176. 1-*p*-Menthene-8-thiol[1]): A Powerful Flavor Impact Constituent of Grapefruit Juice (*Citrus paradisi* MACFAYDEN)

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Summary

1-*p*-Menthene-8-thiol (**B**) is shown to be a potent character-donating constituent of grapefruit juice, in which it occurs at the ppb-level or below. A convenient synthesis is described for this terpene-thiol, apparently the most powerful flavor compound ever found in nature.

The peel and juice oils from *Citrus spp.* are important flavoring ingredients for the food and beverage industries [1]. Considerable research work has already been done in order to identify many individual constituents of these natural flavors. Since about 1950, both cold-pressed oil and juice of grapefruit (*Citrus paradisi* MACFAYDEN) have been investigated and a total of some 126 volatile constituents were characterized [2] (not including less volatile components such as coumarins [3], sugars, hydroxy-acids, and other water-soluble substances which do not contribute substantially to the specific grapefruit flavor). Among the volatiles identified, nootkatone (**A**) [4] is considered as a primary flavor-impact compound in grapefruit, although it also occurs in most other *Citrus spp.* Recently, however, authors have questioned the true flavoring importance of **A**, even whether or not this ketone is necessary for good grapefruit flavor [5] [6]. In any case, there is no doubt that still unidentified compounds co-occur with nootkatone (**A**) in grapefruit flavor and contribute importantly to the flavor and aroma of grapefruit oil and juice [5–7].

We now report that a prominent and unexpected representative of these hitherto unknown flavor components is *1-p-menthene-8-thiol* (**B**) [8]. When adequately diluted, this novel, powerful flavor-impact compound displays a genuine, unmistakable aroma of *fresh grapefruit juice* (in which it naturally occurs at or below the ppb-level). The identification of **B** practically settles the long-standing problem of synthetically reproducing the full-bodied flavor of fresh grapefruit juice. Other previously identified S-compounds in grapefruit were hydrogen sulfide [9], carbonyl sulfide [10], methyl sulfide [10], methanediol [10], and sulfur dioxide [10]. Also, a series of bicyclic sulfides related to *p*-menthane were reported to occur in grapefruit

[1]) Patent applications relative to the use of 1-*p*-menthene-8-thiol (**B**) have been filed in several countries by *Firmenich SA*, Geneva (Priority: 23.12.1980).

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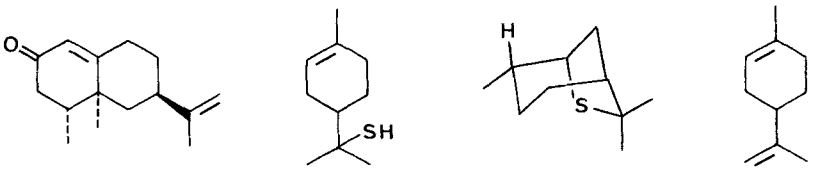
peel oil [11]. Unfortunately, no rigorous structural proof was provided for the latter substances which bear a close resemblance to *2,8-epithio*-cis-p-*menthane* (**C**) [12a] and to the well-known bicyclic terpene sulfides formed by reaction of elemental sulfur with limonene (**1**) at elevated temperatures [12].



