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MEROTERPENOIDS – III

PSORALEA CORYLIFOLIA LINN. – 3. SYNTHESIS OF (±)-BAKUCHIOL METHYL ETHER†‡

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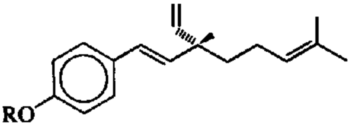
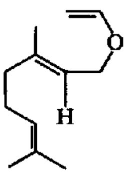
Abstract – A synthesis of (±)-bakuchiol methyl ether, involving Claisen rearrangement of geranyl vinyl ether as the key step, is described. Further thermal reorganisation of the intermediate 3-vinylcitronellal is discussed.

The structure[3] and absolute stereochemistry[4] of (+)-bakuchiol (**1**), a novel monoterpene phenol from *Psoralea corylifolia* Linn. has already been described. We now report on a synthesis of its methyl ether (**2**) as the racemate.



1: R = H
2: R = Me

Geraniol on interaction with ethyl vinyl ether in the presence of $Hg(OAc)_2$[5] smoothly gave, in ~ 70% yield, the desired geranyl vinyl ether (**3**). Structure **3** is fully supported by its spectral characteristics; IR: vinyl ether[6] 1630, 1205 and 1060 cm^{-1}; PMR: 3 vinylic Me's, 3H, s, 1·60 ppm and 6H, s, 1·66 ppm; $=CH-C\underline{H}_2-O-$ and $C\underline{H}_2=CH-O-$, 4H, overlapping multiplets located between 3·80–4·25 ppm; $CH_2=C\underline{H}-O-$, 1H, dd, 6·38 ppm; two $-\underset{|}{C}=C\underline{H}-CH_2-$, 1 H, t, 5·06, J = 7 Hz and, 1 H, t, 5·36 ppm, *J* = 7 Hz.



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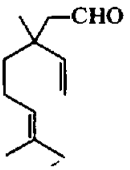

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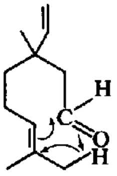

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The key intermediate (**4**) needed for the synthesis, was sought to be prepared by thermal treatment (Claisen rearrangement[7]) of the vinyl ether **3**. Since, the expected product **4** is capable (see **5**) of undergoing a further thermal reorganisation (*cf* behaviour of citral[8], citronellal), the product from a 3 hr reaction at 200° turned out to be rather complex (four products, GLC) and somewhat poor in content of the desired aldehyde **4**. A systematic study (Table 1) helped to underscore the optimum conditions (180°, 30 min), resulting in ~ 85% yield of the required aldehyde **4**. Structures of products (alcohols) resulting from further thermal rearrangement of **4** are discussed in a subsequent section. Structure of the aldehyde **4** is fully consistent with its spectral data; IR: —CHO 2700, 1725 cm^{-1}; $-CH=CH_2$ 1005, 920 cm^{-1}; PMR: $-\overset{|}{\underset{|}{C}}-Me$, 3H, s, 1·15 ppm; two vinylic Me's, 3H, s, 1·59 ppm and, 3H, s, 1·66 ppm; $-\overset{|}{\underset{|}{C}}-C\underline{H}_2-CHO$, 2H, d,

Table 1. Thermal rearrangement of geranyl vinyl ether

No.	Temp (°C ± 2°)	Time (min)	Product, % composition (GLC)* Aldehyde (IV)	Alcohols†	Starting material
1	170	30	52	—	48
2	180	30	85	9	6
3	195	30	68	32	—
4	205	30	67	33	—
5	200	180	30	70	—

*Column: 300 cm × 0·6 cm packed with 20% diethylene glycol polysuccinate on Chromosorb W (60–80 mesh); temp. 100°; gas flow (H_2): 30 ml/min.

†Mixture of isomeric alcohols resulting from further rearrangement of **4**.

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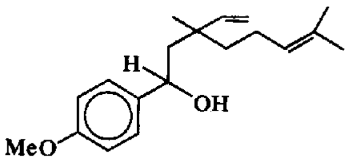
†Communication No. 1688, National Chemical Laboratory, Poona, India.

