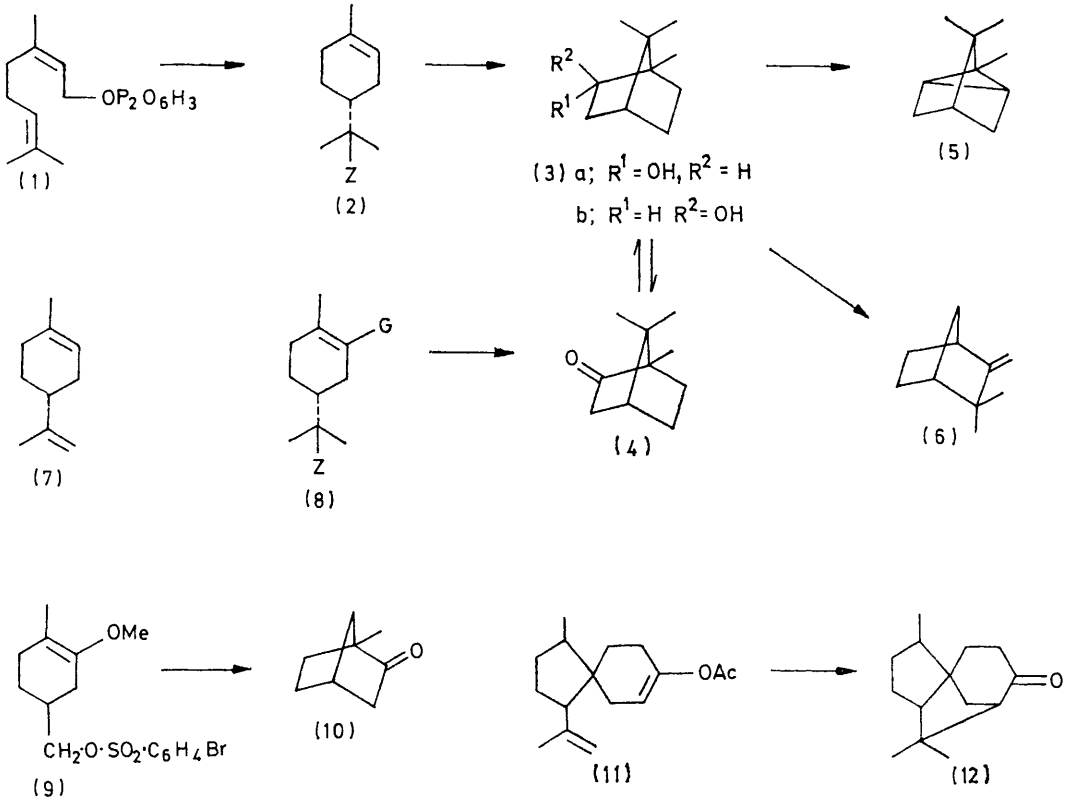
Synthesis of (±)-Camphor [1]

By **John C. Fairlie, Gordon L. Hodgson,** and **Thomas Money,*** Department of Chemistry, University of British Columbia, Vancouver 8, British Columbia, Canada

An alternative proposal for the biosynthesis of the bornane series of bicyclic monoterpenes forms the basis of a new synthesis of camphor from *p*-menth-8-en-2-one (dihydrocarvone).

It has been suggested [2,3] that the biosynthesis of bicyclic monoterpenes involves conversion of neryl (3,7-dimethylocta-2,6-dienyl) pyrophosphate (1) (or the corresponding linalool or geraniol derivative) into a monocyclic intermediate (2; Z = biological leaving group) which can subsequently cyclise to produce the bornane, pinane, carane, and thujane series of bicyclic monoterpenes.† analogy. Moreover the suggested biosynthetic relationship between camphor, borneol, camphene, and tricyclene is indirectly supported by their co-occurrence in nature.[4] Although recent studies [3] have provided fresh insight into the biosynthesis of bicyclic monoterpenes no conclusive evidence [3,5] has been presented which demonstrates the exact nature of the monocyclic intermediate