A **B** **C** **1**

1. Preparation[2]) and fractionation of the volatile flavor of grapefruit juice. – About 100 l of commercial canned grapefruit juice[3]) were subjected to concurrent steam-distillation/heptane[4])-extraction under 100 Torr (b.p. $(H_2O) \approx 52°$; b.p. $(C_7H_{16}) \approx 42°$) in a *Likens-Nickerson* apparatus [13]. The main flask of this apparatus was large enough to permit treatment of 16–17 l batches of juice for 24 h each time; cooling of the condenser was efficiently ensured by satd. NaCl-solution at $-5°$. The resulting crude heptane extract (1 l), carefully dried over $MgSO_4$ and evaporated at 50°/30 Torr, left 7.7 g (0.0077% by weight of starting grapefruit juice) of a concentrate having quite satisfactory organoleptic characteristics[5]). Chromatography of this concentrate on silica gel afforded five fractions, one of which (Fr. 2: 0.165 g, see *Exper. Part*) exhibited a peculiar *sulfurous* odor typical of grapefruit juice. This fraction was examined by capillary GC. *(Carbowax 20 M*, 80–160°, +3.5°/min, 53 m × 0.3 mm column), using a multi-detector instrument[6]) with which it was possible to simultaneously 'sniff' the column effluent and selectively detect the N-, P- and S-containing compounds. It was thus observed that the 'sulfurous odor' emerged sharply in a practically empty part of the chromatogram, giving rise to a concomitant but very weak response of the S-detector. Essentially the same result *(Fig. 1)* could be attained by semipreparative GC. on packed silicone oil columns previously 'deactivated' by treatment with dimethylaminoethanol and 'Silyl-8'[7]), using temperatures not exceeding 200° at any point of the (gas + vapor)-path (omission of these precautions led in general to complete disappearance of the 'sulfurous odor'). Sub-fraction 2 H from this separation *(Fig. 1)* was further separated into four sub-groups of constituents (2 Ha–2 Hd) under more efficient GC. conditions. Sub-group 2 Hd, finally examined by GC./MS. coupling, proved to be a mixture of 8-ethoxy-1-*p*-menthene, geranyl

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[2]) This preparation was carried out at our Pilot laboratory under the direction of Dr. *A.F. Boschung*, to whom we are grateful.

[3]) 'Libby's', produce of Swaziland.

[4]) *Puriss.* (*Fluka AG*, Buchs, Switzerland). Very pure solvents were used throughout this work.

[5]) We thank Dr. *P. Dietrich* and Messrs. *A. Y. Smith* and *F. Benzi* (*Firmenich SA*, Geneva) for having carried out this and many other sensory evaluations.

[6]) *Fractovap 2900, Carlo Erba*, conveniently modified by Drs. *J. Flament* and *E. Palluy* (*Firmenich SA*, Geneva) according to *Hřivnač et al.* [14].

[7]) *Pierce Chemical Company*, Rockford, Ill., U.S.A.

