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# ASYMMETRIC SYNTHESIS OF CHIRAL GERANIOL-1-d AND RELATED TERPENIC ALCOHOLS[1]

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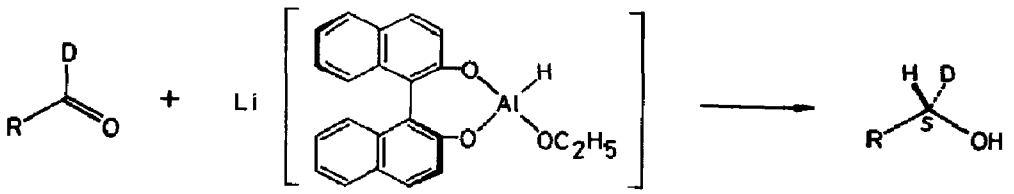
Summary: A convenient procedure for the synthesis of deuterium labeled terpenic alcohols of high optical purity is described.

Isotopically labeled chiral terpenic alcohols serve as key substances in mechanistic studies of the biological transformations.[2] To our surprise, however, there exist no literature reports which describe relationship between the absolute configuration and optical properties of chiral geraniol-1-d, one of the most fundamental compounds.[3] Here we report a convenient synthesis of optically active geraniol-1-d and its stereochemical assignment.

The synthesis was accomplished by the asymmetric reduction of geranial-1-d with a chiral complex aluminum hydride reagent developed in our laboratories.[1,4] The reducing agent formulated as (S)-I (empirical formula) was prepared in situ by mixing lithium aluminum hydride, ethanol, and (S)-(-)-2,2'-dihydroxy-1,1'-binaphthyl [(S)-II][5] (1:1:1 mol ratio) in THF at room temperature. When geranial-1-d[6] was treated with 3 equiv of (S)-I in THF at -100 °C for 2 h, geraniol-1-d was obtained in 91% isolated yield after usual workup and removal of the auxiliary ligand, (S)-II, by recrystallization from hexane. Preparative gas chromatographic purification (10% FFAP column, 170 °C) afforded analytically pure sample of (S)-(+)-geraniol-1-d, $[\alpha]_D^{24}$ +1.38° (c 1.70, cyclopentane).[7] The absolute configuration of the dominant enantiomer was unumbiguously established by comparison with the authentic S alcohol with $[\alpha]_D^{24}$ +1.51° (c 1.06, cyclopentane) obtained by reduction of the deuterio aldehyde with yeast alcohol dehydrogenase and NADH (pH 7.4 phosphate buffer, 20 °C, 60 h).[8] Magnitude of the




