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Short Communication

A New Compound, (4*R*,6*R*)-(+)-6,8-Oxidomenth-1-en-9-ol Produced by Microbial Conversion of (−)-*cis*-Carveol

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In the previous paper,[1] (−)-carvone was shown to be converted to (−)-*cis*-carveol or (−)-*trans*-carveol as one of the main metabolic products by some species such as strains of *Streptomyces*, A-5-1, and *Nocardia*, 1-3-11. Further, carveol is known to be converted to carvone[1～3] or 1-*p*-menthene-6,9-diol[2] by microorganisms. However, the microbial conversion of (−)-*cis*-carveol has not yet been studied in detail.

In this paper, we report on the conversion of (−)-*cis*-carveol to a new bicyclic monoterpene oxide (**1**) by a strain SY-2-1, which was isolated from soil and identified to be *Streptomyces bottropensis*.

S. bottropensis, SY-2-1, was statically cultivated at 30°C for three days in 50 ml of a medium containing 1% glucose, 0.5% meat extract, 0.5% polypepton and 0.3% NaCl in distilled water (pH 7.5). After full growth of the microorganisms, (−)-*cis*-carveol (18.4 mg per 50 ml of the medium) was added into the medium and the microorganisms were further cultivated for ten days under the same conditions as described above. One ml aliquots of the cultured broth were extracted with ether every 24 hr. The ether extract was analyzed by gas liquid chromatography (GLC): Shimadzu GC-4C; column, 10% PEG-20M coated on Celite 545, 3 m × 3 mm i.d.; column temperature, 160°C or 160°C to 200°C (4°C/min); carrier gas (N_2) flow rate, 40 ml/min. The ratios of the compositions were calculated on the basis of the peak area of (−)-*cis*-carveol, the starting material, and the products. The time course for the conversion of (−)-*cis*-carveol is shown in Fig. 1. After ten days, (−)-*cis*-carveol was converted to product **1**, the main product (85%), and to other products such as **2** (7%), **3** (0.7%) and **4** (5%). Product **1** was separated and purified by column chromatography on silicic acid and preparative GLC on 10% PEG-20M -Celite 545 (3 m × 5 mm i.d.) at 180°C under a nitrogen flow (80 ml/min). Product **2** was obtained in small amounts from the cultured broth. However, products **3** and **4** could not be isolated.

Product **1**, a colorless oil, $[\alpha]_D^{26}$ +6.8° (c = 0.402, $CHCl_3$), had no characteristic odor. The IR spectrum of **1** showed absorptions due

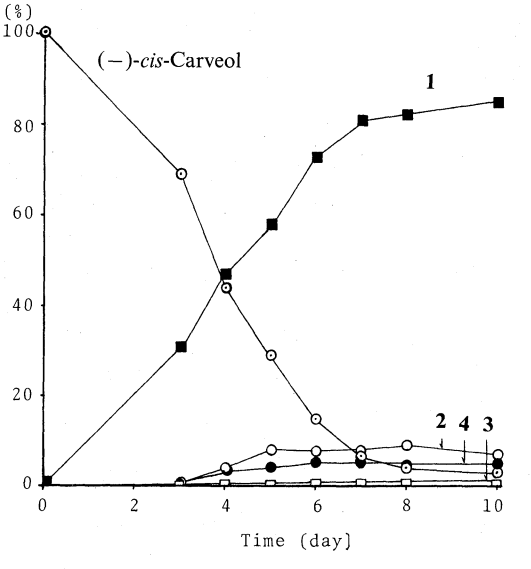


FIG. 1. Time Course for the Conversion of (−)-*cis*-Carveol by *S. bottropensis*, SY-2-1.

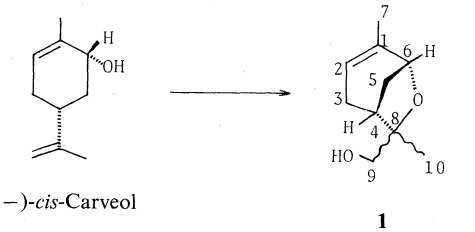
to a hydroxyl group at 3420 cm^{-1} and olefin at 1640 cm^{-1}. The IR spectrum differed from that of (−)-*cis*-carveol, the starting material, in terms of the lack of absorption due to the isopropenyl group at 880 cm^{-1}. The molecular formula of **1** was determined to be $C_{10}H_{16}O_2$ from high resolution FI-MS spectrum, 168.1139 (M^+). The ^{1}H-NMR spectrum (JEOL JNM-FX 200 FT, 200 MHz) indicated the presence of a methyl group on a tertiary carbon (δ 1.236, 3H, s, H-10), a methyl group on a trisubstituted double bond (δ 1.690 ~ 1.718, 3H, H-7), a trisubstituted double bond adjacent to methylene (δ 5.232, 1H, broad s, H-2), a methylene carrying a hydroxyl group (δ 3.566 and 3.712, 1H each, d, J=11.4 Hz, H-9), and a methine between a double bond and an ethereal oxygen (δ 4.053, 1H, broad d, band width=12 Hz, H-6 cf. in (−)-*cis*-carveol, band width=24 Hz; in (−)-*trans*-carveol, band width=6 Hz). The ^{1}H-NMR spectrum of **1** differed from that of (−)-*cis*-carveol in terms of the lack of any signal due to the *exo*-methylene protons at about δ 4.65, the appearance of a pair of 1H-doublets (H-9) at δ 3.5 ~ 3.8, and the high field shift of a methyl proton signal to δ 1.236. In addition, the change of band width of the peak of H-6 suggested some conformational changes.

In the ^{1}H-NMR spectrum of the monoacetate, which was obtained by acetylation of **1** with acetic anhydride in pyridine, the carbinyl proton signals shifted to lower fields (δ 4.078 and 4.165). This result confirmed the presence of a hydroxymethyl group.

Based on the evidence mentioned above, it was concluded that product **1** was (4*R*,6*R*)-(+)-6,8-oxidomenth-1-en-9-ol, as shown in Fig. 2.

Product **2** is assumed to be a diastereomer of **1** (C_8-epimer) from the results of GLC, mass (M^+, 168) and ^{1}H-NMR spectra.

We tested the effects of compound **1** on the germination of lettuce seeds to explore an effective usage of the microbial conversion products of terpenes. Compound **1** (200 μg/ml, 2 ml), dissolved in acetone, was allowed to soak into a filter paper in a Petri dish (dia. 6 cm) and then the paper was dried. After a Tween 80 solution (100 μg/ml, 2 ml) was poured onto the dish and left overnight, 50 lettuce seeds (*Lactuca sativa* L. cv. Wayahead) were sown on the filter paper and incubated at 22°C for 24 and 48 hr in the dark. This bioassay was repeated twice under the same conditions. The germinated seeds were counted and compared with the control. Compound **1** exhibited an inhibitory effect of 97% in 24 hr and 52% in 48 hr on the germination of lettuce seeds. The inhibitory activity was comparable to *p*-menthane-3,8-diol isolated from *Eucalyptus citriodora* leaves.[4]



(−)-*cis*-Carveol **1**

FIG. 2.

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