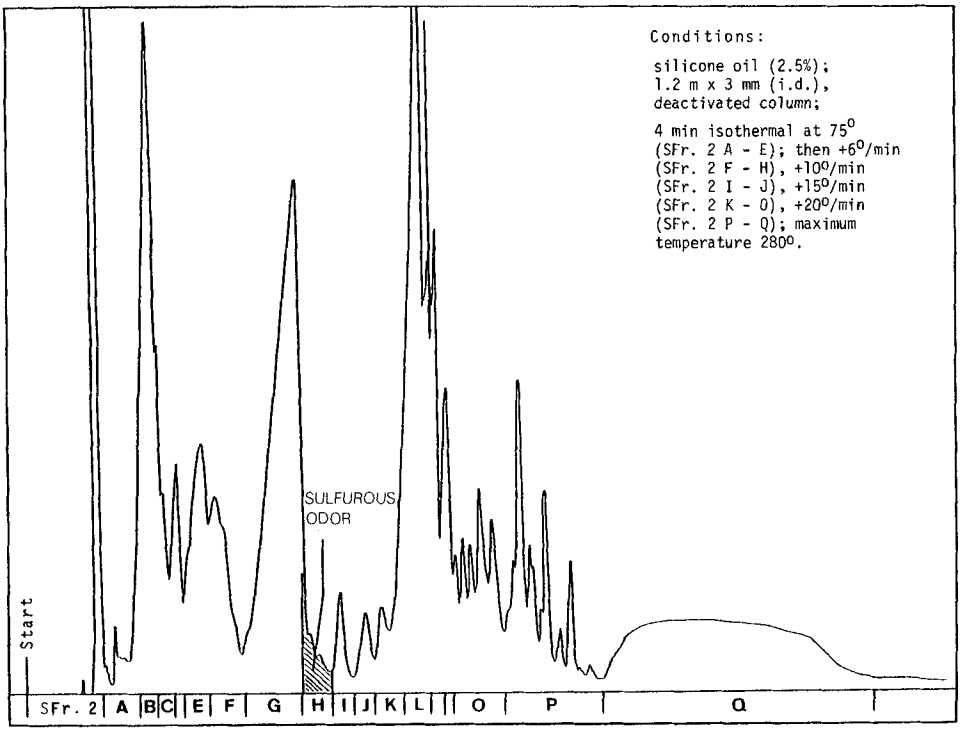


Fig. 1. *Semi-preparative GC. separation of Fr. 2 into sub-fractions 2A–2Q*

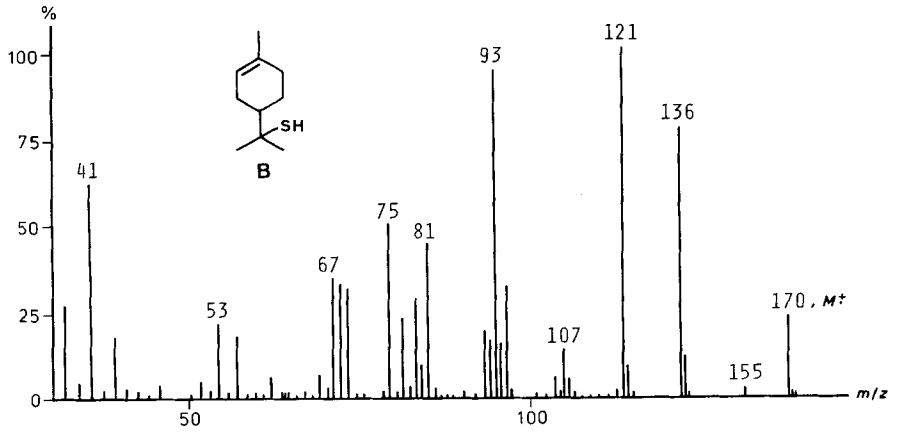


Fig. 2. *Mass spectrum of 1-*p*-menthene-8-thiol* (**B**)

ethyl ether, vitispiranes [15][8]) (2 stereoisomers), 2*endo*- or 2*exo*-bornyl acetate, and propyl octanoate. However, beside these major components, there were minute amounts of two unknown compounds, in fact **B** and **C**, which clearly contained one S-atom as evidenced by the ($M^+ + 2$) ions at *m/z* 172 in their mass spectra (*Fig. 2* and *3*).

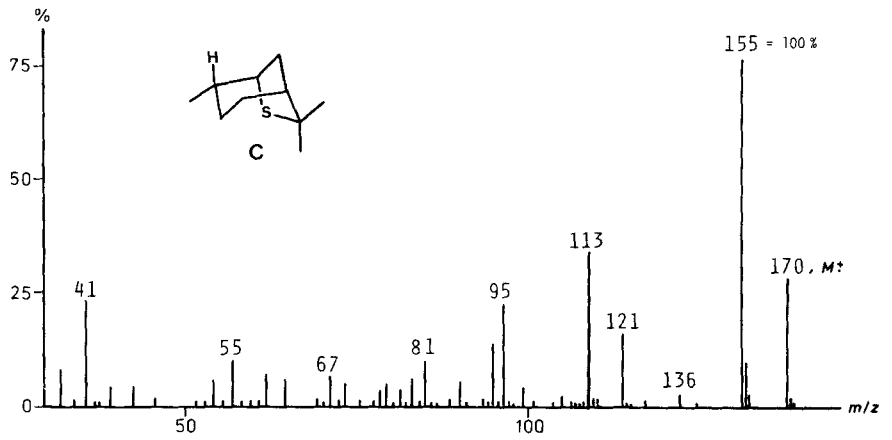
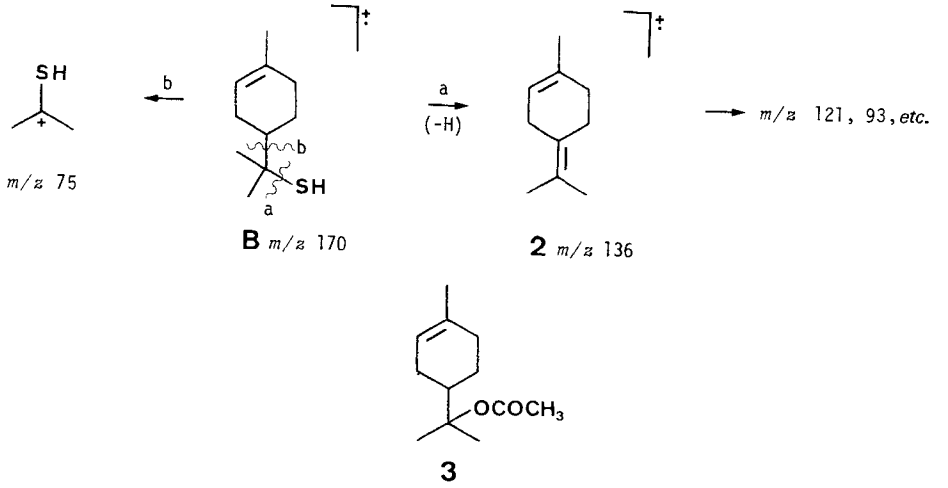