In the bornane group bornan-2α-ol (borneol) (3a) is considered to be the initial product of cyclisation and the subsequent derivation of camphor (4), camphene (6), and tricyclene (5) would involve oxidation or dehydration processes for which there is ample laboratory involved in the cyclisation process. In addition, various laboratory efforts to form bicyclo[2.2.1]heptane derivatives by solvolysis of appropriate cyclohex-3-enylmethyl systems (2; Z = Cl, OH, *p*-$O_2N{\cdot}C_6H_4{\cdot}CO_2$, phosphate, or pyrophosphate) have failed.[6] Efforts in our laboratory

† Alternative explanations for the biosynthesis of bicyclic monoterpenes are available. For example, pin-2-ene and pin-2(10)-ene could be formed directly by concerted cyclisation of neryl pyrophosphate and there is ample chemical analogy for the postulate that pinene or derivatives could act as precursors of the bornane series. A monocyclic intermediate seems necessary, however, to explain the formation of the carane and thujane groups.

[1] Preliminary communication, J. C. Fairlie, G. L. Hodgson, and T. Money, *Chem. Comm.*, 1969, 1196.

[2] L. Ruzicka, *Experientia*, 1953, **9**, 357; *Proc. Chem. Soc.*, 1959, 341.

[3] D. V. Banthorpe, B. V. Charlwood, and M. J. O. Francis, *Chem. Rev.*, 1972, **72**, 115; A. G. Battersby, D. G. Laing, and R. Ramage, *J.C.S. Perkin I*, 1972, 2743.

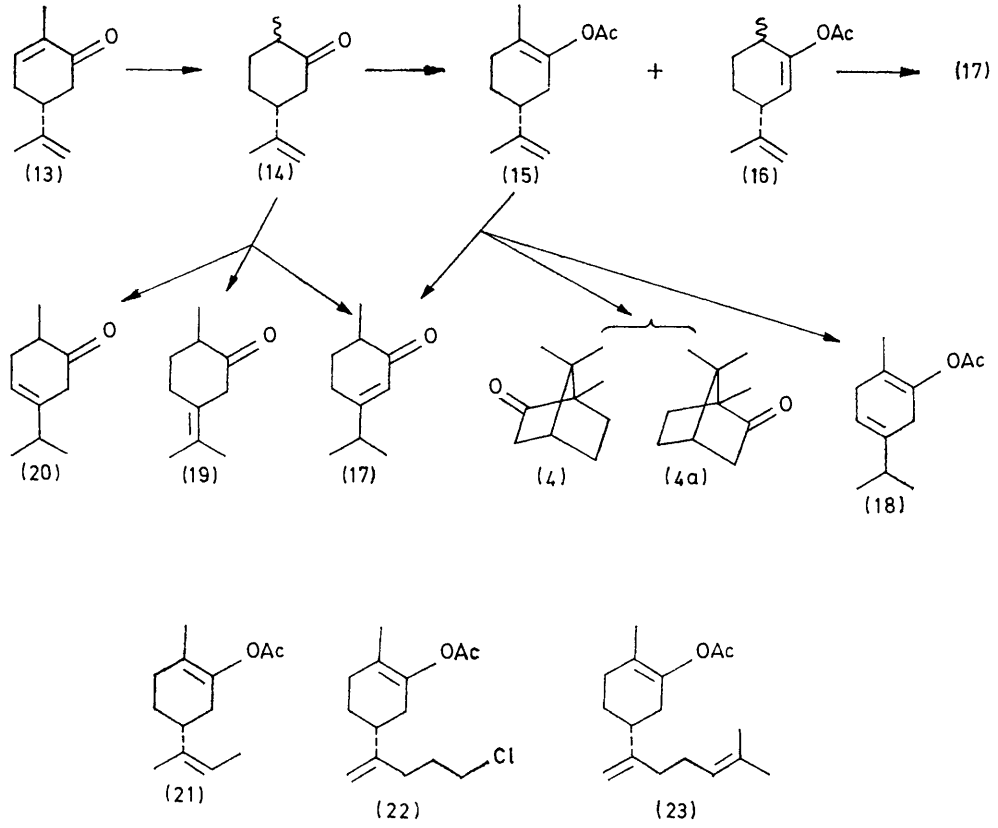
[4] E. von Rudolff, *Phytochemistry*, 1966, **5**, 331; E. Zavarin, *ibid.*, 1970, **9**, 1049.

