One-Step Synthesis of Laurencione

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The synthesis of the marine natural product laurencione from 5-hydroxy-2-pentanone in one step is reported.

Laurencione is the major metabolite (16%) of the lipid extract of the red alga *Laurencia spectabilis*.[1] It occurs as a mixture of two interconverting forms, that is, (±)-2-hydroxy-2-methyldihydrofuran-3(2H)-one (**1**) and 5-hydroxy-2,3-pentanedione (**2**) (Scheme 1). Laurencione is a labile marine natural product that dimerizes on Si gel to produce a spiroacetal, which has been isolated from *Laurencia pinnatifida*.[2] This spiroacetal is probably an artifact formed by dimerization of the laurencione precursor during extraction or chromatography.[1] Laurencione has already been synthesized by us in multistep sequences, utilizing elaboration of γ-butyrolactone, 5-acetoxy-3-chloro-2-pentanone, or 1,1-dichloroacetone.[3,4] Because of our interest in the peculiar structure and the possible interactions of laurencione with certain amino acids, a shorter synthesis that makes available our challenging target molecule in larger amounts and in better overall yield was needed. We now report a very simple and efficient synthesis of laurencione.

The oxidation of α-methylenecarbonyl compounds with selenium (IV) oxide is a well-known procedure.[5−8] We used this method to oxidize the γ-hydroxy ketone **4** to laurencione **1/2**. 5-Hydroxy-2-pentanone **4**, in equilibrium with its cyclic hemiacetal form **3**, is a commercially available product containing about 10% of 5-(4-oxopentoxy)-2-pentanone [$(CH_3COCH_2CH_2CH_2)_2O$] as an impurity.[9] Reaction of the tautomeric mixture **3** ⇄ **4** with 1.5 equiv of selenium dioxide in aqueous dioxane at 85 °C afforded laurencione **1/2** in 48% yield after purification by flash chromatography[10] (purity > 99%; ^{1}H NMR) (Scheme 1).

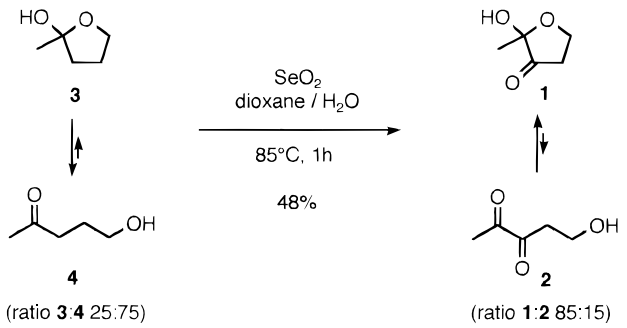
The natural product was obtained as a mixture of the cyclic 2-hydroxy-2-methyldihydrofuran-3(2*H*)-one (**1**) and the open form, 5-hydroxy-2,3-pentanedione (**2**) (ratio, 85:15 in $CDCl_3$; ^{1}H NMR). The impurity present in the commercial product **3/4** did not give rise to any problem during the isolation of the pure marine natural compound **1/2**.

In conclusion, a fast and reliable method for the synthesis of laurencione from a commercial source is described.

Experimental Section

General Experimental Procedures. NMR spectra were run on a JEOL JNM EX 270 spectrometer, using $CDCl_3$ as the solvent and TMS as internal reference.

Scheme 1



TLC was performed on Si gel plates Kieselgel $60F_{254}$ (layer thickness 0.25 mm). Flash chromatography was carried out with Si gel (Merck; particle size 40−63 μm). 5-Hydroxy-2-pentanone was purchased from Acros or Aldrich, chemical purity ca. 90%.

5-Hydroxy-2-pentanone (3/4) and 5-(4-oxopentoxy)-2-pentanone (impurity): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.42 (s, CH_3), 1.68−2.08 (m, CH_2), 2.14 (s, CH_3), 2.16 (s, CH_3), 2.49 (t, J = 7.0 Hz, CH_2C=O), 2.59 (t, J = 7.0 Hz, CH_2C=O), 3.40−3.89 (m, CH_2O); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 22.18 (CH_3), 24.62 (CH_2), 24.71 (CH_2), 26.65 (CH_2), 30.03 (CH_3), 30.15 (CH_3), 38.08 (CH_2), 40.56 (CH_2), 40.85 (CH_2), 60.05 (CH_2), 62.19 (CH_2), 67.69 (CH_2), 107.56 (C_{quat}), 209.27 (C=O), 209.79 (C=O).

Laurencione (1/2). To a stirred solution of 5-hydroxy-2-pentanone **3/4** (1.02 g, 10 mmol) in aqueous dioxane (15 mL; dioxane:H_2O, 20:1) at 85 °C was added selenium dioxide (1.66 g, 15 mmol) in one portion. After being stirred for 1 h at 85 °C, the solution, which first turned yellow and then red, was cooled to room temperature and filtered. The filtrate was evaporated under reduced pressure, 50 mL of EtOAc was added, and the solution was washed with 10% aqueous $NaHCO_3$ (20 mL) and dried ($MgSO_4$). The product was purified by flash chromatography (EtOAc−hexane, 45:55; R_f = 0.33) to give 0.46 g (48%) of laurencione **1/2** as a yellow oil: ^{1}H NMR, ^{13}C NMR, IR, and MS matched completely the data reported in the literature.[1]

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References and Notes

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(9) Acros catalogue no. 10.267.82 and Aldrich catalogue no. A2,-080-4 proved to have identical compositions, including the impurity.
(10) The crude laurencione obtained is fairly pure, but flash chromatography is necessary to remove all traces of selenium compounds.

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