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CONVERSION OF HUMULENE TO ZERUMBONE

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Humulene was first converted to zerumbone through a sequence of chemical reactions.

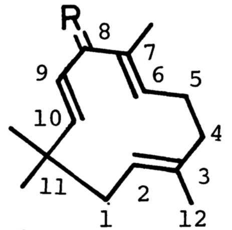
Zerumbone (1)1) is a major constitutent of essential oil of Zingiber zerumbet Smith and recently became a subject of our interest because of its biological activities as a plant growth regulator2) and as a selective cytotoxin against tumor cells3). We are currently interested in the chemistry of humulene4) and attempted a conversion of humulene to zerumbone which are related to each other through an oxidation and reduction system. Moreover, humulene is one of the popular constituents occurring in plant kingdom whereas zerumbone is found only in limited species and hence this conversion will make this potent natural product accessible easily. The methylene group at C-8 of humulene is doubly allylic and seems to be very susceptible to oxidation at first glance. However, Sukh Dev et al,1b) during the structure elucidation of zerumbone attempted the oxidation of humulene by various oxidising agents including enzymatic reactions but always resulted in the formation of humulene oxides. In addition to the work of other groups5) and careful studies at our hands to cause the direct oxidation of humulene at C-8 position proved unsuccessful. But we could achieve this oxidation by indirect method through a series of chemical reactions and our results are presented in this report.

Humulene 6,7-epoxide (3),6) was treated with LDA (3 eq) in THF at rt for 2 hr to give an allylic alcohol (4, mp 70-71°, 70%)7) whose NMR was quite similar to that of (5)1b). Geometry of the newly formed double bond was determined8) as follows. Unusually high field shift of 12-Me group (δ 1.24) indicated that the Me-group must be in the shielding region of opposite side double bond ($\Delta^{7,8}$, see 4a) and solvent shifts9) [$\delta_{CDCl_3} - \delta_{Pyr,ppm}$, −0.09 (8-H), −0.17 (9-H) and −0.18 (C_7-Me)] revealed that 9-H is nearer than 8-H to the C_6-OH group and the dihedral angle HO-C(6)—C(7)—Me is about 60°, these observations coincide well with the stereochemistry as depicted in (4a). Oxidation of (4) with t-BuOOH-VO(AcAc)$_2$10) in CH_2Cl_2 afforded a crystalline epoxyalcohol (6a, mp 68°, 90%)7) with a little amount of a stereoisomeric epoxide (6b, mp 107°, 10%),7) both of which were oxidised quantitatively to the same epoxyketone (7, mp 84°)7,11) under Collins oxidation conditions. The epoxyketone (7) was heated with hydrazine hydrate (2 eq) in n-BuOH for 1.5 hr at 140° and then the temperature was raised to 160° for 0.5 hr after the addition of a few pallets of KOH and finally the mixture was refluxed at 200-210°

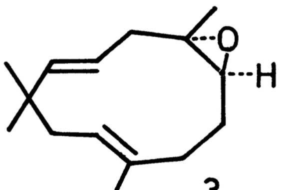
for 1 hr to furnish zerumbol (8, 15%). Zerumbol on oxidation with active MnO_2 gave zerumbone (80%) whose IR and NMR spectra were superimposable with those of an authentic sample.

Difficulty of direct oxidation of humulene to zerumbone together with the present conversion implies that the biosynthetic oxidation of humulene to zerumbone might be occurring through humulene 6,7-epoxide which is often found in plants and is easily accessible by aerial oxidation of humulene.

