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SYNTHESIS AND STEREOCHEMISTRY OF 3,6-EPOXY-5-HYDROXY-5,6-DIHYDRO-β-IONOL, A NOVEL FLAVOR CONSTITUENT OF SUIFU TABACCO

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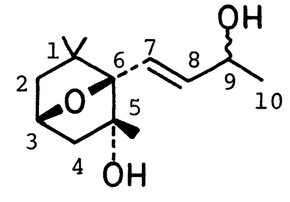
(±)-3,6-Epoxy-5-hydroxy-5,6-dihydro-β-ionol was synthesized from β-ionone *via* 3,6-dihydroxy-α-ionone and its structure including the relative configurations was established as (±)-2β,5β-epoxy-2α-[3α-hydroxy-1(*E*)-butenyl]-1β,3,3-trimethylcyclohexan-1α-ol by X-ray analysis.

A novel flavor substance, (-)-3,6-epoxy-5-hydroxy-5,6-dihydro-β-ionol, was initially found in the volatile fraction of air-cured Suifu tabacco, a Japanese domestic one.¹⁾ Recently Enzell *et al*. have also isolated the compound **1** from sun-cured Greek tabacco and established the relative configurations at C-3, C-5, and C-6 as **1**.²⁾ The configuration at the remaining asymmetric center, C-9, is unsettled. In relation to our own interest in confirming the structure **1**, especially the unknown configuration at C-9, and evaluating the flavor properties of this material, its synthesis has been undertaken. Herein we wish to report the stereoselective synthesis and the stereochemistry of **1**.



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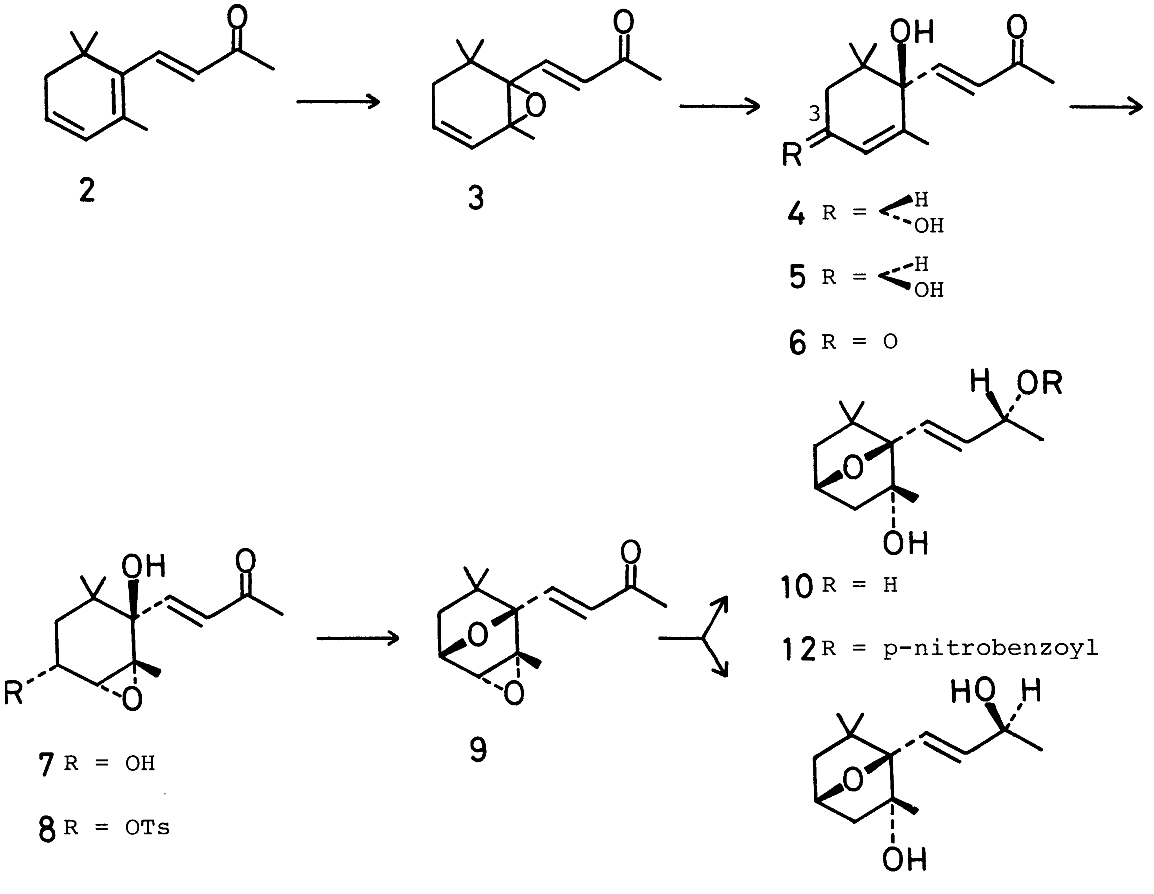
The epoxy ketone **3** was prepared in three steps from β-ionone *via* dehydroionone **2**.3) Hydrolysis of **3**4) in aqueous dioxane at 30 °C afforded the trans- **4** and cis-diols **5** in a ratio 85:15. The minor isomer was assigned to the cis-diol **5**5) by a comparison with the authentic sample obtained by photosensitized oxygenation6) of dehydroionone 2, followed by treatment of the resulting peroxide 13 with thiourea.7) The *trans*- 4 and *cis*-diols 5 were oxidized respectively with Jones reagent to afford the same bisenone 6.5) This defines the relative configurations at C-3 of the diols as 4 and 5.

