CHEMISTRY LETTERS, pp. 1579-1580, 1990.

A Direct Enzymatic Synthesis of Laurencin from Laurediol

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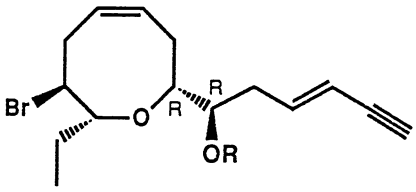
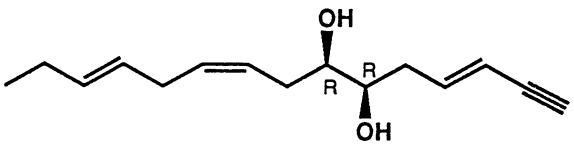
Deacetyllaurencin was synthesized in an enzymatic manner from (3E,6R,7R)-laurediol with lactoperoxidase in the presence of hydrogen peroxide and sodium bromide.

Laurencin (1)[1] has been isolated from the red alga, Laurencia nipponica, and been well known as one of the most representative naturally occurring bromo compounds with an eight-membered cyclic ether ring as well as an enyne unit.[2] On the other hand, (3E,6R,7R)-laurediol (2) and its stereoisomers[3] have been isolated from L. nipponica and assumed to be the direct biogenetic precursors of 1 and related bromo-ether compounds. In the course of the biosynthetic studies on halogenated marine natural products, we have recently reported the preliminary results on some bromo-etherification reactions of olefin alcohols as analogues of 2 by using lactoperoxidase (LPO) originated from milk in the presence of hydrogen peroxide (H_2O_2) and bromide ion.[4] We describe herein the enzymatic synthesis of deacetyllaurencin (1a) starting with 2.

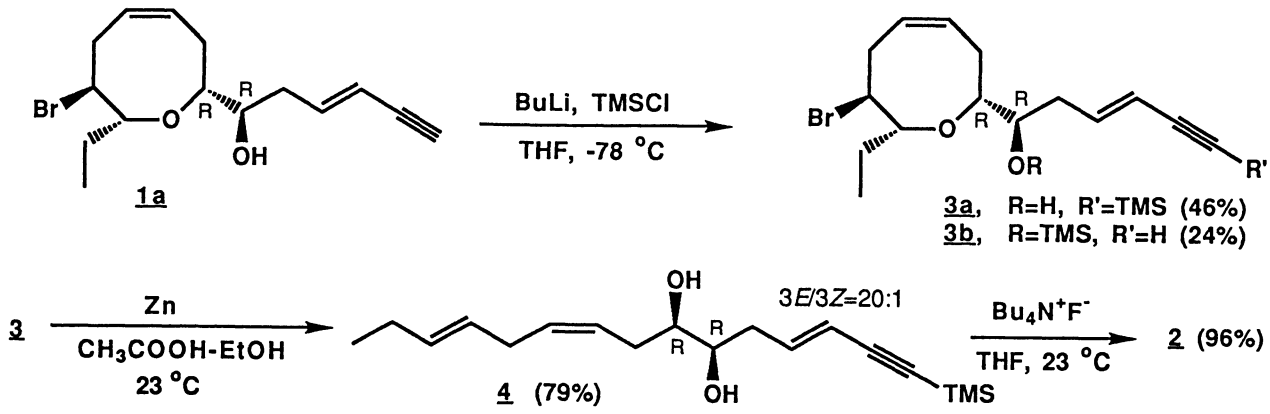


1, R=$COCH_3$
1a, R=H



2

Hydrolysis of natural laurencin (1) with potassium hydroxide in ethanol produced 1a, which was treated with butyllithium and trimethylchlorosilane to afford two separable compounds 3a and 3b (Scheme 1). Compound 3a was allowed to react with zinc powder in acetic acid and ethanol to give a 20:1 (3E/3Z)-mixture of 4, which was found to be completely free from the starting compounds, 1a and 3a, from MS and ^{1}H NMR (400 MHz) spectra. Compound 4 was deprotected to yield a 20:1 (3E/3Z)-mixture of (6R,7R)-laurediol (2), of which the homogeneity was reconfirmed also by MS and ^{1}H NMR



Scheme 1. Preparation of the starting (3E,6R,7R)-laurediol (2).

spectra. The compound (2) was highly labile and immediately subjected to the enzymatic reaction.

Compound 2 (73.8 mg, 7.9 mM) in dimethyl sulfoxide (0.3 ml) was injected into phosphate buffer (pH 5.5, 50 mM, 40 ml) containing sodium bromide (7.0 mM), and the mixture was fitted with argon balloon and kept at 5 °C. To the mixture was added an aliquot of each solution of H_2O_2 (1.8 mM) and LPO (64 nM) by dividing into 12 portions during 2 h. The mixture was stirred at 5 °C for 24 h and worked up as usual to lead to production of crude deacetyllaurencin (1.0 mg), an unknown cyclic ether (0.9 mg), an undetermined mixture of bromohydrins (29.2 mg), and the recovered starting material (38.4 mg). The impure deacetyllaurencin was acetylated under the usual conditions and separated over silica gel to afford a pure sample of laurencin (0.8 mg, 0.73%, 3.2%*).[5] Comparison of ^1H NMR (400 MHz) spectra showed that synthetic laurencin was completely identical with a natural sample (1). The results provide a strong support to the hypothesis that laurediols are the real biosynthetic precursors of 1 and its related cyclic ether compounds in marine origins.

References

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2) Cf., K. L. Erickson, "Constituents of Laurencia," in "Marine Natural Products, Chemical and Biological Perspectives," ed by P. J. Scheuer, Academic Press, New York (1983), Vol. 5, Chap. 4, pp. 131-257.
3) E. Kurosawa, A. Fukuzawa, and T. Irie, Tetrahedron Lett., 1972, 2121.
4) A. Fukuzawa, Mya Aye, M. Nakamura, M. Tamura, and A. Murai, Chem. Lett., in press.
5) The star marked percentage (%*) denotes the stoichiometric yield based on H_2O_2.

(Received June 13, 1990)