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Conversion of (+)-(*R*)-Limonene into (+)-(1*S*,4*R*)-*p*-Mentha-2,8-dien-1-ol, an Intermediate in the Synthesis of Tetrahydrocannabinoids

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Abstract

(+)-(1*S*,4*R*)-*p*-Mentha-2,8-dien-1-ol (3), an important intermediate in the synthesis of (−)-Δ^9-*trans*-6a,10a-tetrahydrocannabinol (1) and other tetrahydrocannabinoids, is conveniently prepared from (+)-(*R*)-limonene (5) by rearrangement of its (1*S*,2*R*)-1,2-epoxide (7). Similar rearrangement of the diastereoisomeric (1*R*,2*S*)-1,2-epoxide (6) yields (+)-(2*S*,4*R*)-*p*-mentha-1(7),8-dien-2-ol (12), a major constituent of gingergrass oil.

Introduction

Current syntheses of (−)-Δ^9-*trans*-6a,10a-tetrahydrocannabinol (Δ^9-THC) (1), the principal psychoactive component of *Cannabis sativa*,[1] and of various metabolites[1,2] and potentially therapeutic analogues[3] of this compound, involve the condensation of a monoterpenoid with olivetol or other substituted resorcinols. Reaction of a Lewis acid catalyst with the appropriate functionality in the terpenoid generates carbocationic sites which alkylate both carbon and oxygen of the aromatic system to close the pyran ring. The synthesis of 'natural' (6a*R*,10a*R*)-Δ^9-THC (1) itself requires a cyclic monoterpenoid with suitable chirality at the isopropyl junction to establish the (*R*)-chirality at C6a in the product. The reaction is very sensitive to the specific Lewis acid and also the conditions used. A mixture of the (6a*R*,10a*R*)-*trans*- and (6a*R*,10a*S*)-*cis*-tetrahydrocannabinol frequently results, together with by-products, and double bond migration to the thermodynamically more stable Δ^8-position may also occur. Chiral cyclic terpenoids which have been used include (+)-(1*R*,4*R*)- or (+)-(1*S*,4*R*)-*p*-mentha-2,8-dien-1-ol (2) and (3),[4] (+)-*trans*-2,3-epoxycarane,[5] (−)-*cis*- or (−)-*trans*-verbenol,[6] and (+)-(1*R*,4*R*)-*p*-menth-2-ene-1,8-

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[2] Fahrenholtz, K. E., *J. Org. Chem.*, 1972, **37**, 2204; Pitt, C. G., Seltzman, H. H., Sayed, Y., Twine, C. E., and Williams, D. L., *J. Org. Chem.*, 1979, **44**, 677.
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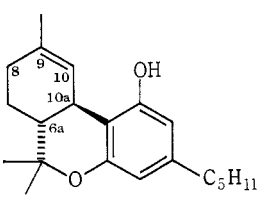
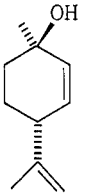
diol (4).[7]* Of these, the monohydric alcohols (2) and (3) and the diol (4) appear[4,7] to offer advantages in terms of fewer by-products in the preparation of Δ^9-THC (1).



(1)



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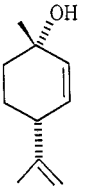

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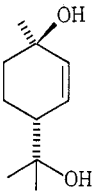

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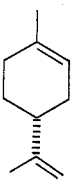

(5)

Previous preparative syntheses[8] of (+)-(1*R*,4*R*)-*p*-mentha-2,8-dien-1-ol (2) and (+)-(1*R*,4*R*)-*p*-menth-2-ene-1,8-diol (4) have involved acid-catalysed rearrangement of (+)-*trans*-2,3-epoxycarane, itself derived from natural (+)-3-carene through isomerization to (+)-2-carene. The more readily available natural monoterpene (+)-(*R*)-limonene (5) on photo-oxygenation and reduction of the resulting hydroperoxides yields the (+)-(1*R*,4*R*) and (+)-(1*S*,4*R*) alcohols (2) and (3).[9] However, their isolation from the mixture of six isomeric alcohols which is produced is difficult. We describe here a more convenient conversion of (+)-(*R*)-limonene (5) into (+)-(1*S*,4*R*)-*p*-mentha-2,8-dien-1-ol (3).