References and notes 1)a) S.Dev, Tetrahedron 8, 171 (1960) b) N.P.Damodaran, S.Dev, Tetrahedon Lett., 1965, 1977. 2) P.S.Kalsi, O.S.Singh, B.R.Chhabra, Phytochem., 17, 576 (1978); Experientia, 35, 481 (1979). 3) H.W.P.Mathes, B.Luu, G.Ourisson, Phytochem., 19, 2643 (1980). 4) H.Shirahama, E.Ōsawa, T.Matsumoto, J.Am.Chem.Soc.,102, 3208 (1980). H.Shirahama, K.Hayano, Y. Kanemoto, S.Misumi, T.Ohtsuka, N.Hashiba, A.Furusaki, S.Murata, R.Noyori, T.Matsumoto, Tetrahedron Lett., 21, 4835 (1980) and references cited threin. 5) J.A.Picket, F.R.Sharpe, T.L.Peppord, Chem. Ind. (London) 1977, 30; T.Shimazu, N.Hashimoto, Y.Kuroiwa, Am.Soc. Brewing Chem. Proc., 33, 7 (1974); P.Sandra, M.Verzele, Proc.Europ.Brewery Conv., 1975, 109. 6) N.P.Damodaran, S.Dev, Tetrahedron 24, 4123 (1968). 7) For all new compounds elemental analysis and spectral data coincided with the formulae depicted in the figure. NMR spectra were measured in $CDCl_3$ and IR spectra were observed in nujol. NMR (δ_{ppm}, J in Hz) and IR (cm^{-1}) are listed as; 4: IR 3600-3100; NMR 1.06 and 1.12 (each 3H, s), 1.24 and 1.74 (each 3H, bs), 4.7 (1H, dd, J=5 and 3), 5.06 (1H, d, J=15), 5.22 (1H, bt, J=8.5), 5.67 (1H, d, J=8.7), and 5.98 (1H, dd, J=8.7 and 15). 6a: IR 3500, 1660, 1370, 1180, 1060, 956, 870, 840 and 770; NMR 1.04, 1.12 and 1.34 (each 3H, s), 1.45 (3H, bs), 3.35 (1H, d, J=6), 3.43 (1H, t, J=4), 5.06 (1H, dd, J=6 and 16) and 5.42 (1H, d, J=16). 6b: IR 3500, 1380, 1365, 1230, 1075, 1030, 970, 880 and 840; NMR 1.05, 1.10, 1.34 (each 3H, s), 1.58 (3H, bs), 3.36 (1H, s), 3.9(1H, dd, J=2 and 6), 5.05 (1H, dd, J=12 and 6) and 5.38 (2H, s). 7: IR 1720, 1390, 1370, 1230, 980, 860, 825 and 770; NMR 0.9, 1.10 and 1.60 (each 3H, s), 1.5 (3H, bs), 3.44 (1H, d, J=6), 4.92 (1H, dd, J=6 and 16 1H hidden under this $>C=C<^{H}$) and 5.48 (1H, d, J=16). 8) In the literature, ref. 1b, the formula 5 was simply figured without any explanation of geometry of 7-8 double bond. 9) P.V.Demarco, E.Farkas, P.Doddrell, B.L.Mylari, E.Wenkert, J.Am.Chem.Soc, 90, 5480 (1968). 10) K.B.Sharpless, R.C.Michaelson, J.Am.Chem.Soc., 95, 6136 (1973); K.B. Sharpless, T.R.Verhaeven, Aldrichimica Acta, 12, 63 (1979). 11) The epoxy-alcohol 6b gave an antipode of 7 on Collins oxidation.



1 R=O
2 R=H
8 R=<OH H



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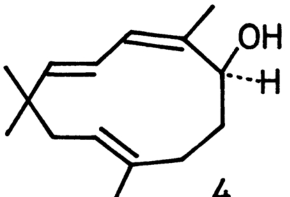

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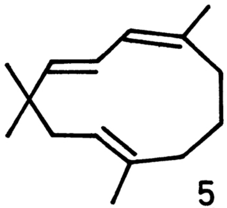

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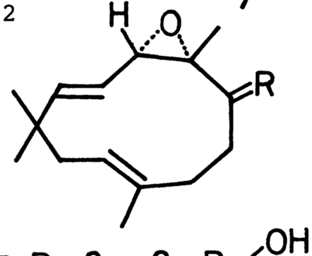
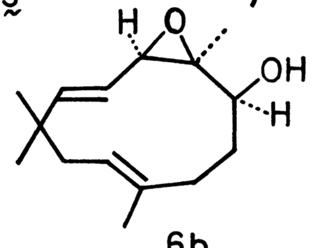
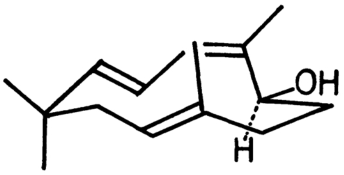


7 R=0 6a R=<OH H



6b



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