The *trans*-diol 4 was epoxidized with *m*-chloroperbenzoic acid in dichloromethane at 25 °C to afford the crystalline diol epoxide 7 in 70% yield. Treatment of 7 with *p*-toluenesulfonyl chloride in dry pyridine at 0 °C yielded the tosylate 8 which, upon treatment with sodium hydride in tetrahydrofuran at 25 °C, was converted into the epoxy ether 9 in 97% yield. The ^{1}H-NMR signals of the *gem*-dimethyl protons appear at 0.81 and 1.31 ppm in 9. The lower field signal was assigned to the *endo*-methyl protons and the difference in the chemical shifts of the *gem*-dimethyl protons is ascribed to a deshielding effect of the *endo*-epoxide ring.8) Reduction of 9 with lithium aluminium hydride in tetrahydrofuran under reflux9) afforded the diol ethers 10 and 11 in 16 and 18% yields respectively. The diol ether 10 was proved to be identical with the natural 3,6-epoxy-5-hydroxy-5,6-dihydro-β-ionol by TLC, IR, ^{1}H and ^{13}C-NMR, and mass spectral comparison.

In order to establish the relative configuration at C-9 of 10, the diol ether 10 was converted into the crystalline *p*-nitrobenzoate 12 which was subjected to a single-crystal X-ray diffraction analysis. Crystal data are as follows: Triclinic (from hexane), space group $P\bar{1}$; a = 11.618(1), b = 12.373(2), c = 7.934(1) Å; α = 108.43(1), β = 108.89(1), γ = 95.95(1)°; U = 996.51 $Å^3$; Z = 2, D_x = 1.252 g cm^{-3}. A total 2333 independent non-zero reflections are measured on a Rigakudenki four circle diffractometer using graphite-monochromated Cu Kα radiation. The structure was solved by the direct method10) using program MULTAN 78 and was refined by the block diagonal least-squares method assuming the anisotropic thermal vibrations. The final R-factor was 9.6% excluding hydrogen atoms. Figure 1 shows a computer-generated perspective drawing of the molecular structure of 12. This defines the relative configurations of the natural 3,6-epoxy-5-hydroxy-5,6-dihydro-β-ionol as (±)-2β,5β-epoxy-2α-[3α-hydroxy-1(*E*)-butenyl]-1β,3,3-trimethylcyclohexan-1α-ol.

Characterizations of the products are as follows. (4): mp 116–117 °C; IR (nujol) 3300, 1684, 1617, 988 cm^{-1}; ^{1}H-NMR11) δ 0.92 (s, 3H), 1.04 (s, 3H), 1.63 (t, J = 2 Hz, 3H), 1.50–2.10 (m, 4H, 2H disappeared on addition of D_2O),



2

3

4 R = H, OH

5 R = H, OH

6 R = O

7 R = OH

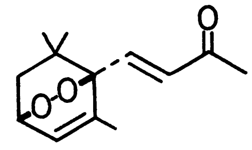
8 R = OTs

9

10 R = H

12 R = p-nitrobenzoyl

11



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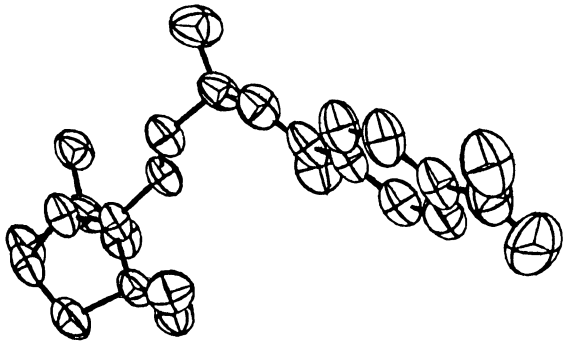