[5] D. V. Banthorpe and A. Wirz-Justice, *J. Chem. Soc.* (*C*), 1969, 541.

[6] C. F. Wilcox, M. F. Wilcox, and S. S. Chibber, *J. Org. Chem.*, 1962, **27**, 2286; W. Rittersdorf, *Angew. Chem. Internat. Edn.*, 1965, **4**, 444; F. Cramer and W. Rittersdorf, *Tetrahedron*, 1967, **23**, 3015; C. F. Wilcox and S. S. Chibber, *J. Org. Chem.*, 1962, **27**, 2332; *cf.* T. Money, *Progr. Org. Chem.*, 1972, **8**, 29.

[7] H. Felkin and C. Lion, *Chem. Comm.*, 1968, 60.

to promote cyclisation of *p*-mentha-1,8-diene (limonene) (7) or *p*-menth-1-en-8-ol (α-terpineol) (2; Z = OH) with various acid catalysts (*e.g.* BF_3, BF_3–Et_2O, $SnCl_4$, silica gel, or ion-exchange resin) were uniformly unsuccessful. In contrast, however, it has been reported that solvolytic cyclisation of the enol ether (9) to the bicyclic ketone (10) can be accomplished in 12% yield.[7] This successful cyclisation, coupled with the known importance of enol derivatives in the biological formation of carbon–carbon bonds, prompted us to consider an alternative explanation for the biosynthesis of bicyclic monoterpenes of the bornane series. Thus an appropriate monocyclic enol ester, enol ether, or enamine (8) was considered as an intermediate potentially capable of cyclisation to camphor (4). The subsequent derivation of structurally related monoterpenes would then involve reduction, dehydration, and rearrangement processes which are well documented. In terms of absolute configuration the hypothesis would predict a biosynthetic relationship between (+)-camphor (4), (+)-bornan-2α-ol (3a), (−)-bornan-2β-ol (3b), (+)-camphene (6), and the appropriate monocyclic intermediate (8).* While the biosynthetic validity of these proposals has yet to be tested, the provision of a new synthetic strategy for bicyclic and tricyclic compounds of the type considered above is obvious. To evaluate this strategy a suitably reactive compound similar to the postulated intermediate (8) was required and the synthetic accessibility of enol acetates prompted us to chose 2-acetoxy-*p*-mentha-1,8-diene (15) as our initial synthetic objective. Moreover the interaction of enol acetate groups with remote alkene linkages had been elegantly demonstrated[8] [*i.e.* (11) ⟶ (12)] and we regarded this as an excellent analogy for our proposed cyclisation.



(+)-*p*-Menth-8-en-2-one (dihydrocarvone) (14) † was obtained in 87% yield by reduction of (−)-*p*-mentha-6,8-dien-2-one (carvone) (13) with zinc and ethanolic potassium hydroxide.[9,10] Subsequent treatment of (14) with isopropenyl acetate in the presence of toluene-*p*-sulphonic acid [11] resulted in a mixture (*ca.* 4 : 1) of (+)-2-acetoxy-*p*-mentha-1,8-diene (15) and 2-acetoxy-*p*-mentha-2,8-diene (16) ($[\alpha]_D^{28}$ +90·5°), which were separated by preparative g.l.c. Treatment of a 0·1% solution of (15) in wet methylene chloride with boron trifluoride gas at room temperature for 10 min ‡ provided

* Several possible precursors of (8) can be considered, *e.g.* (+)-limonene 1,2-epoxide, α-terpineol epoxide, or (+)-dihydrocarvone.