‡An advance communication appeared in *Tetrahedron Letters* 2897 (1967). Almost simultaneously, another group of workers[1] reported, in a preliminary form, synthesis of (±)-bakuchiol; full details of this work have also appeared.[2]

2·31 ppm, $J = 3$ Hz; $-\overset{|}{\underset{|}{C}}-C\underline{H}=C\underline{H}_2$, typical 10 line AB_2 spectrum, 4·80–6·13 ppm; $-\underset{|}{C}=\underset{|}{C}\underline{H}-CH_2-$, 1H, ~ 5·10 ppm; $-\overset{|}{\underset{|}{C}}-CH_2-C\underline{H}O$, 1H, t, 9·95 ppm, $J = 3$ Hz.

Interaction of *p*-anisyl magnesium bromide[10] and **4**, under the usual conditions, furnished a rather complex product, from which the desired alcohol **6** could be obtained as a mixture of diastereoisomers in ~ 30% yield. Besides this, three by-products could be isolated and characterised as **7**, **8** and **9** on the basis of elemental analysis and spectral data (IR, PMR); compound **9** is also a product of thermal rearrangement of **4** and is discussed subsequently. Though, the formation of **8** (Grignard reduction[11] product from **4**) and **9** (conceivably *via* cyclization of the enolate, **10**, at the work-up stage) can be understood, the possible genesis of **7** remains obscure.



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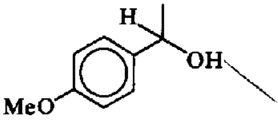

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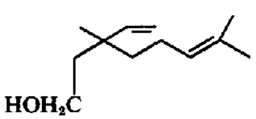

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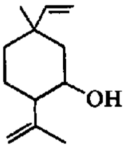

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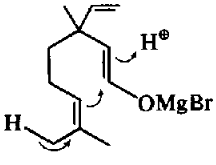

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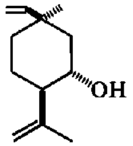
The diastereoisomeric mixture of **6** was dehydrated at ~ 180° with pyridine-treated alumina[12] to give a product identical in all respects (n_D, TLC, IR, PMR) with bakuchiol methyl ether, except that the synthetic product was racemic.

Thermal cyclization of 3-vinyl-citronellal

It has been mentioned earlier that heating vinylgeranyl ether (**3**) at 200°/3 hr resulted in the formation of at least three alcohols, besides ~ 30% yield of the required aldehyde (**4**). That the alcohols arise from a subsequent thermal reorganisation of **4**, was ascertained by heating aldehyde **4** to 200°/2 hr, when practically the same aldehyde-alcohols mixture resulted. The three alcohols with a relative retention time (RRT; with respect to the aldehyde) of 1·25, 1·45 and 1·82 are formed in approx. ratio of 6 : 2 : 3 and will be designated alcohol-1, alcohol-2 and alcohol-3 respectively.

By inverted-dry-column-chromatography (IDCC)[13] it has been possible to get all the three alcohols GLC pure. However, PMR spectrum of alcohol-2 clearly shows that it is ~ 1 : 1 mixture; attempted separation of this mixture on $AgNO_3$-SiO_2 gel proved unsuccessful. Thus, in fact, four alcohols are formed.* The PMR spectra of these compounds are consistent with the gross structure **9**, for which four racemates (**11**–**14**) are possible. It is also clear from the PMR spectra that in both alcohol-1 and alcohol-3 the sec OH is equatorial (alcohol-I: CHOH, 1H, quartet of doublets, 3·53 ppm, $J_1 = 12$ Hz, $J_2 = 10$ Hz, $J_3 = 4·5$ Hz, $W_{1/2} = 26$ Hz; alcohol-3: C$\underline{H}$OH, 1H, quartet of doublets, 3·60 ppm, $J_1 = 12$ Hz, $J_2 = 10$ Hz, $J_3 = 4·5$ Hz, $W_{1/2} = 25$ Hz) while it must be axial in the two minor alcohols ("alcohol-2" C$\underline{H}$OH, 1H, ill-resolved multiplet, 3·96 ppm, $W_{1/2} = 8$ Hz). Thus, alcohol-1 and alcohol-3 are the equatorial alcohols **11** and **14** (see **20**, **19**; from the available data it is not possible to decide which structure represents which alcohol) while **12**, **13** represent the other two alcohols.