Synthesis of (+)-(1*S*,4*R*)-*p*-Mentha-2,8-dien-1-ol

(+)-(*R*)-Limonene (5) is oxidized by perbenzoic acid[10] or *m*-chloroperbenzoic acid[11] in high yield to 'limonene oxide', a 1:1 mixture of the (1*R*,2*S*,4*R*)- and (1*S*,2*R*,4*R*)-1,2-epoxy-*p*-menth-8-enes (6) and (7). Molybdenum catalysis of the epoxidation with 1,1-dimethylpropyl hydroperoxide promotes 1*S*,2*R* attack relative to 1*R*,2*S* in the ratio 7:3.[12] The (+)-(1*S*,2*R*)-epoxide (7) is the required isomer, but its separation from the (+)-(1*R*,2*S*)-epoxide (6) is difficult[13] and unnecessary.

Isomerization of these epoxides with strong bases,[14] dialkylaluminium amides,[15] dialkylboryl trifluoromethanesulfonates,[16] or trimethylsilyl trifluoromethanesulfonate[17] would in each case be expected to proceed through preferential proton loss from the adjacent methyl group, rather than from the C3 methylene, to give the undesired *p*-mentha-1(7),8-dien-2-ols [e.g. (12) from (6)]. However, treatment of

* These authors do not state the relative stereochemistry of the diol used; they depict the (1*S*,4*R*)-diol, but refer to the preparation of the (1*R*,4*R*)-diol.

[7] Handrick, G. R., Uliss, D. B., Dalzell, H. C., and Razdan, R. K., *Tetrahedron Lett.*, 1979, 681.
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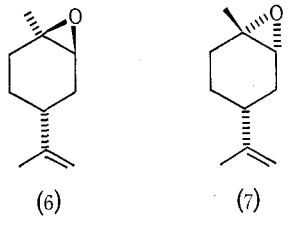
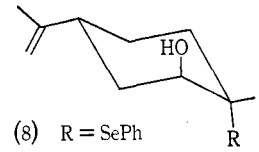
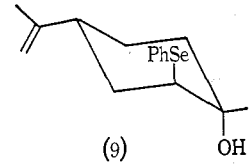
the mixture of epoxides (6) and (7) with sodium phenylselenide[18] effects *trans*-diaxial opening of each epoxide ring with complete regiospecificity. Thus the (1*R*,2*S*)-epoxide (6) affords the tertiary selenide (8), the (1*S*,2*R*)-epoxide (7) the secondary selenide (9). The ^{1}H n.m.r. spectrum ($CDCl_3$) of the mixture of selenides (8) and (9) shows multiplets for the C2 protons at δ 3·89 and 3·42 with widths at half height of 7·5 and 9 Hz respectively; this reflects the axial orientation of the 2-substituent in each case.[19] This mixture of selenides (8) and (9) is oxidized directly with hydrogen peroxide to the corresponding selenoxides (10) and (11). The tertiary selenoxide (10) undergoes regiospecific elimination of phenylselenic acid at room temperature to generate the exocyclic methylene function of (+)-(2*S*,4*R*)-*p*-mentha-1(7),8-dien-2-ol (12). This monoterpene alcohol (12), which occurs naturally as a major constituent of gingergrass oil, is obtained in 79% overall yield from (+)-(1*R*,2*S*,4*R*)-1,2-epoxy-*p*-menth-8-ene (6). Its ^{1}H n.m.r. spectrum confirms the expected axial orientation of the hydroxyl group.



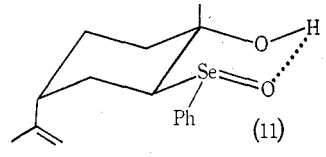
(6) (7)



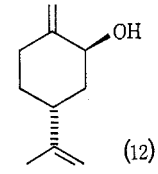
(8) R = SePh
(10) R = Se(O)Ph



(9)



(11)



(12)

In contrast to the tertiary selenoxide (10), the secondary selenoxide (11) is stable at room temperature, and is readily isolated from the oxidation mixture in 84% overall yield from (+)-(1*S*,2*R*,4*R*)-1,2-epoxy-*p*-menth-8-ene (7). Unlike the parent selenide (9), the selenoxide (11) assumes a conformation in which the selenium substituent is equatorial and hydrogen-bonded to the neighbouring hydroxyl group. The resulting axial proton at C2 now shows a discrete 9 Hz coupling to the vicinal axial proton at C3.[19] Thermolysis of this secondary selenoxide (11) in ethanol-free chloroform[20] affords the required terpenoid synthon (+)-(1*S*,4*R*)-*p*-mentha-2,8-dien-1-ol (3) in 53% yield.

