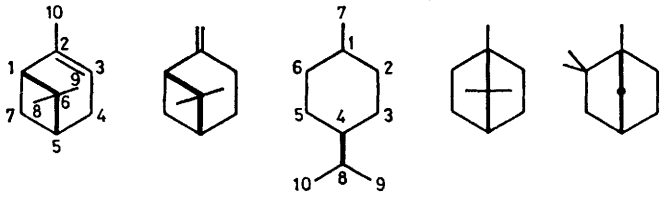
Cyclobutane Ring Opening of Pin-2(10)-ene with Mercury(II) Salts. A New, High-yield Synthesis of *p*-Mentha-1,8-dien-7-ol

By **Norbert Bluthe, Jules Ecoto, Marcel Fetizon,** and **Sylvain Lazare,*** Laboratoire de Synthese Organique, Ecole Polytechnique, 91128 Palaiseau Cedex, France

The nucleophilic attack of pin-2(10)-ene–mercury(II) complex systems by water results in the opening of the four-membered ring leading to an allylic organomercury(II) derivative (11) with the *p*-menthane skeleton. This intermediate can be reduced by hydride to *p*-menth-1(2)-en-8-ol (6a) or can undergo an *in situ* S_E2' elimination yielding *p*-menth-1(7)-en-8-ol (9a), in high yields. (−)-2,10-Epoxypinane (15) reacts with mercury(II) salts at room temperature, giving the diol (16) in a quantitative yield. Compound (16) is a suitable intermediate for convenient preparation of *p*-mentha-1,8-dien-7-ol (17) and its derivatives.

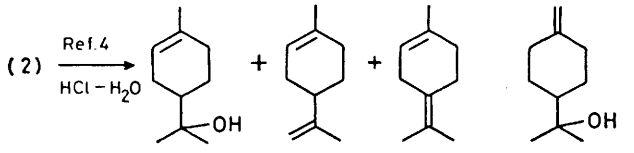
THE reaction of pin-2-ene (1) and pin-2(10)-ene (2) with acids has been extensively studied.[1-3] Although the chemistry of the pinenes is well documented, work continues in this area, since the rearrangement of (1) or (2) may take place *via* several pathways, now clearly



(1) (2) (3) (4) (5)

delineated,[4] and usually leads to mixtures. The structure of the compounds isolated, as well as their rate of formation, is highly dependent on the nature of the acid used.[5] Menthane (3), bornane (4), or the fenchane (5) derivatives are usually obtained.

Although the complexity of the reaction of the pinenes (1) and (2) with organic and inorganic protic acids has led to many investigations, the course of this rearrangement must be controlled if it is required as a key step in a synthesis. In connection with other work,[6] we wished to optimize the conversion of pin-2(10)-ene (2) into *p*-menth-1(6)-en-8-ol (6a). Since most of the



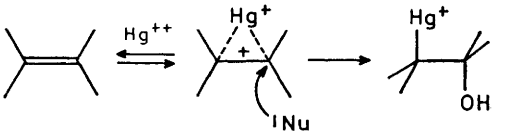
SCHEME 1

acids which had been used previously[4] are very hard (Scheme 1), a detailed study of the behaviour of the pinenes (1) and (2) in the presence of soft Lewis acids was needed. Among these, mercury(II) salts seemed to be promising, since Hg^{2+} is one of the softest electrophiles according to Pearson,[7] and mercuration–demercuration reactions of olefins are well known.[8]

In the event pin-2(10)-ene (2) was smoothly converted in high yield by mercury(II) salts [except $Hg(OAc)_2$: see later] in aqueous tetrahydrofuran either into *p*-menth-1(7)-en-8-ol (9a) or into *p*-menth-1(2)-en-8-ol (6a), depending on the conditions. This method was also extended to the synthesis of *p*-mentha-1,8-dien-7-ol (17).