Fig. 3. *Mass spectrum of 2,8-epithio*-cis-p-*menthane* (**C**)

2. Structure elucidation and synthesis of 1-*p*-menthene-8-thiol (*B*). – A clue to the structure of compound **B** was given by its mass spectrum which exhibits three noticeable features *(Fig. 2)*. First, there is an easy loss of 34 mass units (H_2S or equivalent) leading to the large *m/z* 136 ion. Second, this and the two other prominent ions at *m/z* 121 and 93 have practically the same relative abundances (0.77:1.00:0.97) as in the mass spectrum of terpinolene (**2**) [16]. Third, the peak at *m/z* 75, quite unexpected for a monoterpene [16], is best accounted for by the fragment $(CH_3)_2\overset{+}{C}SH$. As shown in *Scheme 1*, structure **B** would represent the simplest possibility to reconcile these data. This interpretation was substantiated by the fact that the large peaks at *m/z* 136, 121 and 93 in the mass spectrum of α-terpinyl acetate (**3**) are virtually identical to those of **B**. To our knowledge, 1-*p*-menthene-8-thiol (**B**) has been described only once, in a Russian work dealing with the synthesis of thiols by addition of hydrogen sulfide to olefins catalyzed by alkylaluminum dichlorides [8]. However, judging from the scarce data given, this process leads to a low yield of impure **B** when it is applied to limonene (**1**). We devised a more efficient synthetic procedure shown in *Scheme 2*. Reaction of racemic 8,9-epoxy-1-*p*-menthene (**4**) [17] with thiourea [18] followed by alkaline treatment of the resulting thiouronium salt **5** afforded 8,9-epithio-1-*p*-menthene (**6**), the reduction of which with $LiAlH_4$ in refluxing THF proceeded quite regioselectively to give 98% pure (±)-1-*p*-menthene-8-thiol (**B**) (overall yield 41%). The

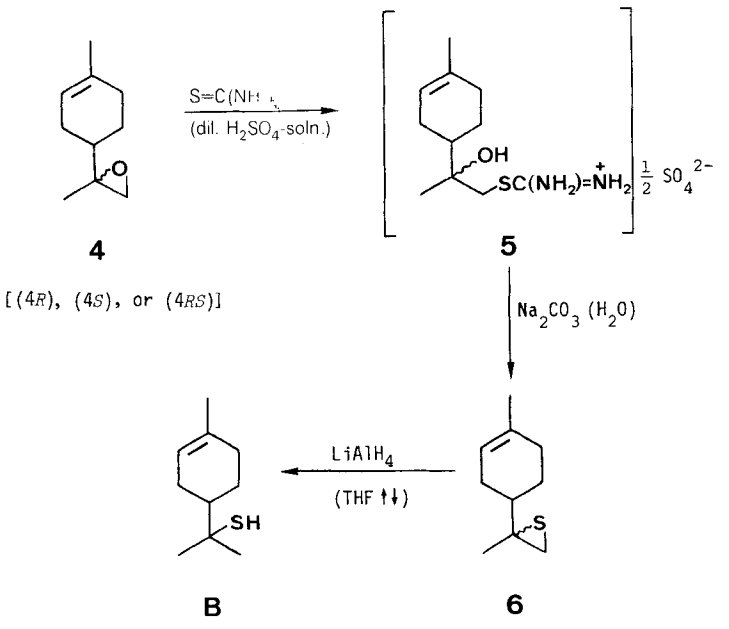
[8]) Formerly identified in grapefruit by Dr. *A. F. Thomas* (*Firmenich SA*, Geneva, personal communication).

