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FUNGAL METABOLISM OF (±)-EPOXYFARNESOL AND ITS ABSOLUTE STEREOCHEMISTRY

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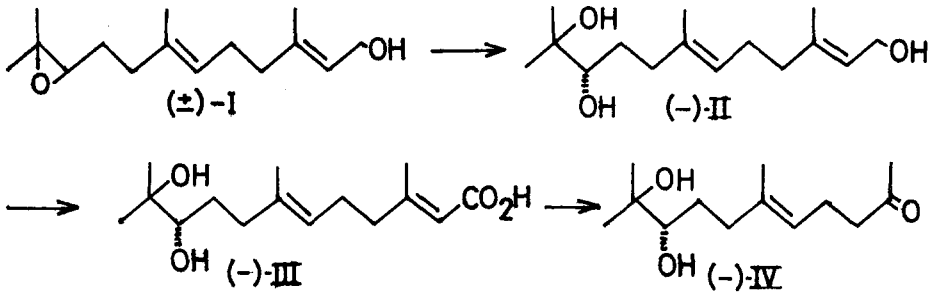
We wish to report that the metabolic transformation of (±)-epoxyfarnesol (I) by Helminthosporium sativum yielded (-)-10,11-dihydroxyfarnesol (II), (-)-10,11-dihydroxyfarnesic acid (III) and (-)-9,10-dihydroxygeranylacetone (IV), and that their absolute stereochemistry, as well as that of epoxyfarnesol have been determined. Epoxyfarnesol, though not isolated from natural sources yet, is possibly an important intermediate in the biosynthesis of certain sesquiterpenoids; e.g., its R-isomer is hypothetically considered as the biogenetic precursor of farnesiferols[1] and iresins[2]. The co-relation between an optical activity of epoxyfarnesol and its absolute stereochemistry has remained ambiguous because of the failure of usual resolution methods for the racemic mixture. We already have reported the chemical derivation of the both of enantiomers of epoxyfarnesol[3], from S-(-)-dihydroxyfarnesol obtained with the aid of fungal metabolism as is described here.



The mycelium, cultured by shaking in the malt-extract medium for 3 days, was washed and incubated with added synthetic (±)-epoxyfarnesol (0.1 % W/V) in a modified Czapeck-Dox medium[4], until the substrate disappeared after about 48 hr. The ethyl acetate extracts of both the mycelium and the filtrate were found by TLC (silica gel) to contain three metabolites, II, III, and IV, which was isolated; yields were 12.4 (II), 21.0 (III, isolated as a methyl ester), and 6.6 % (IV), respectively.

II was an oil, $C_{15}H_{28}O_3$; m/e 238 (M^+-H_2O); $[\alpha]_D$-10.2° (c, 0.75 in methanol); ν^{CHCl_3} 3400~3600 cm^{-1} (OH); $\delta^{CDCl_3}_{TMS}$ 1.10 and 1.13 (each 3H, s; two C_{11}-CH_3), 1.58 (3H, s; C_7-CH_3), 1.65 (3H, s; C_3-CH_3), 3.28 (1H,d.d, J=2.5 and 12.5 Hz; C_{10}-CH<), 4.08 (2H, d, J=7.0 Hz; C_1-CH_2-), 5.12 (1H, broad s; C_6-vinyl H), 5.33 (1H, t, J=7.0 Hz; C_2-vinyl H), and 3.03 (three OH). The structure suggested by spectral data, trans,trans-10,11-dihydroxyfarnesol, was confirmed by comparison with authentic sample derived from (±)-I by acid hydrolysis.

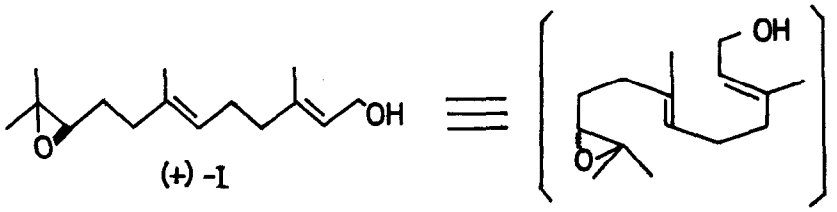
III as a methyl ester was an oil, $C_{16}H_{28}O_4$; m/e 266 (M^+-H_2O); $[\alpha]_D$-12.1° (c, 1.0 in methanol); ν^{CHCl_3} 3500 (OH) and 1700cm^{-1} (ester); $\delta^{CDCl_3}_{TMS}$ 1.15 and 1.20 (each 3H, s; two C_{11}-CH_3), 1.63 (3H, s; C_7-CH_3), 2.16 (3H, s; C_3-CH_3), 3.33 (1H, d.d, J=2.5 and 10.0 Hz; C_{10}-CH<), 5.17 (1H, broad s; C_6-vinyl H), 5.70 (1H, s; C_2-vinyl H), 3.03 (two OH), and 3.70 (3H, s; -$COOCH_3$). The structure was tentatively assigned as methyl trans,trans-10,11-dihydroxyfarnesoate, which was justified by reducing III with $LiAlH_4$ and finding the product identical with II.