RESULTS AND DISCUSSION

An MO approach to the mechanism of addition of mercury(II) salts to ethylene[9] suggested that a complex is first formed[10] (Scheme 2). This postulated intermediate has been detected by n.m.r. spectroscopy[11] and its formation is probably the rate-determining step. Moreover, in the frontier orbital approximation, the

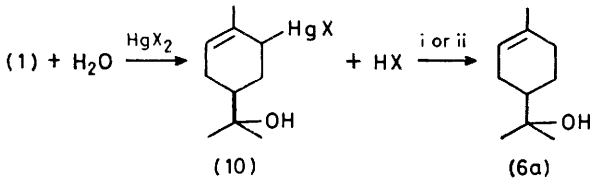


SCHEME 2

reaction, which is under orbital control,[12] occurs because of a favourable bonding interaction between the HOMO of ethylene (π-orbital) and the 6s LUMO of the mercury(II) ion.† A more refined approach[9] shows that there is virtually no participation of the 5d mercury orbitals (*i.e.* the interaction between the LUMO of ethylene and the HOMO of Hg^{2+} is negligible). Further, displacement of the mercury(II) ion parallel to the C–C bond of ethylene does not require a large amount of energy owing to the shape of the potential energy surface associated with the Hg^{2+}–ethylene system. In other words, one of the two olefinic carbon atoms readily develops a relatively high positive character thereby becoming much harder. Thus, nucleophiles such as water, alcohols, and acetate ion can react very rapidly with mercurinium ions yielding the Markownikov addition compound exclusively.[8,13] An important synthetic application has been reported recently.[14]

† The electronic configuration of mercury is $[Xe]4f^{14}5d^{10}6s^2$. Although not strictly valid, the abbreviation LUMO (HOMO) has been used even for the mercury(II) ion.

In agreement with previous results,[15] we have established that pin-2(10)-ene (2) reacts rapidly with various mercury(II) salts in aqueous tetrahydrofuran (THF). Although pin-2(3)-ene (1) is less reactive, it undergoes the same cyclobutane ring opening (Scheme 3).

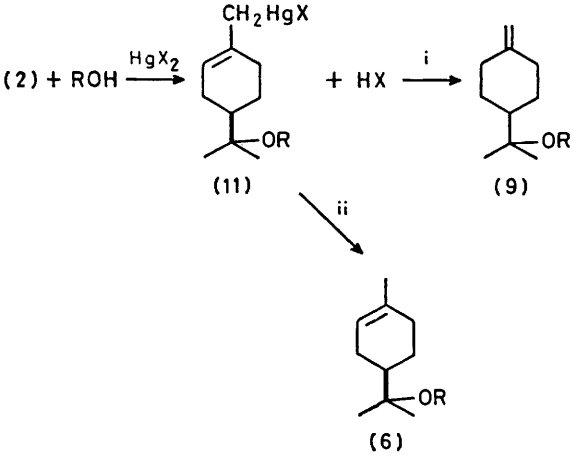


SCHEME 3 $X_2 = (ClO_4)_2$, $(NO_3)_2$, or SO_4; solvent: H_2O–THF (50 : 50); i, on standing [60% yield of (6a)]; ii, $NaBH_4$–OH^- [70% yield of (6a)]

For convenience, the mercury salts have been divided into four classes:

(a) highly water-soluble salts, *e.g.* $Hg(NO_3)_2$ and $Hg(ClO_4)_2$; (b) almost totally insoluble salts, *e.g.* $HgSO_4$; (c) salts which are insoluble in water, but soluble in various organic solvents (*e.g.* $HgCl_2$, soluble in alcohols and acetone); (d) mercury(II) acetate which has been classified separately owing to the different behaviour of its anion which leads to a different reaction (see later). Mercury(II) salts of classes (a)—(c) lead to the same final product, although their reactivity is somewhat different (Schemes 3 and 4). The presence of a hard nucleophile, such as water or methanol, is essential; no reaction was observed with pin-2(10)-ene (2) and a suspension of anhydrous mercury(II) salts in dry THF.

The reaction is very fast with mercury(II) salts of class (a). After a few minutes at room temperature no pin-2(10)-ene (2) can be detected (t.l.c. and n.m.r.). Further reaction of the mercury(II) intermediate (11a) according to Scheme 4, method i, led to *p*-menth-1(7)-en-8-ol (9a) (yield 95%) as the only isolated compound. It is a fragrant liquid, $C_{10}H_{18}O$, and its structure was assigned from spectroscopic data: i.r., O–H, 3 595 cm^{-1}, $=CH_2$, 1 645 and 880 cm^{-1}; ^1H n.m.r., δ 1.12 (6 H, s) and 4.67 (2 H, s); and ^{13}C n.m.r., 7 peaks upon ^1H irradiation, indicative of a *p*-menthane skeleton (plane of symmetry). Pin-2(10)-ene (2) probably yields the menthenol (9a) *via* the mechanism shown in Scheme 5, experimental evidence for which is described later. The intermediate organomercury(II) compound could not be isolated, however, owing to its sensitivity to heat, acids, and bases. With powdered mercury(II) sulphate (class b), the reaction is still fast, but the overall yield is lower (Scheme 4) because of difficulties in isolation (formation of emulsions).