Scheme 1. *Major fragmentation modes of* **B** *under electron impact*



(+)-(*R*)- and (−)-(*S*)-**B**, with estimated optical purities of 97 and 77%, respectively, were synthesized in the same way from optically active **4**; this was itself derived from both enantiomeric limonenes (**1**) *via* known procedures [17] [19] [20]. Synthetic and

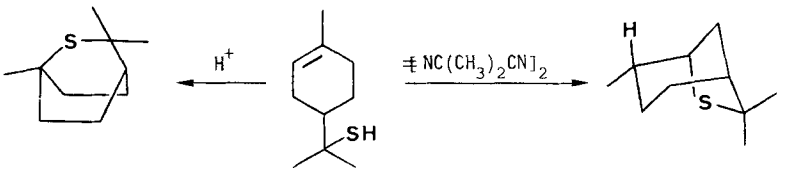
Scheme 2. *Synthesis of 1-*p*-menthene-8-thiol* (**B**) *and its enantiomers*



natural **B** had identical mass spectra *(Fig. 2)* and t_R (capillary GC.) but, at present, no specific rotation data is available for the latter[9]). Pure, liquid **B** smells extremely powerful and nauseous.

3. Preparation of 2,8-epithio-*cis*-*p*-menthane (*C*) from 1-*p*-menthene-8-thiol (*B*). – The structure of natural **C**, isolated as described above, could not be deduced directly from the meagre spectral data available (mass spectrum only, *Fig. 3*). Fortunately, this frustrating situation was resolved when we found that 1-*p*-menthene-8-thiol (**B**) cyclizes easily either under radical or protic conditions, and that the known 2,8-epithio-*cis*-*p*-menthane [12a] formed in the former process[10]) was identical to **C** (MS., t_R on capillary GC.) *(Scheme 3)*. The relative configuration of **C** ([*endo* CH_3–C(1)]) (*p*-menthane numbering), firmly established [12a], implies that the radical cyclization of **B** proceeds stereoselectively *via* antiperiplanar, anti-*Markownikoff* addition of the thiol moiety to the double bond. Analogous, intermolecular addition reactions of thiols are known to exhibit the same type of selectivity [21]. The particular ease of the radical cyclization **B** → **C** explains why these two compounds co-occur in grapefruit juice (we found a **B**/**C**-ratio close to 4:1). This reaction takes place spontaneously at room temperature in the presence of light, usually after a variable induction period. It can be efficiently inhibited, however, by small concentrations (0.1%) of usual antioxidants like 'BHA' (2-*t*-butyl-4-methoxyphenol). Under protic conditions, the cyclization of **B** obeys the *Markownikoff* rule and affords 1,8-epithio-*p*-menthane (**7**) [12] *(Scheme 3)*.

Scheme 3. *Cyclization reactions of 1-*p*-menthene-8-thiol* (**B**)



7 **B** **C**

4. Organoleptic properties of 1-*p*-menthene-8-thiol (*B*) and its bicyclic isomer *C*. – The conspicuous organoleptic properties of **B** had been noticed early in our separation work, well before this compound could be actually isolated from grapefruit flavor and identified. Subsequently, these observations were fully confirmed by

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[9]) A reasonable assumption is that **B** could be biosynthetically related to (+)-(*R*)-limonene (**1**) which constitutes, in a state of high optical purity, > 90% of grapefruit oil. Accordingly, **B** most probably occurs as its (+)-(*R*)-enantiomer in nature.

[10]) Alternative disulfide formation does not seriously compete with the radical cyclization of **B**, although this oxidative dimerization takes place under particular conditions. Clearly, both steric hindrance around the tertiary thiol function and intramolecularity favor the cyclization of **B**.

sensory evaluations[11]) which showed the taste detection threshold[12]) of synthetic, racemic **B** to be slightly lower than 1.10^{-4} ppb in water (this corresponding to a concentration of 1.10^{-4} mg of **B** in one metric ton of water). For (+)-(*R*)- and (−)-(*S*)-**B**, the respective values found were 2.10^{-5} and 8.10^{-5} ppb. To the best of our knowledge, these detection thresholds are the lowest ever recorded for a naturally occurring flavor compound [24]. Qualitatively, there is no significant difference between the organoleptic properties of racemic and optically active **B**: while the (−)-(*S*)-enantiomer appears to have a somewhat more fruity and natural aroma than its antipode, (±)-**B** behaves just like a mixture of both forms. Regarding the taste detection threshold of 2,8-epithio-*cis*-*p*-menthane (**C**), it was found to be as high as 9 ppb in water. This value, about 10^5 times greater than that of **B**, indicates that the contribution of **C** to the overall profile of grapefruit flavor should be negligible.