† The n.m.r. spectrum of this compound indicated that it was a mixture of C-1 epimers (*trans* : *cis* 3 : 1).

‡ Similar treatment of (16) yielded carvenone (17) as major product.

[8] E. J. Corey, N. N. Girotra, and C. T. Mathew, *J. Amer. Chem. Soc.*, 1969, **91**, 1557.

[9] O. Wallach, *Annalen*, 1894, **275**, 377; *cf.* T. G. Halsall, D. W. Theobald, and K. B. Walshaw, *J. Chem. Soc.*, 1964, 1029.

[10] M. Yoshida, *Chem. and Pharm. Bull (Japan)*, 1955, **3**, 215.

[11] H. O. House and H. W. Thompson, *J. Org. Chem.*, 1961, **26**, 3729 and references therein; R. B. Moffet and D. I. Weisblat, *J. Amer. Chem. Soc.*, 1952, **74**, 2183.

(±)-camphor [(4) + (4a)] in 90% yield (estimated by g.l.c.). Higher concentrations of enol acetate (15) resulted in a lower yield of camphor and a corresponding increase in the yield of *p*-menth-3-en-2-one (carvenone) (17) and other unidentified products. For example a 0·7% solution of (15) gave a mixture of at least ten compounds including camphor (10%), carvenone (35%), and an unknown compound (39%). Structure (18) was assigned to the last compound on the basis of its spectral characteristics. When the reaction was run in dry methylene chloride or when other acid catalysts (*e.g.* HCl, HF, $AlCl_3$, or BF_3–Et_2O) were used, negligible yields of camphor were obtained.*

The racemic nature of synthetic camphor obtained by cyclisation of (+)-2-acetoxy-*p*-mentha-1,8-diene (15) was unexpected; we are investigating this aspect of the cyclisation reaction. (+)-Camphor (4) does not racemise under these conditions and it is likely that disruption of the chiral centre in (15) is occurring through double-bond migration or 1,2-hydride shift. In any event the result is probably quite general since we have found that cyclisation of optically active enol acetates [(21),[12] (22),[13] and (23) [14]] provides racemic bicyclic products.

The extension of our biosynthetic ideas and synthetic strategy to an appropriate group of sesquiterpenes is described in the following paper.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. G.l.c. was carried out on either a Varian Aerograph 90-P or an Aerograph Autoprep 700 instrument, and the following columns were employed:

Column	Dimensions	Stationary phase	Support	Mesh
A	10 ft × 1/4 in	3% SE 30	Varoport 30	100—120
B	10 ft × 3/8 in	30% FFAP	Chromosorb W	60—80
C	20 ft × 3/8 in	30% SE 30	Chromosorb W	45—60

Carrier gas (helium) flow-rate for 1/4 in columns was 60 ml min^{-1} and for 3/8 in columns was 170 ml min^{-1}. Optical rotations were measured with either a Perkin-Elmer 141 polarimeter or a Rudolph polarimeter. C.d. spectra were recorded on a JASCO J-20 spectropolarimeter. U.v. spectra were recorded for solutions in methanol on a Unicam SP 800 spectrophotometer. Routine i.r. spectra were recorded on a Perkin-Elmer Infracord 137 spectrophotometer and comparison spectra on a Perkin-Elmer 21 or 457 spectrophotometer. The 60 MHz n.m.r. spectra were recorded on a Varian A-60 or T-60 instrument and 100 MHz spectra on a Varian HA-100 or XL-100 instrument (tetramethylsilane as internal reference) Mass spectra were recorded on an Atlas CH-4 or an A.E.I. MS-9 spectrometer. High resolution mass spectra were determined on the latter instrument. Microanalyses were performed by Mr. P. Borda.