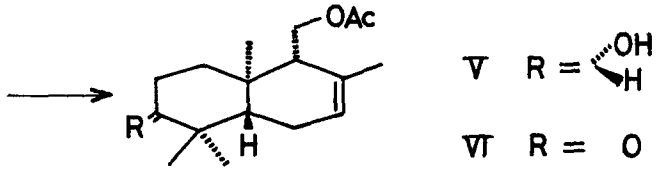
IV was an oil, $C_{13}H_{24}O_3$; m/e 210.1627 (M^+-H_2O), (calcd. 210.1620); $[\alpha]_D$-19.3° (c, 0.78 in methanol); ν^{CHCl_3} 3400~3600 (OH) and 1712 cm^{-1} (C=O); $\delta^{CDCl_3}_{TMS}$ 1.13 and 1.17 (each 3H, s; two C_{10}-CH_3), 1.60 (3H, s; C_6-CH_3), 2.10 (3H, s; -$COOCH_3$), 3.27 (1H, d.d, J=3.0 and 10.0 Hz; C_9-CH<), 5.07 (1H, t, J=6.0 Hz C_5-H), and 2.50(two OH). Its structure was deduced from the following reactions; acetylation giving a monoacetate, periodate oxidation yielding a keto-aldehyde, catalytic hydrogenation (Pt black) and $LiAlH_4$ reduction yielding a dihydro-ketol and a triol, respectively. These results suggested the identity of IV as 9,10-dihydroxygeranylacetone; it was confirmed by five-step synthesis of the racemic IV from geraniol via 9,10-epoxygeranylacetone.

Stereochemical co-relation between II and III was shown by the former's optical value, $[\alpha]_{400}$-64.8°, which is identical with that of the reduction product of III with $LiAlH_4$, $[\alpha]_{400}$-65.0°. It might be concluded that the fungus metabolized (±)-epoxyfarnesol in the way that the stereospecific hydration first occurred on an epoxide ring, then the terminal allylic carbinol was oxidized to a carboxylic acid and, lastly, the β-oxidation follows producing the ketonic compound (IV). Interestingly, the fungus produced only the optically minus compounds from the racemic substrate.

Optically active, although not completely optically pure, epoxyfarnesol could be isolated as follows. The substrate recovered from the cultured filtrate after interrupted fermentation (about 17 hr.) was found to have $[\alpha]_D$-1.4°, presumably owing to the more ready consumption of

(+)-epoxyfarnesol as compared with its (-)-enantiomer. That the C_{10}-configuration is the same for both (-)-epoxyfarnesol and (-)-II was evidenced by hydrolysis of the former to the latter under controlled condition (0.1 N $HClO_4$ in H_2O-THF)[5]; the product showed $[\alpha]_{400}$-43.3°, smaller than that of (-)-II.





The absolute stereochemistry of epoxyfarnesol was determined using its (+)-enantiomer, $[\alpha]_D$+1.8 °, which was chemically prepared from (-)-10,11-dihydroxyfarnesol[3]. The (+)-I acetate was treated with BF_3-etherate[6] (1.2 equiv. mol; 3.5 hr.) in benzene to give a mixture of products, from which a bicyclic product V[7] was isolated (4.3 %). V, an oil, was characterized from spectral data; m/e 280 (M^+-CH_3COOH); ν^{CHCl_3} 3450 (OH) and 1725 cm^{-1} (acetate); $\delta^{CDCl_3}_{TMS}$ 0.82, 0.86 and 0.98 (each 3H, s; three CH_3 at $C_{4,4}$ and C_{10}), 3.25 (1H, m; C_3-CH<), 5.50 (1H, broad s; C_7-vinyl H), 1.67 (3H, s; C_8-CH_3), 3.97~4.35 (2H, ABX; C_{11}-CH_2-). Jone's oxidation afforded a ketone VI, oil, $C_{17}H_{26}O_3$; m/e 278 (M^+-CH_3COOH); ν^{CHCl_3} 1725 and 1700 cm^{-1}. VI exhibited a positive Cotton effect in ORD, $[\phi]^{MeOH}_{315}$ +425° (c, 0.75), unequivocally showing the α-orientation of C_{10}-angular methyl group[8]. This deduced the following conclusion that C_3-OH in V has to be on α-side (on the same as the angular methyl group), considering the chair conformation of A-ring in the transition state of cyclization reaction[9], and therefore β-orientation of the epoxide ring in (+)-I is justified. The R-configuration was thus assigned to (+)-epoxyfarnesol and, therefore, the S-configuration, to the three optically minus metabolites.

Mechanism of this peculiar fungal metabolism of the racemic epoxyfarnesol, producing only the optically minus compounds, will be the subject of our forthcoming papers.

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