Finally, we also synthesized a number of thiols structurally related to **B** (isomers, saturated analogs, etc.). None of these exhibited organoleptic properties matching those of 1-*p*-menthene-8-thiol (**B**), which appears to be a unique flavor compound.

Experimental Part

General. – Specific rotations $[\alpha]_D^{20}$ were measured in a 0.1 dm tube on a *Perkin-Elmer* Model *141* polarimeter. The infrared (IR.) spectra (neat liquids) were taken on a *Perkin-Elmer 720* instrument; characteristic absorption bands are given in cm^{-1}. ^{1}H-NMR. spectra were recorded on a *WH 360 Bruker* instrument, using $CDCl_3$ as solvent. Chemical shifts are expressed in ppm (δ-scale) downfield from TMS as internal standard; abbreviations: *s* = singlet, *d* = doublet, *m* = multiplet, *J* = spin-spin coupling constant (Hz). Mass spectra (MS.) were measured at 70 eV on an *Atlas CH 4* spectrometer, inlet temperature 130–150°; the molecular ions (M^+) and fragment ions are given as *m/z* with relative peak intensities in % of the base peak. Gas chromatography/MS. data (GC./MS.) were obtained using a gas chromatograph *Carlo Erba,* Model *2101 AC* (*UCON HB 50 5100,* 60–180°, 50 m × 0.3 mm glass column), coupled to a *Varian MAT 112* or a *Finnigan 4023-c* mass spectrometer. Unless otherwise stated, GC. was performed on *Varian Aerograph* (Models *1820-3* and *2720-3*) and *Carlo Erba* (Model *2301 AC*) gas chromatographs; carrier gas: He. The liquid-solid chromatographic separation was carried out on 0.05–0.2 mm silica gel for column chromatography (*Merck AG,* Art. No. 7734).

1. Fractionation of volatile grapefruit flavor. – The crude extract (7.7 g) resulting from the concurrent steam-distillation/heptane-extraction [13] of about 100 l of grapefruit juice[3]) (see general part) was chromatographed as follows on silica gel (250 g):

Fr. 1	hexane/ether 100:0 to 95:5	4.910 g	
Fr. 2	hexane/ether 95:5	0.165 g	(sulfurous odor)
Fr. 3	hexane/ether 94:6 to 92:8	0.210 g	
Fr. 4	hexane/ether 90:10 to 20:80	2.230 g	
Fr. 5	ether/methanol 100:0 to 85:15	0.100 g	
		7.615 g	

[11]) We are very grateful to Dr. *W. Pickenhagen* and Mr. *A. Furrer* (*Firmenich SA,* Geneva) for having carefully evaluated our compounds with the cooperation of a tasting panel of 14–20 assessors. The detection thresholds were determined by the 'triangular tests' [22] and 'multiple pairs test' [23] procedures.

[12]) Taste detection threshold: the lowest concentration at which the taste of a substance is *detected,* but not necessarily *recognized.*

Fr. 2 was first separated into 17 sub-fractions (2A to 2Q) by semipreparative GC. as indicated in *Fig. 1*. More efficient GC. conditions (*silicone oil*[13]) 5%, 140°, 2.5 m column previously deactivated by treatment with dimethylaminoethanol and *Silyl-8*[7])) then allowed further partition of sub-fraction 2H into four sub-groups of constituents, 2Ha to 2Hd. The sub-group 2Hd, selected for final study by GC./MS. coupling, was found to contain minute amounts ($\leq 0.5\%$) of both S-compounds **B** and **C**, characterized by their mass spectra (*Fig. 2* and *3*). The other, major constituents of the mixture were more common substances (see general part).