(+)-p-*Menth*-8-*en*-2-*one* (14).[9,10]—A mixture of zinc powder (250 g), potassium hydroxide (100 g, 1·78 mol), 95% ethanol (1000 ml), and water (400 ml) was heated to reflux with *vigorous stirring* and (−)-*p*-mentha-6,8-dien-2-one (13) (203 g), $[\alpha]_D^{30}$ −58·6° (*c* 4·78 in $CHCl_3$), dissolved in 95% ethanol (400 ml), was added dropwise during 6 h. Refluxing was continued (1 h) until the disappearance of u.v. absorption at 234 nm. The cooled mixture was filtered and evaporated under reduced pressure. The residue was extracted with petroleum (3 × 250 ml) and the combined extracts were washed until neutral and dried (Na_2SO_4). Removal of the solvent and distillation of the residual oil afforded (+)-*p*-menth-8-en-2-one (14) (178 g) as a mixture of C-1 epimers [*cis*-1,4 : *trans*-1,4 ; 1 : 3 by n.m.r.], b.p. 80° at 6 mmHg (lit.,[10] 100—104° at 17 mmHg), homogeneous by g.l.c. (column A; 150°); $[\alpha]_D^{29}$ +18·3° (*c* 10·4, $CHCl_3$); † $\lambda_{max.}$ 284 nm (ε 30); $\nu_{max.}$ (neat) 3100, 1710, 1650, and 892 cm^{-1}; τ (CCl_4) 9·04 and 8·99 (3H, two doublets, relative area 76 : 24, *J* 6·0 and 6·5 Hz, respectively, epimeric CH*Me*), and 8·27 (3H, m, C=CH).

(+)-2-*Acetoxy*-p-*mentha*-1,8-*diene* (15) and (+)-2-*Acetoxy*-p-*mentha*-2,8-*diene* (16).—*p*-Menth-8-en-2-one (14) (6·00 g, 0·039 mol) was heated with isopropenyl acetate (15 ml) and toluene-*p*-sulphonic acid monohydrate (100 mg) for 30 h with slow removal of the generated acetone by distillation. The mixture was cooled and diluted with petroleum, and the organic layer was washed with aqueous sodium hydrogen carbonate and dried. Solvent removal under reduced pressure followed by distillation (b.p. 41—44° at 0·02 mmHg) yielded a mixture of (+)-2-acetoxy-*p*-mentha-1,8-diene (15) and (+)-2-acetoxy-*p*-mentha-2,8-diene (16). G.l.c. analysis (column A; 140°) indicated that (15) and (16) were present in a ratio of *ca.* 4 : 1 (relative retention times, 3·7 and 3·0 min, respectively). Pure samples were obtained by preparative g.l.c. (column C; 175°) followed by distillation.

2-Acetoxy-*p*-mentha-1,8-diene (15) showed n_D^{25} 1·4757; $[\alpha]_D^{28}$ +81·1° (*c* 2·46 in $CHCl_3$) (another preparation gave a +77° rotation); $\nu_{max.}$ (neat) 3090, 1745, 1705, 1645, 1210, and 888 cm^{-1}; τ (CCl_4) 8·51br (3H, s), 8·26 (3H, m), 7·95 (3H, s), and 5·26 (2H, m); *m/e* 194 (5·1%, M^+), 152 (67·0), 109 (100), 84 (37·3), 43 (72·9), and 41 (51·7).

