Derivation of *S*-(−)-, and *R*-(+)-10,11-Epoxyfarnesol from *S*-(−)-10,11-Dihydroxyfarnesol

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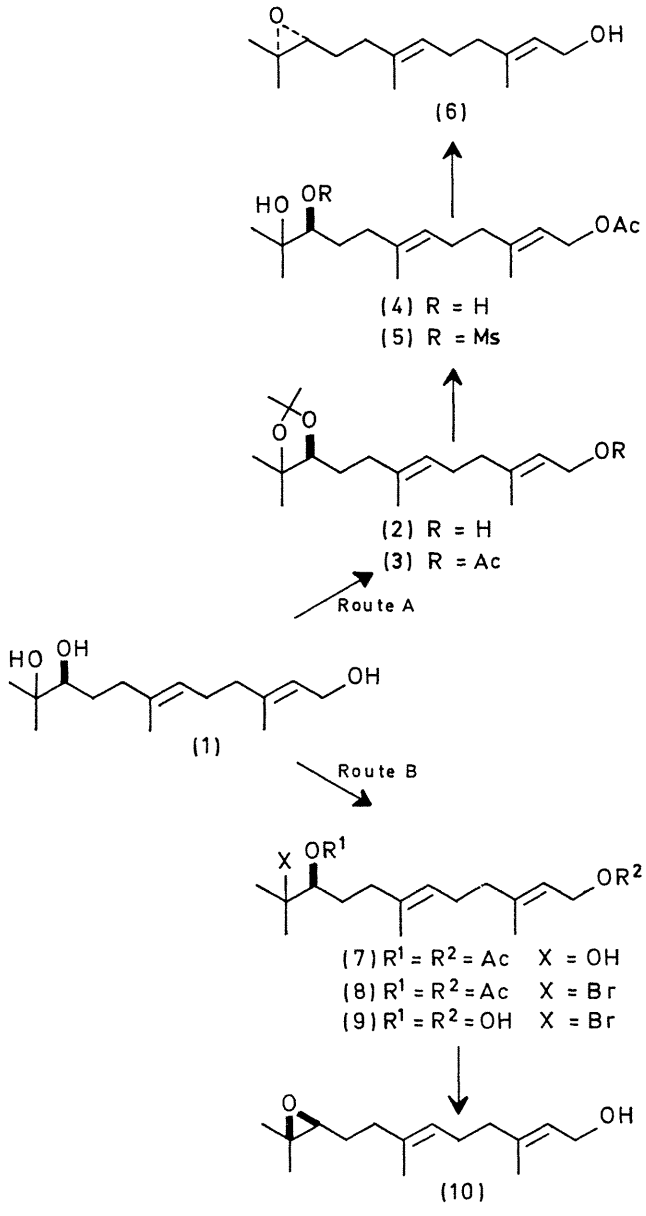
Summary Optically pure *S*-(−)- and *R*-(+)-10,11-epoxyfarnesol have been prepared from *S*-(−)-10,11-dihydroxyfarnesol obtained stereospecifically by metabolism of (±)-epoxyfarnesol by *Helminthosporium sativum*

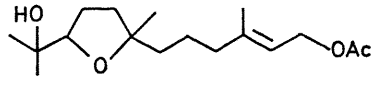
IN our investigation on the abilities of fungi to metabolize farnesol and its derivatives, we found[1] that the metabolic transformation of (±)-epoxyfarnesol by *Helminthosporium sativum* yielded (−)-10,11-dihydroxyfarnesol, (−)-10,11-dihydroxyfarnesic acid, and (−)-9,10-dihydroxygeranylacetone Owing to the more ready consumption of (+)-epoxyfarnesol as compared with its (−)-enantiomer, the latter could be recovered from the culture filtrate after interruption of the fermentation of the racemic substrate.

although not completely optically pure. That (−)-epoxyfarnesol has the same configuration about C-10 as (−)-10,11-dihydroxyfarnesol was shown by the hydrolytic conversion of the former into the latter under controlled conditions,[2] and, also, the *S*-configuration was evidenced



for both compounds by means of cyclization[3] of (−)-epoxyfarnesol into a driman-type compound by boron trifluoride–ether. These results indicate that the fungus stereospecifically hydrolyses an oxiran ring of the racemic epoxyfarnesol, producing only (−)-compounds. We report the stereospecific transformation of optically pure *S*-(−)-10,11-dihydroxyfarnesol, obtained by fungal metabolism, into *R*-(+)-epoxyfarnesol or into *S*-(−)-epoxyfarnesol, either of which is difficult to obtain from the racemic compound by the usual methods of resolution.

