Enzymatic Single-step Formation of Laureatin and Its Key Intermediate, Prelaureatin, from (32,65,75)-Laurediol

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Abstract: A bicyclic natural bromo ether, laureatin (7), and its monocyclic key intermediate, prelaureatin (6), have enzymatically been transformed from their original precursor, (3Z, 6S, 7S)-laurediol in single-step by lactoperoxidase.

More than one hundred compounds of small and medium sized cyclic halo ethers, having a straight 15-carbon chain with a terminal engue or a bromo allene moiety, have been isolated from marine organisms such as red algae of Laurencia species.¹ (3E, 6R, 7R) - And (3Z, 6S, 7S)-laurediols (1 and 2), already isolated from L. nipponica, have been assumed to be the common precursors of the two groups of Laurencia-ethers with (6R, 7R) - and (6S, 7S)-configurations,^{2,3} respectively. Really, 1 have been partially established to be the precursor of laurefucin (4) and laureoxanyne (5), which were formed via the key intermediate, deacetyllaurencin (3) by using the oxidizing enzyme, lactoperoxidase (LPO) as an analogue of bromoperoxidase (BPO) detected in the alga.^{4*, b}



In this paper, we report the direct enzymatic cyclization of (3Z, 6S, 7S)-laurediol (2) into both of 6 and 7 in a single-step procedure.

The enzymatic substrate, (3Z, 6S, 7S, 12E)-laurediol (2) containing 10 % of inseparable (12Z)-isomer of 2, was prepared from TMS-protected laureatin (7) along with the reaction intermediates (6, 8, and 9) as shown in Scheme-1.⁵ The substrate (2) containing the geometric isomer was subjected to the enzymatic reaction.



To a vigorously stirred solution of $\frac{2}{2}$ (24 mg, 3.4 mM)⁶ in DMSO (0.3 ml) were added 30 ml of phosphate buffer (50 mM, pH 5.5) and 0.9 ml of NaBr solution (3 mM).⁶ Two solutions of LPO (64 nM)⁶ and H₂O₂ (0.8 mM)⁶ were added, in 10 times installments, to the above mixture every 1 h at 0 °C under argon. After stirring for 1 day, the conventional workup⁴ provided 27 mg of a crude mixture, which was separated by repeated column chromatography on silica gel and HPLC (Develosil, hexane:CH₂Cl₂:CH₃CN/80:19:1) to give 1 mg of prelaureatin (<u>6</u>) (3 %, 13 %⁺),⁷ 0.1 mg of laureatin (<u>7</u>) (0.3 %, 1.3 %⁺), two inseparable oxetanes (<u>8</u> and <u>9</u>) (0.3 mg, 1 %, 4.3 %⁺),⁸ unidentified bromohydrins (3.4 mg, 11 %) and the starting substrate <u>2</u>, (17.5 mg, 72 %). The MS and 'H NMR spectra of prelaureatin (<u>6</u>) and laureatin (7) obtained by this enzymatic reaction were completely identical with those of the natural <u>6</u> and <u>7</u>, respectively. The 'H NMR spectrum of the above inseparable mixture of oxetanes indicated this material to be a 2:1 mixture of (12*E*)- and (12*Z*)-isomers (<u>8</u> and <u>9</u>).

The result obtained in this enzymatic reaction suggests that laurediols would be the real precursors of *laurencia*-ethers in nature and that LPO has very low substrate specificity. However, the configurations of the vicinal diol units (6R, 7R or 6S, 7S) perfectly control the pathways for either the laurencin type (e.g. $\underline{3}$ and $\underline{4}$) or the laureatin type (e.g. $\underline{6}$ and $\underline{7}$). References and Notes

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- 6. The concentrations of $\underline{2}$, etc indicate the final values after addition.
- 7. The asterisked percentages ($\%^*$) denote the stoichiometric yields based on H_2O_2 .
- 8. The compound $(\underline{8})$ may be an intermediate for laureatin (7).