2. Synthesis of (±)-1-*p*-menthene-8-thiol (*B*) *(Scheme 2).* – 2.1. [18]. *Preparation of 8,9-epithio-1-p-menthene* (**6**). (±)-8,9-Epoxy-1-*p*-menthene (**4**) [17] (17.65 g, 0.116 mol) was added dropwise over 1 h at 5° to a stirred mixture of thiourea (8.82 g, 0.116 mol), water (40 ml), and conc. sulfuric acid (3.48 ml, 0.06 mol). After 10 min further stirring at 5° and 14 h at 20°, the mixture was diluted with 20 ml of water and cooled to 0°. The precipitated crystals, collected, washed with water and dried at 40°/0.01 Torr, represented 30.66 g (95%) of thiouronium salt **5**, m.p. 159–160° (uncorrected). A solution of Na_2CO_3 (11.66 g, 0.11 mol) in water (60 ml) was added dropwise over 1 h at 25° to a stirred mixture of **5** (30.66 g, 0.11 mol) with water (430 ml). After 20 min further stirring at 20–25° and 15 min at 50°, the mixture was extracted with pentane (3×) and the combined organic layers washed with water (3×). Distillation of the crude product (15.16 g) obtained after usual workup gave 10.67 g (57%) of 8,9-epithio-1-*p*-menthene (**6**), b.p. 43°/0.001 Torr; $d_4^{20} = 0.991$; $n_D^{20} = 1.522$. – IR.: 1435, 1060, 1380, 920, 795, 805. – ^{1}H-NMR.: 1.50 and 1.52 (2 *s*, total 3 H[14])); 1.64 (*s*, 3 H); 1.30–1.60 (*m*, 2 H); 1.85 (*m*, 1 H); 2.00 (*m*, 4 H); 2.34, 2.37, 2.40 and 2.43 (4 *s*, total 2 H[14])); 5.37 (*m*, 1 H). – MS.: 168 (~0, M^+, $C_{10}H_{16}S$), 136 (20), 121 (17), 94 (19), 93 (54), 79 (21), 68 (100), 67 (45), 53 (17).

$C_{10}H_{16}S$ (168.29) Calc. C 71.39 H 9.59% Found C 71.43 H 9.61%

2.2. *Preparation of (±)-1-p-menthene-8-thiol* (**B**). A solution of **6** (1.00 g, 5.95 mmol) in anhydrous THF (20 ml) was added dropwise, under N_2, to a stirred slurry of $LiAlH_4$ (0.114 g, 3.00 mmol) in refluxing THF (5 ml). After 1 h further stirring/refluxing, water (6 ml) was cautiously added at 0°. The mixture was stirred for 10 min, 'stabilized' by addition of 5 mg of BHA (2-*t*-butyl-4-methoxyphenol), extracted with ether (3×), and the combined organic layers washed twice with satd. NaCl-solution. Usual workup followed by distillation of the crude product (to which a further 5 mg portion of BHA had been added) afforded 0.767 g (76%) of (±)-1-*p*-menthene-8-thiol (**B**), b.p. 40°/0.001 Torr (98% pure according to capillary GC.); $d_4^{20} = 0.948$; $n_D^{20} = 1.503$. – IR.: 1450, 1365, 1385, 1130, 1155, 800. – ^{1}H-NMR.: 1.35 (*s*, 3 H); 1.42 (*s*, 3 H); 1.57 (*s*, 1 H); 1.2–1.6 (*m*, 2 H); 1.66 (*s*, 3 H); 1.8–2.2 (*m*, 5 H); 5.39 (*m*, 1 H). – MS.: see *Figure 2*.

$C_{10}H_{18}S$ (170.30) Calc. C 70.54 H 10.66% Found C 70.22 H 10.49%

Table. *Specific rotations of limonene* (**1**) *enantiomers*[15]) *and derived compounds* **4**, **6** *and* **B**

	$[\alpha]_D^{20}$		Values corrected to 100% optical purity[a])
	(*R*)-	(*S*)-	
Limonene (**1**)	+ 120.5° (neat)	− 96.4° (neat)	± 123.8°[b])
8,9-Epoxy-1-*p*-menthene (**4**)[c])	+ 91.6° ($c = 1.54$, $CHCl_3$)	− 72.9° ($c = 1.66$, $CHCl_3$)	± 93.8°
8,9-Epithio-1-*p*-menthene (**6**)[c])	+ 56.4° ($c = 1.72$, $CHCl_3$)	− 46.6° ($c = 1.48$, $CHCl_3$)	± 58.8°
1-*p*-Menthene-8-thiol (**B**)	+ 79.8° ($c = 1.44$, $CHCl_3$)	− 63.9° ($c = 1.91$, $CHCl_3$)	± 82.0°

[a]) Assuming that no epimerization occurred throughout the synthesis. [b]) Mean of the values reported for (+)-(*R*)- and (−)-(*S*)-limonenes (**1**) [26]. [c]) As mixtures of diastereoisomers (4*R*,8*RS*) and (4*S*,8*RS*), respectively.