a; R = H
b; R = Me
c; R = Et

SCHEME 4 i, on standing; ii, $NaBH_4$–OH^-

Expt.	Solvent	Hg^{2+} salt	Yield of product: Method i	Yield of product: Method ii
1	H_2O–Me_2CO (10 : 90)	$HgCl_2$	(9a) 90%	(9a) 90%, (6a) 10%
2	H_2O–THF (50 : 50)	$Hg(ClO_4)_2$	(9a) 90%	(6a) 95%
3	H_2O–THF (50 : 50)	$Hg(NO_3)_2$	(9a) 90%	(6a) 90%
4	H_2O–THF (50 : 50)	$HgSO_4$	(9a) 60%	(6a) 70%
5	MeOH (100%)	$HgCl_2$	(9b) 95%	(6b) 95%
6	EtOH (100%)	$HgCl_2$	(9c) 95%	(6c) 95%

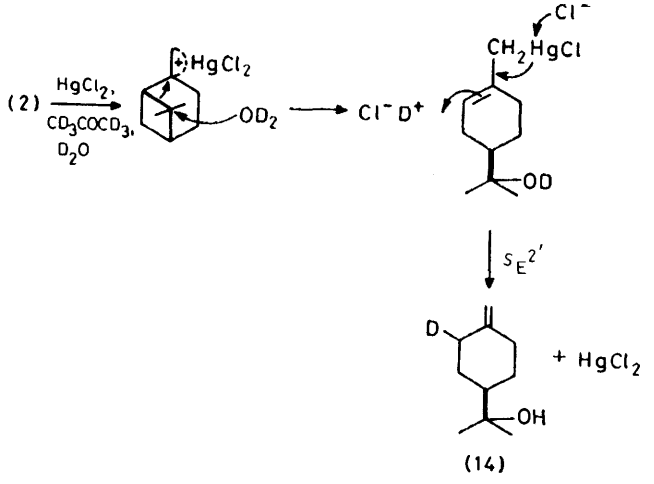
Mercury(II) chloride (class c) is soluble in acetone and aqueous acetone (1 : 9); its reaction with pin-2(10)-ene (2) is slower than the reactions with salts of classes (a) and (b). The ^1H n.m.r. spectrum of the reaction mixture [in $(CD_3)_2CO$–D_2O] shows the virtual absence of pin-2(10)-ene after 1 h at room temperature, and the appearance of a sharp singlet at δ 5.40 may be attributed to the

allylic methylene group bonded to mercury in the expected intermediate (11a). The olefinic protons of *p*-menth-1(7)-en-8-ol (9a) give rise to an incompletely resolved signal at δ 4.65, the intensity of which increases with time as the intensity of the δ 4.65 signal decreases, showing the solvolytic cleavage of the organomercury intermediate. After 2 h the reaction is complete. Although it was not possible to isolate the pure organomercury intermediate the solution was carefully evaporated, as soon as the pinene (2) could no longer be detected, and the pasty residue was dissolved in methanol and reduced ($NaBH_4$), leading to a mixture of *p*-menth-1(6)-en-8-ol (6a) (path ii, Scheme 4) and (9a).

A similar reaction takes place in methanol (Scheme 4, expt. 5), which may be followed by ^1H n.m.r. spectroscopy (in CD_3OD). The signal at δ 4.80, due to the intermediate, decreases in intensity as the intensity of the singlet at δ 4.68, due to the product (9a), increases.

The intermediate (11b) may be reduced easily with an excess of an alkaline solution of sodium borohydride, and the oily fragrant ether (6b) is obtained in high yield. When ethanol is the solvent the same procedures lead to (9c) or (6c).