(S)-I

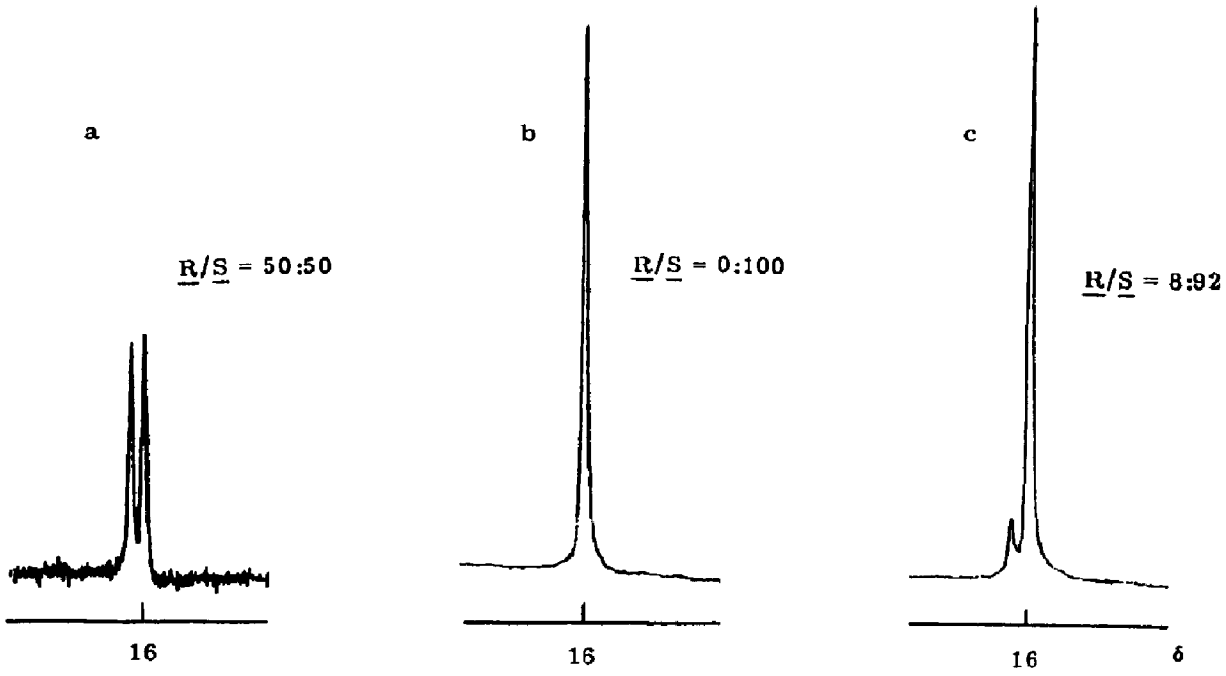
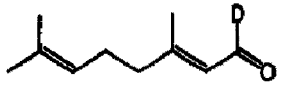
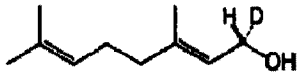
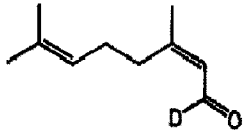
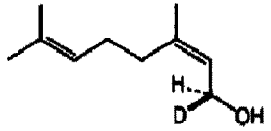
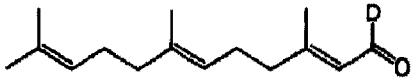
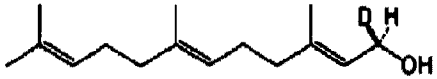
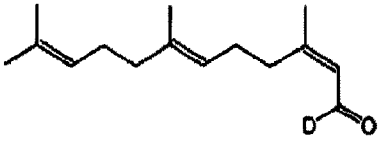
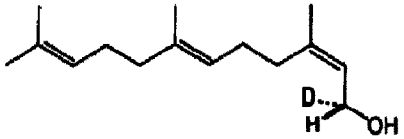



Figure 1. NMR signals due to the C-1 proton(s) of geraniol-1-d with irradiation at the C-2 proton (100 MHz, $CDCl_3$ solution containing 0.4 equiv of $Eu(hfbc)_3$. a: racemate. b: enzymatic reduction product. c: asymmetric reduction product.

optical rotation of the product indicated the optical purity of 91%. The value of 84% ee was suggested by NMR analysis by combining use of a chiral lanthanide shift reagent, tris(3-hept fluorobutyryl-(+)-camphorato)europium(III) [$Eu(hfbc)_3$], and a decoupling technique (Figure 1 Although the optical purity of the synthetic alcohol was lower than that of the enzymatic reduction product (100% pure within the limits of NMR detection), this operationally simple method would be even more convenient for making the chiral alcohol in a large quantity. Bot enantiomers can be prepared by choosing handedness of the chiral ligand II.

Similarly this asymmetric reduction was applied to the synthesis of optically active deuterated nerol and farnesols. The results are given in Table I. The absolute configuratio of these products were deduced from the sign of optical rotation and NMR behavior of the C-1 protons in the presence of $Eu(hfbc)_3$.[9] These assignments are also consistent with empirica correlation of binaphthol chirality with product configuration observed in the reduction of benzaldehyde-α-d[4] and some open-chain alkyl alkenyl ketones.[1]

Table I. Asymmetric Synthesis of Chiral Primary Terpene Alcohols[a]

| aldehyde | reducing agent | chemical yield, %[b] | product[c] | $[\alpha]_D^{24}$, degree (c)[d] | optical purity, % ee[e] (configuration) |
|---|---|---|---|---|---|
|  | (S)-I | 91 |  | +1.38 (1.70) | 91,[f] 84 (S) |
|  | (S)-I | 90 |  | +1.21 (1.41) | 72 (S) |
|  | (R)-I | 91 |  | -0.80 (4.0) | 88 (R) |
|  | (R)-I | 93 |  | -0.78 (2.5) | 82 (R) |

[a] Reduction of the deuterio aldehyde was carried out with 3 equiv of I at -100 °C for 2 h. [b] Isolated yield of the product of >98% purity. [c] Deuterium content was >99% (mass spectral analysis). [d] Determined for the GLC-purified sample in cyclopentane using a JASCO DIP-4 polarimeter with digital read-out with a 1-dm, center-filled water-jacketed cell(readings were ±0.002°). [e] Determined by NMR in the presence of $Eu(hfbc)_3$. [f] Determined on the basis of optical rotation.

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