R-(+)-Epoxyfarnesol (6) was prepared by route A (Scheme). Treating (−)-dihydroxyfarnesol (1) with dimethoxypropane and toluene-*p*-sulphonic acid (trace) in acetone[4] afforded acetonide (2), oil, δ 1·32 and 1·41 (2 × CH_3 of acetonide), 3·63 (d.d, *J* 5·0 and 7·5 Hz, 10-CH), and 4·13 p.p.m. (d, *J* 6·5 Hz, 1-CH_2).† Upon acetylation, followed by methanolysis (toluene-*p*-sulphonic acid), (2) was converted into the glycol acetate (4), oil, δ 2·03 (s, CH_3CO_2), 3·34 (d.d, *J* 2·5 and 10·0 Hz, 10-CH), and 4·58 p.p.m. (d, *J* 7·0 Hz, 1-CH_2). Attempts to halogenate the secondary hydroxy-group on C-10 with retention of configuration was unsuccessful; *e.g.*, thionyl chloride in ether gave a cyclic sulphite, and phosphorus tribromide in ether afforded a tetrahydrofuran derivative.‡ Compound (4) was converted into a mesylate (5)[5], oil, δ 1.26 [s, 11-$(CH_3)_2$] and 3·13 p.p.m. (s, S-CH_3). The 10-CH signal was obscured by the doublet signal of 1-CH_2 (δ 4·57, *J* 7·0 Hz). Epoxide formation and subsequent hydrolysis of (5) with aqueous potassium hydroxide in pyridine gave *R*-(+)-epoxyfarnesol (6), oil, $[\alpha]_D^{25}$ + 1·81° (*c*, 1·91 in methanol); yield 38·0% from (3).



S-(−)-Epoxyfarnesol (10) was prepared by route B (Scheme). Compound (1) was acetylated to the diacetate (7), oil, δ 2·06 and 2·10 (two CH_3CO_2), 1·19 [s, 11-$(CH_3)_2$], 4·57 (d, *J* 7·0 Hz, 1-CH_2), and 4·78 p.p.m. (d.d, *J* 3·0 and 7·5 Hz, 10-CH). Compound (7) was brominated in ether with phosphorus tribromide (0·36 equiv.)[6] to afford (8), oil, no OH in i.r. spectrum, δ 1·56 p.p.m. [s, 11-$(CH_3)_2$]. Reductive deacetylation of (8) with an excess of lithium aluminium hydride in ether at −70° gave the bromo-diol (9), oil, δ 3·98 (d.d, *J* 2·5 and 10·0 Hz, 10-CH), 1·34 [s, 11-$(CH_3)_2$], and 4·16 p.p.m. (d, *J* 7·5 Hz, 1-CH_2). Epoxide formation with an excess of potassium carbonate in methanol afforded *S*-(−)-epoxyfarnesol (10), oil, $[\alpha]_D^{25}$ −1·83° (*c*, 1·70 in methanol); yield 38·8% from (7).

R-(+)- and *S*-(−)-Epoxyfarnesol thus obtained were identical with respect to i.r., n.m.r., and mass spectra, but the optical rotations were equal in magnitude but opposite in sign. These enantiomers exhibited similar but slightly differing juvenile hormone activities, which will be reported elsewhere. Although epoxyfarnesol has not been isolated from natural sources, it is hypothetically considered to play an important role in sesquiterpenoid biogenesis, *e.g.*, *R*-(+)-epoxyfarnesol as a biogenetic precursor of iresins[7] and

† All n.m.r. spectra were measured at 100 MHz in $CDCl_3$ solution, and chemical shifts quoted are relative to $SiMe_4$.

‡ Its structure was determined as compound (11).

farnesiferols.[8] The availability of these enantiomers may clarify some stereochemical problems in the natural product field, especially that of juvenile hormones[9] and 2,3-epoxysqualene[10] which is a precursor of steroid biosynthesis.

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