2-Acetoxy-*p*-mentha-2,8-diene (16) showed $[\alpha]_D^{28}$ +90·5° (*c* 2·56 in $CHCl_3$); $\nu_{max.}$ (neat) 3090, 1745, 1680, 1645, 1210, and 890 cm^{-1}; τ (CCl_4), 9·04 (3H, *J* 6·5 Hz, CH*Me*), 8·26 (3H, m, C=CMe), 7·93 (3H, s, OAc), 5·23 (2H, m, $=CH_2$), and 4·86 (1H, m, C=CH); *m/e* 194 (5·5%, M^+), 152 (90·4), 137 (79·4), 109 (35·2), 95 (35·8), 43 (100), and 41 (51·5).

Cyclisation of (+)-2-*Acetoxy*-p-*mentha*-1,8-*diene* (15).—A vigorously stirred solution of (+)-2-acetoxy-*p*-mentha-1,8-diene (15) (203 mg, 1·04 mmol), $[\alpha]_D^{23}$ +77°, in methylene chloride (Baker reagent grade; 0·012% water) (200 ml) was treated with boron trifluoride gas for 10 min. The reaction was quenched by shaking with saturated aqueous sodium hydrogen carbonate (50 ml) and the organic phase was washed twice with water and dried (Na_2SO_4). Solvent removal afforded a faintly yellow residue which became

* In our description we have assumed that prior formation of enol acetate functionality was essential for successful cyclisation. To provide support for this assumption dihydrocarvone (14) was treated with boron trifluoride under conditions identical with those described. Three main reaction products were isolated by preparative g.l.c. and on the basis of their spectral characteristics were assigned structures (17), (19), and (20).

† In another preparation using the original procedure [9] the product exhibited a rotation of +12°, indicating a different ratio of C-1 epimers.

[12] G. L. Hodgson, J. C. Fairlie, and T. Money, unpublished observations.

[13] G. L. Hodgson, D. F. MacSweeney, and T. Money, *Chem. Comm.*, 1971, 766.

[14] G. L. Hodgson, D. F. MacSweeney, and T. Money, following paper.

crystalline when cooled to −10°. Sublimation (50° at 14 mmHg) afforded (±)-camphor [(4) + (4a) (103 mg, 64%)]; $[\alpha]_D^{23}$ 0° (*c* 1·96 in 95% EtOH); $\lambda_{max.}$ 288 nm (ε 36); $\nu_{max.}$ (CCl_4) 1740, 1422, and 1050 cm^{-1} (identical with spectrum of authentic camphor); τ (CCl_4) 9·17 (3H, s), 9·15 (3H, s), and 9·04 (3H, s); τ (C_6H_6) 9·41 (3H, s), 9·37 (3H, s), and 9·10 (3H, s) (spectrum in either solvent identical with that of authentic camphor). In other cyclisations higher yields were obtained by presaturation of the solvent with boron trifluoride. A solution of (15) (100 mg) in methylene chloride (50 ml) was added in portions during 4 min to methylene chloride (50 ml) presaturated with boron trifluoride gas. After 10 min, work-up as before afforded a colourless product, estimated to be 90% camphor by g.l.c. analysis (column B; 170°).

Higher concentrations of (15) led to reduced yields of camphor. Thus (15) (335 mg) in methylene chloride (50 ml) was treated for 1 h with boron trifluoride gas. After the usual work-up the product (300 mg) was shown to consist of at least ten components by g.l.c. analysis. The three major components were isolated by preparative g.l.c. (column B; 170°) and had retention times (t_R) of 10, 25, and 29 min. The component (10%) of t_R 10 min was identified as camphor [(4) + (4a)] by comparison of its i.r., n.m.r., and mass spectra with those of an authentic sample. The component (35%) having t_R 25 min was identified as *p*-menth-3-en-2-one (17) on the basis of the following data: $\lambda_{max.}$ 234 nm (ε 13,200); $\nu_{max.}$ (neat) 1670, 1210, and 880 cm^{-1}; τ (CCl_4) 8·95 (3H, d, *J* 6·5 Hz), 8·89 (6H, d, *J* 6·5 Hz), and 4·27 (1H, s). The component (39%) with t_R 29 min was assigned structure (18) on the basis of the following data: u.v. end absorption; $\nu_{max.}$ (neat) 1745, 1210, 840, and 805 cm^{-1}; τ (CCl_4) 8·97 (6H, d, *J* 6·5 Hz), 8·50br (3H, s), 7·92 (3H, s), 7·72 (1H, m), 7·32br (4H, s), and 4·65 (1H, s).