The behaviour of mercury(II) acetate (class d) is

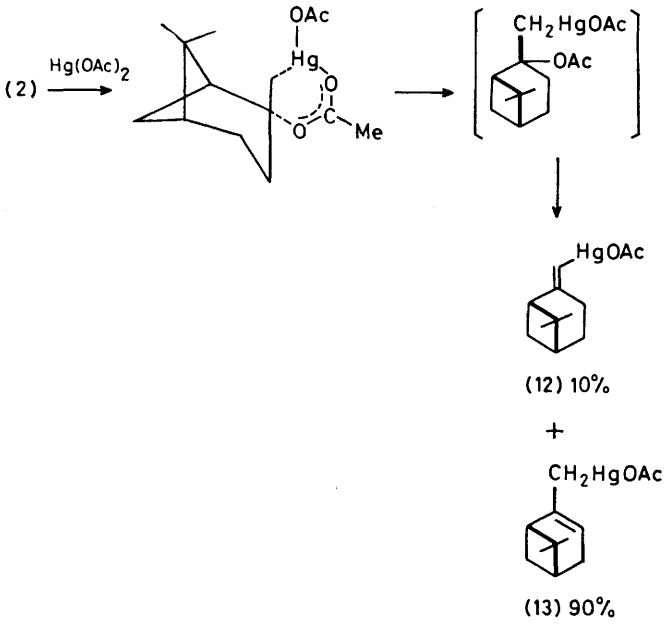


SCHEME 5

entirely different. It has been shown [15a] that pin-2(10)-ene (2) affords a mixture of mercury acetate derivatives which, on reduction with sodium borohydride, give the pinenes (1) and (2). We found exactly the same results.

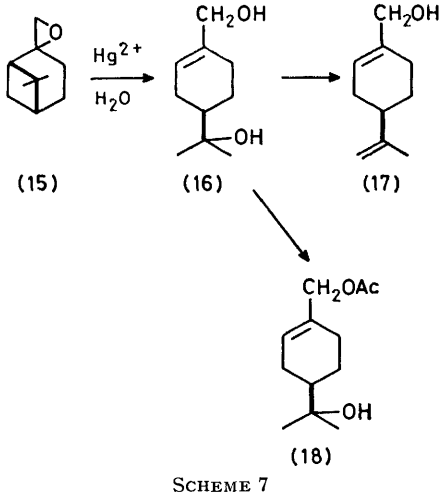
Although the mechanism of acetoxy-mercuration is still unclear [8,16-18] this surprising result can be explained as suggested by Famey [19] (Scheme 6). Acetoxy-mercuration *via* a six-membered cyclic transition state should proceed faster than attack of any intermediate mercurinium ion by water. If mercury(II) acetate approaches from the less hindered side of the pinene (2) the resulting tertiary acetate is axial, and hence very readily transformed through thermal elimination into (12) and (13) (Scheme 6). In boiling methanol these intermediates could react further.[15b]

Evidence for an S_E2' *Mechanism in the Conversion of* (11a) *into* (9a).—Allylic organomercurials have been reported [20] to undergo electrophilic substitution (S_E2') easily in acidic media. We thought that compound



SCHEME 6

(11a) should react further by a typical S_E2' mechanism with the acid formed *in situ* (*e.g.* expt. 1). In such a case, if water and acetone were replaced by deuteriated solvents a specifically labelled product (14) might be expected from the mechanism in Scheme 5. This expectation was fulfilled; the deuteriated product (14) was isolated, its structure being based on its i.r. spectrum, which exhibits a C–D stretching vibration at 2 230 cm^{-1}, and its ^{13}C n.m.r. spectrum, which shows a new triplet



SCHEME 7

centred just upfield of a methylene peak at δ 34.8 p.p.m., indicating the presence of a deuterium atom at C-6.

Synthesis of p-*Mentha*-1,8-*dien*-7-*ol*.[21]—Under conditions similar to those just described [$HgSO_4$, $Hg(NO_3)_2$,

or $Hg(ClO_4)_2$], (−)-2,10-epoxypinane (15) is smoothly transformed into *p*-menth-1(6)-ene-7,8-diol (16), in virtually quantitative yield, at room temperature in a few minutes (Scheme 7). In the presence of inorganic acids the diol (16) affords *p*-mentha-1,8-dien-7-ol (17) in 90% yield, one of the constituents of the essential oil of ginger grass. Although other synthesis of the dienol (17) or the related aldehyde have been described, starting from either limonene,[22] the pinene (2),[23] or the epoxide (15),[24] the yields are usually rather low and the separation of the expected compound somewhat tedious.