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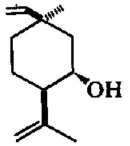

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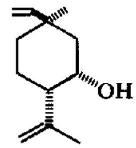

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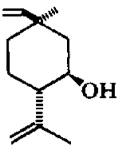

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The reorganisation of the aldehyde **4** to the alcohols **11**–**14** involves an intramolecular thermal Prins reaction and is of the sigmatropic [1,5]-hydrogen-shift type. The genesis of each racemate is related to a distinct, transition state and this is depicted in Fig. 1. Kinetically, there should be preference for **19** (≡ **11**) as in the transition states (**15**, **16**) there are less non-bonded interactions; this is borne out from the experimental results.

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*These results parallel those reported for the thermal cyclization of citronellal[9].

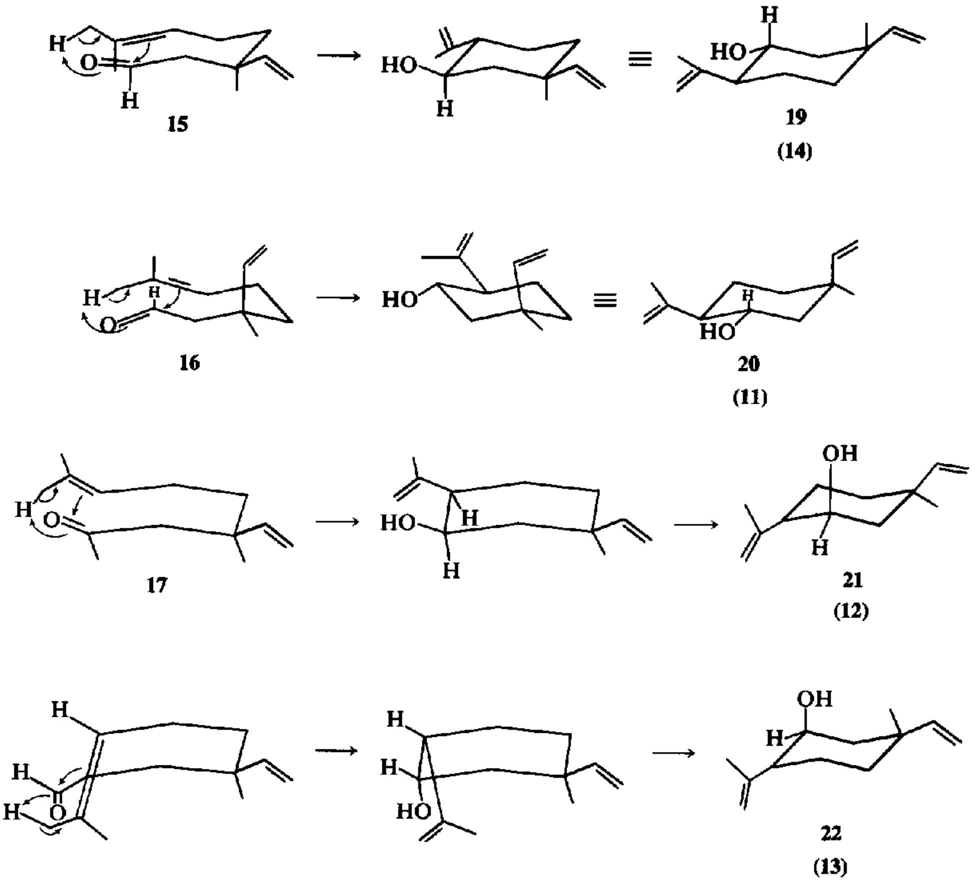

Fig 1. Stereochemistry of thermal rearrangement of 3-vinyl-citronellal

EXPERIMENTAL

For general remarks see Part I[3] of this series.