Experimental

Infrared spectra were recorded on a Perkin–Elmer 257 spectrophotometer. ^{1}H n.m.r. data for solutions with tetramethylsilane as internal reference were obtained on Jeol Minimar MH-100 or Varian HA-100 spectrometers. Unresolved proton signals falling within broad envelopes are not listed. Mass spectra of pure compounds were run on a GEC–AEI MS902 instrument operating at 70 eV ionizing voltage. Optical rotations were measured in a Bendix-NPL automatic polarimeter type 143C.

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(+)-(2S,4R)-p-*Mentha-1(7),8-dien-2-ol* (*12*)

Sodium borohydride (187 mg, 4·92 mmol) was added portionwise, in a stream of argon, to a stirred suspension of diphenyl diselenide (700 mg, 2·24 mM) in dry ethanol (11 ml) under argon, until the yellow solution became colourless.[18] A 1:1 mixture[11] of (+)-(1*S*,2*R*,4*R*)- and (+)-(1*R*,2*S*,-4*R*)-1,2-epoxy-*p*-menth-8-enes (7) and (6) (608 mg, 4·0 mmol) was added and the resulting solution was heated at reflux for 2 h. After cooling, tetrahydrofuran (10 ml) was added, followed by dropwise addition of 30% hydrogen peroxide during 0·5 h, the temperature being maintained below 20° by ice-cooling. The solution was stirred for 5 h at 20°, then diluted with water. The organic layer was separated, combined with a dichloromethane extract of the aqueous phase, and washed successively with 10% aqueous sodium carbonate and saturated brine. Evaporation of the dried extract gave a semi-solid from which the alcohol (12) was extracted with cold light petroleum (b.p. 40–60°). Distillation gave pure (+)-(2*S*,4*R*)-*p*-mentha-1(7),8-dien-2-ol (12) (240 mg, 79%), b.p. 75°/1 mm (Kugelrohr), $[\alpha]_D^{20}$ +87·7° (*c*, 1·0 in $CHCl_3$) (lit.[9] b.p. 85°/5 mm, $[\alpha]_D^{22}$ +92·4° (liquid)). *m/z* 152 (M, 9%), 137 (11), 134 (99), 119 (64), 109 (100), 95 (28), 93 (38), 91 (62), 79 (42), 69 (46), 67 (47), 55 (52), 53 (31), 41 (86). ^{1}H n.m.r. δ ($CDCl_3$) 1·75, s, CH_3C=; 4·38, t, *J* 3 Hz, CHOH; 4·74, br s, CH_2=CMe; 4·78 and 4·87, m, CH_2=C.

(*1*S,2S,*4*R)-*2-Phenylseleninyl*-p-*menth-8-en-1-ol* (*11*)

The selenoxide (11) (549 mg, 84%) remained after the crude product obtained from oxidation of the selenides (8) and (9) had been completely extracted with petroleum. Recrystallization from ethanol at −20° gave the *selenoxide* (11) as needles, m.p. 115° (Found: C, 59·0; H, 6·6. $C_{16}H_{22}O_2Se$ requires C, 59·1; H, 6·8). ν_{max} ($CHCl_3$) 3660 (OH), 3590 (OH), 3280 br (OH), 1640, 1575 cm^{-1}. ^{1}H n.m.r. δ (CD_3OD) 1·46, br s, CH_3C=; 1·48, s, CH_3COH; 2·45, m, $W_{h/2}$ 12 Hz, CHC=; 3·08, dd, *J* 6 and 9 Hz, CHSe(O)Ph; 4·69, m, CH_2=; 7·5–7·8, m, ArH.

(+)-(*1*S,*4*R)-p-*Mentha-2,8-dien-1-ol* (*3*)

The selenoxide (11) (326 mg, 1 mmol) was heated under nitrogen for 0·5 h in refluxing chloroform (5 ml, previously percolated through basic alumina (activity I)). After cooling, the solvent was evaporated under reduced pressure, and the alcohol (3) was extracted from the residue with ether. Concentration of the extract followed by medium pressure column chromatography[21] on silica gel (30 g, 230–400 mesh) eluting with ether–light petroleum (b.p. 40–60°) (2:3) yielded pure (+)-(1*S*,4*R*)-*p*-mentha-2,8-dien-1-ol (3) (80 mg, 53%) as a colourless oil, $[\alpha]_D^{22}$ +63·6° (*c*, 3·9 in $CHCl_3$) (lit. $[\alpha]_D^{21}$ +67·3° (*c*, 1–5 in $CHCl_3$),[9] $[\alpha]_D^{20}$ +66°[22]), having spectral properties (m.s., i.r., and p.m.r.) in agreement with those reported.[9,22] If desired, the selenium reagent can be regenerated by reduction to diphenyl diselenide of the oxyacids formed from the elimination.[23]

Acknowledgments

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