Both *p*-menth-1-ene-7,8-diol (16) and 7-acetoxy-*p*-menth-1-en-8-ol (18) are fragrant compounds. Their structures, as well as the structure of *p*-mentha-1,8-dien-7-ol (17) were proved by the usual spectroscopic techniques (i.r., and ^1H, and ^{13}C n.m.r.) which do not deserve special comment.

The reaction of pin-2(10)-ene (2) with mercury(II) salts [with the exception of $Hg(OAc)_2$] has thus been shown to yield, in the presence of water, a single compound with a *p*-menthane skeleton, and *p*-mentha-1,8-dien-7-ol (17) has been synthesized easily.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer model 399 spectrometer. ^1H N.m.r. spectra were recorded on a JEOL PMX 60 spectrometer and ^{13}C n.m.r. spectra on a Varian CFT 20 spectrometer with tetramethylsilane as internal standard. All reactions were carried out at room temperature and commercial grade reagents were used.

p-*Menth*-1(7)-*en*-8-*ol* (9a) (*Expts.* 1—4, *method i*).—Pin-2(10)-ene (2) (1.4 g) was added dropwise to a stirred suspension or a solution if the salt is soluble, *e.g.* expts. 1—3, of the appropriate mercury(II) salt (1.5 equiv.) in THF–water (10 cm^3 each) [or acetone (18 cm^3) and water (2 cm^3) for expt. 1]. The consumption of the pinene (2) was then monitored by t.l.c.; it was not usually detectable after 30 min. The mixture was set aside overnight and then filtered (expt. 4 only). Extraction with chloroform led to almost pure (9a), which was chromatographed on silica gel with pentane–ether (4 : 6) as eluant and obtained as an oil in 90% yield with $HgCl_2$, $Hg(ClO_4)_2$, and $Hg(NO_3)_2$, and in 60% yield with $HgSO_4$: $\nu_{max.}$ ($CHCl_3$) 3 595 (free OH), 3 060 (=C–H), 1 645 (C=C), and 880 (=CH_2) cm^{-1}; δ (^1H; $CDCl_3$) 1.18 (s, 6 H, Me) and 4.67 (s, 2 H, olefinic-H); δ (^{13}C; $CDCl_3$) 27.1 (C-9 and -10), 28.9 (C-3 and -5), 34.9 (C-2 and -6), 48.9 (C-4), 72.8 (C-8), 106.8 (C-7), and 148.9 (C-1) p.p.m.

p-*Menth*-1-*en*-8-*ol* (6a) (*Expts.* 1—4, *method ii*).—After the pinene (2) had disappeared completely in the foregoing reaction, the mixture was treated with aqueous sodium borohydride (0.5 M) and sodium hydroxide (3 M) (10 cm^3) (in reaction 1, acetone was evaporated off at room temperature under reduced pressure before reduction). The oily product (6a) was extracted with chloroform and purified by chromatography on silica gel impregnated with 8% silver nitrate: $\nu_{max.}$ (film) 3 060 (=CH) cm^{-1}; δ (^1H; $CDCl_3$) 1.18 (s, 6 H, Me) and 5.42br (s, 1 H, olefinic H); δ (^{13}C; $CDCl_3$) 23.3 (C-7), 24.0 (C-3), 26.0 (C-9), 27.0 (C-5), 27.3 (C-10), 31.1 (C-2), 45.0 (C-4), 72.2 (C-8), 120.9 (C-6), and 133.3 (C-1) p.p.m.

8-*Methoxy*- (9b) *and* 8-*Ethoxy*-p-*menth*-1(7)-*ene* (9c) (*Expts.* 5 *and* 6, *method i*).—Pin-2(10)-ene (2) (1.4 g) was added dropwise to a stirred solution of mercury(II) chloride (1.5 equiv.) in methanol or ethanol (20 cm^3), and the mixture was left overnight. The product was extracted as in the previous experiments, to give, respectively (9b), oil: $\nu_{max.}$ (film) 3 060 (=C–H), 1 645 (C=C), and 880 (=CH_2) cm^{-1}; δ ($CDCl_3$) 1.12 (s, 6 H, Me), 3.22 (s, 3 H, OMe), and 4.68 (s, 2 H, olefinic-H) and (9c), oil; $\nu_{max.}$ (film) 3 060 (=C–H), 1 645 (C=C), and 880 (=CH_2) cm^{-1}; δ ($CDCl_3$) 1.05 (s, 9 H, Me), 3.37 (q, 2 H, $-OCH_2-$), and 4.57 (s, 2 H, =CH_2).