Geranyl vinyl ether (3)

A mixture of geraniol (23·4 g, 0·15 mole) and purified[5b] vinyl ethyl ether (144 g, 2·0 moles) was chilled (−5°) and finally powdered $Hg(OAc)_2$ (15 g) was added portionwise, under stirring (N_2). The mixture was allowed to attain room temp (~ 27°) during one hr and stirring was continued at this temp for another 21 hr, after which it was cooled (0°) and treated (30 min) with ice-cold 10% Na_2CO_3 aq (60 ml). The organic phase was separated, washed with cold 10% Na_2CO_3 aq, ice-water, brine and dried (K_2CO_3). This was distilled to recover the excess vinyl ethyl ether and to the residue light petroleum extract (20 ml × 3) of the original aqueous part added. The solvent was removed and the residue (40 g) chromatographed on Al_2O_3/II–III (3 cm × 55 cm). Light petroleum (250 ml × 2) eluted 23·6 g of geranyl vinyl ether, which was distilled: b.p. 79–81°/3·5 mm, n_D^{30} 1·4647. (Found: C, 80·82; H, 11·24. $C_{12}H_{20}O$ requires: C, 79·94; H, 11·18%).

3-*Vinyl-citronellal* (4)

Geranyl vinyl ether (3 g lots) was heated in sealed ampoules (N_2) at the required temp for a given period after which they were rapidly cooled to room temp by suddenly immersing in cold oil. The GLC analysis of products from different experiments are given in Table 1.

The product (0·844 g) from 180° ± 2°/30 min expt was subjected to IDCC[13] (SiO_2 gel/III, 2·2 cm × 22 cm; solvent: light petroleum ether-$CHCl_3$, 1:2) to furnish 0·555 g of TLC pure 4: b.p. 92–94°/5 mm, n_D^{30} 1·4604. (Found: C, 80·35; H, 11·33; $C_{12}H_{20}O$ requires: C, 79·94; H, 11·18%).

Semicarbazone (pyridine method), m.p. 108–110° (aq. EtOH). (Found: N, 17·60; $C_{13}H_{23}ON_3$ requires: N, 17·71%).

Action of p-anisyl magnesium bromide on 3-vinyl-citronellal

To a cooled (ice), filtered, ethereal soln of *p*-anisyl magnesium bromide (50 ml, 0·165 molar), the above aldehyde (0·815 g, 0·0034 mole) in ether (10 ml + 10 ml) was introduced (15 min) dropwise with stirring. The mixture was stirred at room temp (~ 27°) for 18 hr and then at reflux for another 1 hr, after which it was cooled (0°) and treated with saturated NH_4Cl aq (25 ml). The ether layer was separated, aqueous phase extracted with ether (20 ml × 3) and the combined ether extracts washed with 10% NaOH aq (15 ml × 4), water, brine and then dried. The solvent was flashed off and the residue (2·18 g) take up in light petroleum, chilled to −15° and filtered to remove the precipitated dianisyl (m.p. 162–165°). The filtrate was freed of solvent to give a viscous residue (1·89 g) showing at least four distinct spots on TLC (solvent: 5% EtOAc in

C_6H_6; spray reagent: 1% vanillin in 30% H_3PO_4 aq)—pink, brick red, brown and green in the increasing order of mobility. This product (2·74 g) was subjected to IDCC[13] (SiO_2 gel/III, 4·7 × 22 cm; solvent: 5% EtOAc in C_6H_6) to furnish the following products (in the increasing order of mobility):

2-(p-*Anisyl*)-*ethan*-2-*ol* (**7**). The product (100 mg; TLC, pink spot) was distilled: b.p. 110–120° (bath)/1 mm, n_D^{30} 1·5235; IR (liq.): 3300, 1612, 1580, 1520, 1250, 1180, 1092, 1040, 1010, 905, 840, 815 cm^{-1}; PMR (CCl_4): $C\underline{H}_3-\overset{|}{\underset{|}{C}}H$, 3H, d, 1·35 ppm, $J = 6·5$ Hz; $CH_3-\overset{|}{C}\underline{H}OH$, 1H, q, 4·68 ppm, $J = 6·5$ Hz; $C\underline{H}_3O-$, 3H, s, 3·75 ppm; *p*-disubstituted benzene ring, 4H, q, 6·98 ppm, $J = 9$ Hz. (Found: C, 71·45; H, 7·92. $C_9H_{12}O_2$ requires: C, 71·02; H, 7·95%).