Fig. 1

2.28 (s, 3H), 4.30 (m, 1H), 5.63 (m, 1H), 6.33 (d, J = 16 Hz, 1H), 6.84 (d, J = 16 Hz, 1H); MS m/e 224 (M^+), 206, 108, 59, 43; MW12) 224.1450. (7): mp 138–139 °C; IR (nujol) 3450, 1675, 1648, 990 cm^{-1}; ^{1}H-NMR11) δ 0.79 (s, 3H), 0.97 (s, 3H), 1.30 (s, 3H), 1.36–1.80 (m, 4H, 2H disappeared on addition of D_2O), 2.32 (s, 3H), 3.28 (d, J = 3 Hz, 1H), 4.17 (m, 1H), 6.37 (d, J = 16 Hz, 1H), 7.04 (d, J = 16 Hz, 1H); MS m/e 241 (M^++ 1), 222, 179, 125, 43; MW12) 241.1405 (M^++ 1). (8): IR (nujol) 3480, 1679, 1655, 1592, 1172, 928 cm^{-1}. (9): IR (neat) 1675, 1628, 980, 941, 868 cm^{-1}; ^{1}H-NMR11) δ 0.81 (s, 3H), 1.12–1.92 (m, 2H), 1.31 (s, 3H), 1.42 (s, 3H), 2.29 (s, 3H), 3.94 (d, J = 3 Hz, 1H), 4.44 (dd, J = 3 and 6 Hz, 1H), 6.41 (d, J = 16 Hz, 1H), 6.79 (d, J = 16 Hz, 1H); MS m/e 222 (M^+), 207, 125, 98, 43; MW12) 222.1260. (12): mp 96–97 °C; IR ($CHCl_3$) 1722, 1605, 1525, 1350, 1270, 1018, 963 cm^{-1}; ^{1}H-NMR11) δ 0.89 (s, 3H), 1.17 (s, 3H), 1.41 (s, 3H), 1.50 (d, J = 6 Hz, 3H), 1.58–2.20 (m, 5H, 1H disappeared on addition of D_2O), 4.38 (t, J = 6 Hz, 1H), 5.5–5.8 (m, 1H), 5.83–5.98 (m, 2H), 8.24 (A_2B_2, 4H); MS m/e 376 (M^++ 1), 358, 301, 208, 150, 43; MW12) 376.1738 (M^++ 1).

References and Notes

1) Y. Takagi, T. Fujimori, H. Kaneko, T. Fukuzumi, and M. Noguchi, 22nd Symposium on the Chemistry of Terpenes, Essential Oils and Aromatics, Yokohama, Japan, Oct. 1978, Abstr. No. A23.
2) D. Behr, I. Wahlberg, T. Nishida, and C. R. Enzell, Acta Chem. Scand., B33, 701 (1979).
3) J. A. Findlay and W. D. MacKay, Can. J. Chem., 49, 2369 (1971).
4) W. Cocker, K. J. Crowley, and K. Srinivason, J. Chem. Soc., Perkin Trans. 1, 1973, 2485.
5) M. Koreeda, G. Weiss, and K. Nakanishi, J. Am. Chem. Soc., 95, 239 (1973).
6) M. M. Canet, J. C. Mani, J. R. Dalle, and J. L. Olive, Bull. Soc. Chem. Fr., 3874 (1966).
7) K. H. Schulte-Elte, M. Gadola, and G. Ohloff, Helv. Chim. Acta, 56, 2028 (1973).
8) K. Tori, K. Kitahonoki, T. Takano, H. Tanida, and Y. Tsuji, Tetrahedron Lett., 1964, 559.
9) N. M. Yoon and H. C. Brown, J. Am. Chem. Soc., 90, 2927 (1968).
10) G. Germain, P. Main, and M. M. Woolfson, Acta Cryst., A27, 368 (1971).
11) All ^{1}H-NMR spectra were determined in $CDCl_3$.
12) Determined by high resolution mass spectroscopy.

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