8-*Methoxy*- (6b) *and* 8-*Ethoxy*-p-*menth*-1(6)-*ene* (6c) (*Expts.* 5 *and* 6, *method i*).—After the pinene (2) had disappeared completely in the foregoing reaction, the solution was evaporated at room temperature under reduced pressure and the crystalline residue obtained dissolved in THF (10 cm^3). Aqueous sodium borohydride (0.5 M) and sodium hydroxide (3 M) (10 cm^3) was then added. Mercury was precipitated. The product was extracted with chloroform and purified by chromatography on silica gel impregnated with 8% silver nitrate to give, respectively, (6b), oil: $\nu_{max.}$ (film) 3 060 (=C–H) cm^{-1}; δ ($CDCl_3$) 1.12 (s, 6 H, Me), 1.68 (s, 3 H, =C*Me*), 3.22 (s, 3 H, OMe), and 5.50br (s, 1 H, olefinic H) and (6c), oil: $\nu_{max.}$ (film) 3 060 (=C–H) cm^{-1}; δ ($CDCl_3$) 1.05 (s, 9 H, Me), 1.67 (s, 3 H, C=CMe), 3.37 (q, 2 H, $-OCH_2-$), and 5.33 br (s, 1 H, olefinic H).

(−)-2,10-*Epoxypinane* (15).—Pin-2(10)-ene (2) (13.6 g) was added dropwise to a stirred solution of *m*-chloroperoxybenzoic acid (17.2 g) in THF (100 cm^3) maintained at 0 °C. The epoxidation was complete within 3 h (t.l.c.). The product was extracted with chloroform and distilled under reduced pressure to give the epoxide (15) as an oil, b.p. 30—33 °C at 0.5 mmHg; $\nu_{max.}$ (film) 3 020 and 770 cm^{-1}; δ ($CDCl_3$) 0.92 (s, 3 H, Me) and 1.13 (s, 3 H, Me).

p-*Menth*-1-*ene*-7,8-*diol* (16).—2,10-Epoxypinane (15) (1.5 g) was added dropwise to a stirred solution of the mercury(II) salt [$Hg(NO_3)_2$, $Hg(ClO_4)_2$, or $HgSO_4$; suspension for $HgSO_4$] in THF–water (20 cm^3; 1 : 1). After a few minutes, the product was extracted with chloroform and distilled under reduced pressure to give the oil (16): $\nu_{max.}$ (film) 3 425 (OH) and 1 625 (C=C) cm^{-1}; δ (^1H; $CDCl_3$) 1.03 (s, 6 H, Me), 2.30 (s, 2 H, CH_2OH), and 5.53br (s, 1 H, olefinic H); δ (^{13}C; $CDCl_3$) 23.4 (C-3), 26.0 (C-2 and -9), 26.8 (C-5), 27.3 (C-10), 45.0 (C-4), 67.0 (C-7), 72.2 (C-8), 121.9 (C-6), and 137.0 (C-1) p.p.m.

p-*Mentha*-1,8-*dien*-7-*ol* (17).—A solution of the diol (16) (1 g) in chloroform (30 cm^3) was treated at room temperature with 1.5 N hydrochloric acid (30 cm^3). After completion of the reaction (t.l.c.) the product was extracted with chloroform to give the almost pure oily alcohol (17) in 95% yield, which was purified further by distillation under reduced pressure: $\nu_{max.}$ (film) 3 425 (OH), 3 065 (=CH–), 1 640 (C=C), and 880 (=CH_2) cm^{-1}; δ (^1H; $CDCl_3$) 1.80 (s, 3 H, Me), 4.07 (s, 2 H, $-CH_2O-$), 4.73 (s, 2 H, =CH_2), and 5.77br (s, 1 H, =CH–); δ (^{13}C; $CDCl_3$) 20.0 (C-10), 26.0 (C-2), 27.4 (C-3), 30.4 (C-5), 41.2 (C-4), 67.0 (C-7), 108.7 (C-9), 122.0 (C-6), 137.0 (C-1), and 149.5 (C-8) p.p.m