3-*Vinyl-citronellol* (**8**). This product (150 mg) corresponds to the brick-red spot (TLC): b.p. 115–120° (bath)/1 mm, n_D^{30} 1·4765, IR (liquid): OH 3350, 1055, 1040 cm^{-1}; $-CH{=}CH_2$ 3090, 1650, 1010, 915 cm^{-1}; $-\underset{|}{C}{=}\underset{|}{C}H-$ 840 cm^{-1}; PMR (CCl_4): $-\overset{|}{\underset{|}{C}}-C\underline{H}_3$, 3H, s, 1·0 ppm; $(CH_3)_2C{=}CH-$ 3H singlets at 1·55 and 1·65 ppm; $-C\underline{H}_2$-OH, 2H, t, 3·5 ppm, $J = 7$ Hz; $-\overset{|}{\underset{|}{C}}-C\underline{H}{=}CH_2$, 3H, typical ABC pattern at ~ 5·00 ppm. (Found: C, 78·70; H, 11·80. $C_{12}H_{22}O$ requires: C, 79·06; H, 12·16%).

1-*Vinly*-iso*pulegol* (**9**). The product (260 mg; TLC, brown spot) was distilled: b.p. 115–120°/1 mm, n_D^{30} 1·4852. It was recognised, from its PMR spectrum, to be essentially a mixture of two equatorial alcohols corresponding to **9** (alcohol-1 and alcohol-3, with the former predominating). (Found: C, 79·71; H, 11·12. $C_{12}H_{20}O$ requires: C, 79·94; H, 11·18%).

8-(p-*Anisyl*)-2,6-*dimethyl*-6-*vinyl*-*oct*-2-*en*-8-*ol* (**6**). The IDCC cut (650 mg; TLC, green spot) corresponding to the required compound **6** was somewhat contaminated with 1-vinyl-isopulegol (**9**; TLC, brown spot) and hence was purified further by PLC (SiO_2 gel layers; solvent: C_6H_6-EtOAc-EtOH, 100:3:0·3). An analytical sample was prepared by thorough pumping (1 mm) of a TLC pure sample to remove last traces of solvent (distillation was avoided as in an attempted distillation at 1·5 mm, the product got partially dehydrated); IR (liquid); st. bands at 3300, 2880, 1610, 1520, 1250, 1180, 1040, 915 and 836 cm^{-1}; PMR (CCl_4): clearly a ~ 1:1 mixture of expected diastereoisomers as the $-\overset{|}{\underset{|}{C}}-C\underline{H}_3$ signal is observed as two singlets (total integration 3H) at 1·05 and 1·08 ppm, of almost equal intensity; $(C\underline{H}_3)_2C{=}CH-$, 3H singlets at 1·57 and 1·65 ppm; $OC\underline{H}_3$, 3H, s, 3·75 ppm; olefinic protons and $C\underline{H}OH$, 5H overlapping signals between 4·50–6·27 ppm; *p*-disubstituted benzene ring, 4H, q, 6·97 ppm, $J = 9$ Hz. (Found: C, 79·20; H, 9·98. $C_{19}H_{28}O_2$ requires: C, 79·12; H, 9·79%).

(±)-*Bakuchiol methyl ether* (**2**)

The above alcohol (**6**; 90 mg) was added to pyridine-treated Al_2O_3[12] (250 mg), well-mixed and heated at 180 ± 2° (4 hr) under N_2. The mixture was cooled and extracted with 3% EtOH in light petroleum. Removal of solvent gave a gum (64 mg) which was filtered through a column Al_2O_3/II–III (2·5 g, 10 cm) using light petroleum (10 ml × 3). The product (32 mg) was distilled: b.p. 160–170°/1·5 mm, n_D^{30} 1·5349; IR, PMR identical with those of an authentic sample. (Found: C, 84·26; H, 9·66. $C_{19}H_{26}O$ requires: C, 84·40; H, 9·70%).