[13]) 'Embaphase', *May & Baker*, Ltd., Dagenham, England.

[14]) Splitting corresponding to a mixture (≈45:55) of both diastereoisomers of **6** (capillary GC., *UCON HB 505100*, 100°, 50 m × 0.3 mm column).

[15]) *Fluka AG*, Buchs, Switzerland, Art. No. 62120 and 62130.

3. Synthesis of (+)-(*R*)- and (−)-(*S*)-1-*p*-menthene-8-thiols ((+)- and (−)-*B*). – Both enantiomers of **B** were prepared by applying the preceding synthetic procedure *(Scheme 2)* to the optically active 8,9-epoxy-1-*p*-menthenes (**4**). The latter, resulting from the direct epoxidation [19] of (+)-(*R*)- and (−)-(*S*)-limonenes (**1**)[15] under *Payne*'s conditions [25], were thus respectively converted into (+)-(*R*)- and (−)-(*S*)-**B** *via* their epithio-derivatives (+)- and (−)-**6**. The specific rotations measured throughout this process in both enantiomeric series are given in the *Table*, together with corresponding values corrected to 100% optical purity.

4. Cyclization of 1-*p*-menthene-8-thiol (*B*) under radical conditions [27] **(→ 2,8-epithio-*cis*-*p*-menthane (C)).** – A mixture of **B** (0.170 g, 1 mmol), α,α'-azo-isobutyronitrile[16] (0.082 g, 0.5 mmol) and 1 ml hexane was stirred for 2 h at 70° under N_2. The cooled mixture, quenched with water, was extracted with hexane (3×) and the combined organic layers washed to neutrality. Distillation of the crude product resulting from usual workup afforded 110 mg (65%) of 2,8-epithio-*cis*-*p*-menthane (**C**) [12a], b.p. ~40°/0.001 Torr (91% pure according to capillary GC.), which was finally purified by semi-prep. GC. (*Carbowax 20 M* 15%, 160°, 2.5 m column). – IR.: 1450, 1365, 1155, 1295, 1100. – ^{1}H-NMR.: 0.77 (*d*, J = 6.5, 3 H); 1.40 (*s*, 3 H); 1.43 (*s*, 3 H); 1.20–1.50 (*m*, 2 H); 1.50–1.65 (*m*, 1 H); 1.70–1.80 (*m*, 2 H); 1.83 (*m*, 2 H); 2.40 (*m*, 1 H); 3.27 (pseudo *d*, J ~ 5, 1 H). – MS.: see *Figure 3*.

5. Cyclization of 1-*p*-menthene-8-thiol (*B*) under protic conditions (→ 1,8-epithio-*p*-menthane (7)). – A solution of **B** (0.100 g, 0.59 mmol) and *p*-toluenesulfonic acid (0.050 g) in anhydrous toluene (10 ml) was stirred for 1 h at 70° under N_2. The mixture taken up in ether was washed with 5% KOH-solution (3×) and water (2×). Usual workup gave 0.094 g of crude **7** [12] (97% pure according to capillary GC.), which was purified by semi-prep. GC. (*Carbowax 20 M* 15%, 150°, 2.5 m column). – IR.: 1450, 1070, 1220, 1350, 1140, 1190. – ^{1}H-NMR.: 1.10 (*s*, 3 H); 1.37 (*s*, 6 H); 1.40–1.65 (*m*, 5 H); 1.77 (*m*, 2 H); 2.04 (*m*, 2 H). – MS.: 170 (87, M^+, $C_{10}H_{18}S$), 155 (100), 136 (32), 121 (53), 97 (42), 95 (41), 87 (26), 81 (22), 41 (39).

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