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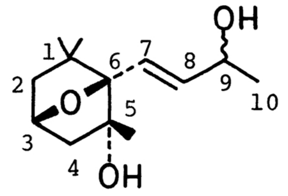
(±)-3,6-Epoxy-5-hydroxy-5,6-dihydro-β-ionol was synthesized from β-ionone _via_ 3,6-dihydroxy-α-ionone and its structure including the relative configurations was established as (±)-2β,5β-epoxy-2α-[3α-hydroxy-1(_E_)-butenyl]-1β,3,3-trimethylcyclohexan-1α-ol by X-ray analysis.

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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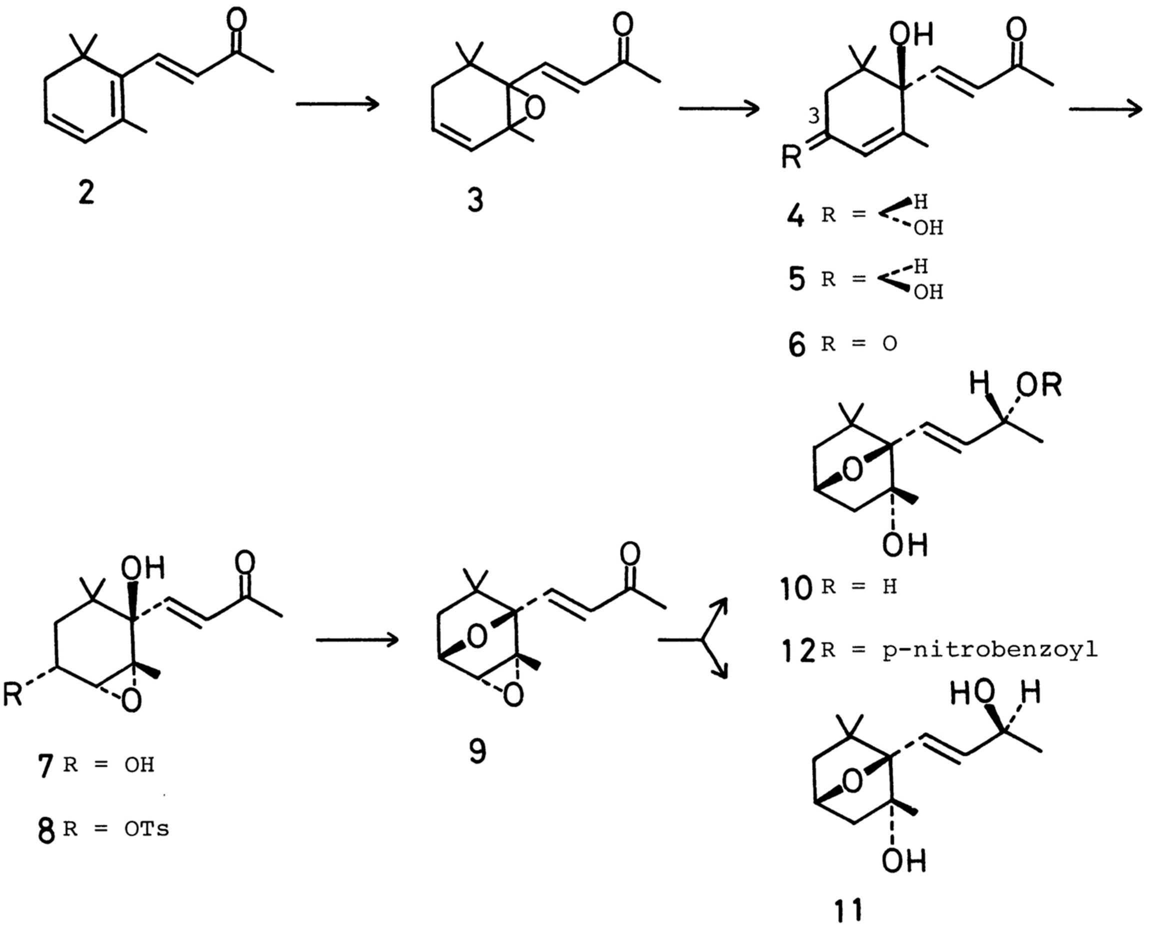
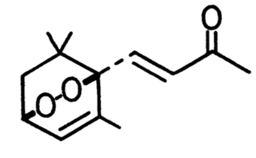
The epoxy ketone _3_ was prepared in three steps from β-ionone _via_ dehydroionone _2_.[3)] Hydrolysis of _3_[4)] in aqueous dioxane at 30 °C afforded the _trans_- _4_ and _cis_-diols _5_ in a ratio 85:15. The minor isomer was assigned to the _cis_-diol _5_[5)] by a comparison with the authentic sample obtained by photosensitized oxygenation[6)] 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 reflux[9)] 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; $\alpha = 108.43(1)$, $\beta = 108.89(1)$, $\gamma = 95.95(1)°$; $U = 996.51$ 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 method[10)] 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-NMR[11)] 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 $D_2O$),


O
2
3
OH
3
R
4 R = H, OH
5 R = H, OH
6 R = O
H OR
OH
10 R = H
12 R = p-nitrobenzoyl
R
7 R = OH
8 R = OTs
9
HO H
OH
11



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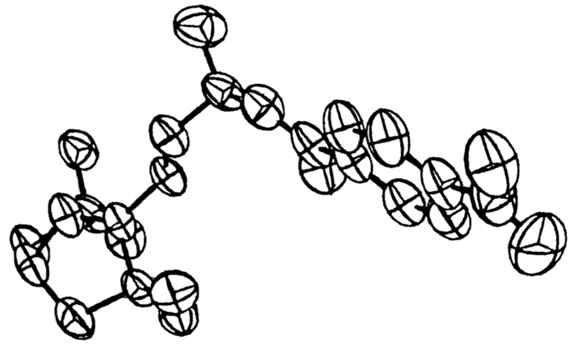

Fig. 1

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; MW[12)] 224.1450. (7): mp 138–139 °C; IR (nujol) 3450, 1675, 1648, 990 $cm^{-1}$; $^1$H-NMR[11)] 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; MW[12)] 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-NMR[11)] 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; MW[12)] 222.1260. (12): mp 96–97 °C; IR ($CHCl_3$) 1722, 1605, 1525, 1350, 1270, 1018, 963 $cm^{-1}$; $^1$H-NMR[11)] 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; MW[12)] 376.1738 ($M^+$+ 1).

## References and Notes

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