Thermal cyclization of 3-*vinyl-citronellal*

Isolation of stereoisomeric 1-*vinyl-isopulegols* (**9**). The pyrolysis product (0·5 g; Expt. No. 5, Table 1) was subjected to IDCC (SiO_2 gel/III, 2·2 cm × 22 cm; solvent: $CHCl_3$-pet. ether–EtOAc, 10:5:1) to finally get two pooled cuts: (1) more polar, b.p. 94–95°/4 mm, 339 mg, mixture of alcohol-1 and alcohol-3, (ii) less polar, b.p. bath 140–50°/5 mm, n_D^{30} 1·4832, 114 mg, alcohol-2.

Cut (i), above, was subjected to IDCC on 5% $AgNO_3$-SiO_2 gel/III (3·5 cm × 22 cm; solvent: $CHCl_3$-EtOAc-EtOH, 100:16:5; wt. of material chromatographed, 450 mg) to finally get pure alcohol-3 (more polar, 130 mg) and pure alcohol-1 (less polar, 230 mg).

Alcohol-**1** (**11** *or* **14**). B.p. 120–25° (bath)/4 mm, n_D^{30} 1·4810; IR (liquid): OH 3340, 1035 cm^{-1}; $C{=}CH_2$ 3000, 1650, 1010, 920, 895 cm^{-1}; PMR (CCl_4): $-\overset{|}{\underset{|}{C}}-C\underline{H}_3$, 3H, s, 1·0 ppm; $-\underset{|}{C}{=}\underset{|}{C}\cdot C\underline{H}_3$, 3H, d, 1·67 ppm, $J = 0·5$ Hz; $-C\underline{H}OH$, 1H, quartet of doublets, 3·53 ppm, $J_1 = 12$ Hz, $J_2 = 10$ Hz and $J_3 = 4·5$ Hz; $-\overset{|}{\underset{|}{C}}-C\underline{H}{=}C\underline{H}_2$, 3H, typical ABC pattern located at 4·9–6·1 ppm; $-\overset{}{\underset{|}{C}}{=}C\underline{H}_2$, 2H, essentially a singlet, 4·8 ppm. Mass: major signals (relative intensity) at *m*/*e* 180 (M^+, 11%), 97 (40%), 93 (30%), 81 (46%), 79 (33%), 69 (55%), 68 (90%), 67 (100%), 55 (70%), 53 (80%). (Found: C, 79·97; H, 11·27. $C_{12}H_{20}O$ requires: C, 79·94; H, 11·18%).

Alcohol-**3** (**14** *or* **11**). B.p. 110–115° (bath)/2 mm, n_D^{30} 1·4845, IR (liquid): OH 3320, 1065, 1040 cm^{-1}; $C{=}CH_2$ 3000, 1650, 1008, 920, 895 cm^{-1}; PMR (CCl_4): $-\overset{|}{\underset{|}{C}}-C\underline{H}_3$, 3H, s, 1·04 ppm; $-C{=}\underset{|}{C}\cdot C\underline{H}_3$, 3H, d, 1·71 ppm, $J = 0·5$ Hz, $-C\underline{H}OH$, 1H, quartet of doublets, 3·60 ppm, $J_1 =$ 12 Hz, $J_2 = 10$ Hz and $J_3 = 4·5$ Hz; $-\overset{|}{\underset{|}{C}}-C\underline{H}{=}C\underline{H}_2$, 3H, typical ABC pattern located at 4·7–6·1 ppm; $-\overset{|}{\underset{|}{C}}{=}C\underline{H}_2$, 2H, essentially a singlet, ~ 4·8 ppm. Mass: major signals (relative intensity) at *m*/*e* 180° (M^+, 8%), 97 (62%), 94 (52%), 93 (35%), 81 (80%), 79 (27%), 69 (48%), 68 (100%), 67 (58%), 55 (43%), 53 (40%). (Found: C, 79·75; H, 11·27. $C_{12}H_{20}O$ requires: C, 79·94; H, 11·18%).

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