Attempted Racemisation of (+)-*Camphor*.—A solution of (+)-camphor ($[\alpha]_D$ +46·4°; commercial grade used without further purification) (152 mg) in methylene chloride (150 ml) was saturated with boron trifluoride gas and kept in a stoppered vessel for 4 h at room temperature. The mixture was washed with saturated aqueous sodium hydrogen carbonate and water and dried (Na_2SO_4). Solvent removal followed by two sublimations (50° at 0·15 mmHg) afforded (+)-camphor, $[\alpha]_D^{25}$ +43·6° (*c* 1·52 in 95% EtOH) {lit.,[15] $[\alpha]_D^{20}$ +44·3° (95% EtOH)}. Another sample of (+)-camphor (200 mg) in methylene chloride (200 ml) was treated similarly except that the period of exposure to boron trifluoride was 66 h; two sublimations afforded (+)-camphor, $[\alpha]_D^{25}$ +43·4° (*c* 5·23 in 95% EtOH).

Treatment of p-*Menth*-8-*en*-2-*one* (14) *with Boron Trifluoride*.—*p*-Menth-8-en-2-one (14) (100 mg, 0·66 mmol), $[\alpha]_D^{24}$ +12° (*c* 2·70 in 95% EtOH), in methylene chloride (50 ml) was added during 3·5 min to vigorously stirred methylene chloride (50 ml) which had been saturated with boron trifluoride gas. After 10 min stirring the solution was washed with saturated aqueous sodium hydrogen carbonate and water and dried (Na_2SO_4). G.l.c. analysis (column B; 170°) indicated that the product consisted of three major components with t_R 13, 20, and 25 min.

The component with t_R 13 min was assigned structure (20) on the basis of the following data: u.v. end absorption $\nu_{max.}$ (neat) 1710 and 805 cm^{-1}; τ (CCl_4) 8·96 (9H, d, *J* 6·5 Hz, 3 × CH*Me*), 7·26br (2H, s, CH_2·CO), and 4·46br (1H, s, C=CH); τ (C_6H_6) 9·18 (6H, d, *J* 5 Hz) and 9·01 (3H, d, *J* 5 Hz). The component with t_R 20 min did not appear pure on spectral analysis but was assigned a tentative structure (19) based on the following evidence: $\nu_{max.}$ (neat) 1705 cm^{-1}; τ (CCl_4) 8·97 (3H, d, *J* 6 Hz) and 8·32br (6H, s). The component with t_R 25 min exhibited spectral properties (u.v., i.r., n.m.r.) in agreement with those for *p*-menth-3-en-2-one (17).

Treatment of 2-*Acetoxy*-p-*mentha*-2,8-*diene* (16) *with Boron Trifluoride*.—2-Acetoxy-*p*-mentha-2,8-diene (16) (19 mg) in methylene chloride (9 ml) was added at room temperature to methylene chloride (10 ml) which had been saturated with boron trifluoride gas. A slow stream of the gas was maintained through the solution for 10 min. The solution was washed with saturated aqueous sodium hydrogen carbonate (5 ml) and water and dried (Na_2SO_4). Solvent removal afforded almost pure material (93% by g.l.c.; column B; 170°; t_R 25 min) exhibiting spectral characteristics (u.v., i.r.) in agreement with those for *p*-menth-3-en-2-one (17).

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

[3/154 *Received*, 23*rd January*, 1973]

[15] 'Handbook of Chemistry and Physics,' 52nd edn., ed. R. C. Weast, The Chemical Rubber Co., Cleveland, Ohio.