[9/1365 *Received*, 29*th August*, 1979]

REFERENCES

1 G. Wagner, *Ber.*, 1894, **27**, 2270.
2 J. L. Simonsen and L. N. Owen, 'The Terpenes,' vol. 2, Cambridge University Press, 1949.
3 D. V. Banthorpe and D. Whittaker, *Quart. Rev.*, 1966, 373.
4 G. Valkanas and N. Ikonomou, *Helv. Chim. Acta*, 1963, **46**, 1089.
5 G. N. Valkanas. *J. Org. Chem.*, 1976, **41**, 1179.

[6] M. Fetizon, S. Lazare, C. Pascard, and T. Prange, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1407.
[7] R. G. Pearson, *J. Chem. Educ.*, 1968, **45**, 581, 643.
[8] R. Larock, *Angew. Chem., Int. Ed. Engl.* 1978, **17**, 27.
[9] R. D. Bach and H. F. Henneike, *J. Am. Chem. Soc.*, 1970, **92**, 5589.
[10] J. Halpern and H. P. Tinker, *J. Am. Chem. Soc.*, 1967, **89**, 6427.
[11] G. A. Olah and P. R. Clifford, *J. Am. Chem. Soc.*, 1971, **93**. 1261.
[12] G. Klopman, 'Chemical Reactivity and Reaction Path,' Wiley, New York, 1974, p. 59.
[13] H. C. Brown and P. J. Geoghegan, *J. Org. Chem.*, 1970, **35**, 1844.
[14] E. J. Corey and H. Estreicher, *J. Am. Chem. Soc.*, 1978, **100**, 6294.
[15] (*a*) J. M. Coxon, M. P. Hartshorn, and A. J. Lewis, *Tetrahedron*, 1970, **26**, 3755; (*b*) A. Kergomard, J. C. Tardivat, and J. P. Vuilerme, *Bull. Soc. Chim. Fr.*, 1974, 2572.
[16] D. J. Pasto and J. A. Gontraz, *J. Am. Chem. Soc.*, 1970, **92**, 7480.
[17] H. C. Brown and J. H. Kawakani, *J. Am. Chem. Soc.*, 1975, **95**, 8665.
[18] W. L. Walters, T. G. Traylor, and A. Factor, *J. Org. Chem.*, 1973, **38**, 2306.
[19] R. C. Famey, *Top. Stereochem.*, 1968, **3**, 237.
[20] P. D. Sleezer, S. Winstein, and W. G. Young, *J. Am. Chem. Soc.*, 1963, **85**, 1890.
[21] I. Ecoto, M. Fetizon, and S. Lazare, Fr. P. 1 915 676 (1979).
[22] H. Ansari and P. Fido (Bush, Boake, Allen Ltd.), Ger. P. 2 513 910 (1975) (*Chem. Abs.*, 1976, **84**, 122 072).
[23] Japan Terpene Chemical Co, Ltd., Br. P. 1 094 875 (1967), (*Chem. Abs.*, 1968, **68**, 87 418); M. Julia (Rhone-Poulenc S. A.), Ger. P. 2 162 882 (1972) (*Chem. Abs.*, 1972, **77**, 101 937); D. H. R. Barton, I. A. Blair, and P. D. Magnus, *J. Chem. Soc., Perkin Trans.* 1, 1972, 614; C. Walling and C. Willis (Unilever Ltd.), Can. P. 981 695 (1976) (*Chem. Abs.*, 1976, **84**, 122 072).
[24] N. Prilejaiev and V. Verchouk, *Zh. Fiz. Khim.*, 1929, **61**, 456; A. Kergomard and J. Philibert-Bigou, *Bull. Soc. Chim. Fr.*, 1958, 393; A. Kergomard, J. Philibert-Bigou, and M. T. Geneix, Fr. Pat. 1 183 849 (*Chem. Abs.*, 1961, **55**, 27 404); J. M. Coxon, E. Darnsted, M. P. Hartshorn, and K. E. Ridchards, *Tetrahedron*, 1969, **25**, 3307.