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Synthesis of Biologically Active Natural Component 4-Hydroxyderricin Through Water-Accelerated [3,3]-Sigmatropic Rearrangement

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Angelica keiskei has been used in traditional medicine, food and beverages, and exhibited various biological activities, such as antitumor,[1] antibacterial,[2] antioxidant,[3] antidiabetic,[4] antiallergic,[5] antimetastatic,[6] antiulcer,[7] hypotensive,[8] lipid regulatory,[8] and cancer chemopreventive[9] effects. The plant has been reported to contain chalcones, flavanones, and coumarines.[7] Two types of polyphenolic chalcones, 4-hydroxyderricin (**1**) and xanthoangelol (**2**), are especially rich in the plant, and the 4-hydroxyderricin exhibited the major responsibility for the various biological activities.[10] Sugamoto reported the synthesis of 4-hydroxyderricin *via* [1,3]-sigmatropic rearrangement of chalcone ether using montmorillonite K10 which showed relatively low rearrangement yield (Scheme 1), and this is the only reported total synthesis of **1** as far as we know.[11] We recently developed the water-accelerated [3,3]-sigmatropic rearrangement reaction for licochalcone A synthesis[12] and showed advantages promising higher yield and preventive effect to abnormal rearrangement which was known disadvantage[13] of [3,3]-sigmatropic rearrangement reactions. We now report herein the effective total synthesis of biologically active natural product 4-hydroxyderricin.

There are two possible approaches to the 4-hydroxyderricin as shown in retrosynthetic analysis (Scheme 2). One is Claisen-Schmidt condensation of benzaldehyde **3** with acetophenone **4**, which is derived from the [3,3]-sigmatropic rearrangement of acetophenone **5** to build chalcone structure (method a), and the other is [3,3]-sigmatropic rearrangement reaction of chalcone **6**, which is derived from Claisen-Schmidt condensation of benzaldehyde **3** with acetophenone **5** (method b).

The order of the reaction sequence for the synthesis of prenylated chalcones is important. For example, the [3,3]-sigmatropic rearrangement of aryl allyl ether **7** produced the expected product **8** in 40% yield along with a deprenylated product **9** (10%). However, the reaction of chalcone **10** yielded licochalcone A **11** in 86% yield without any side product (Scheme 3).[12] In licochalcone D synthesis, the [3,3]-sigmatropic rearrangement reaction of aryl allyl ether **12** produced the desired product **13** in 72% yield without any side product, and the conjugated aryl ether **14** also yielded licochalcone D directly without additional deprotection procedure in water-accelerated [3,3]-sigmatropic rearrangement

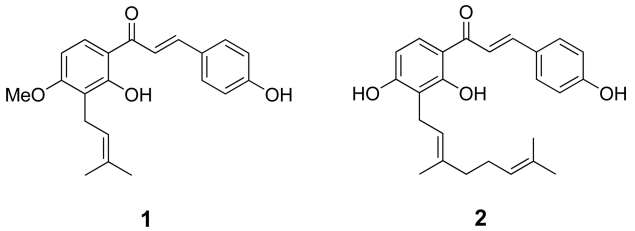
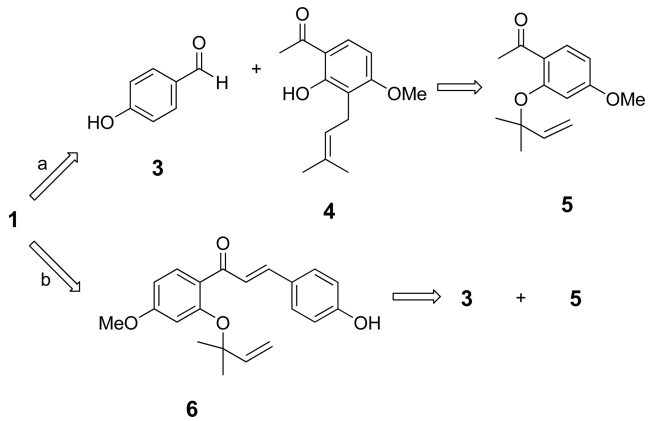
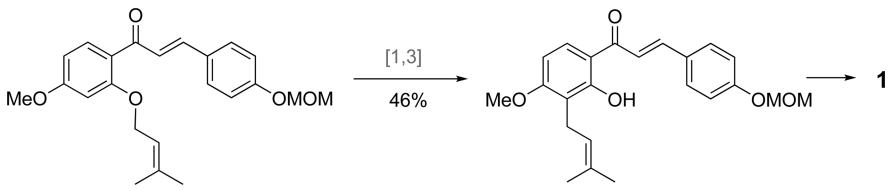


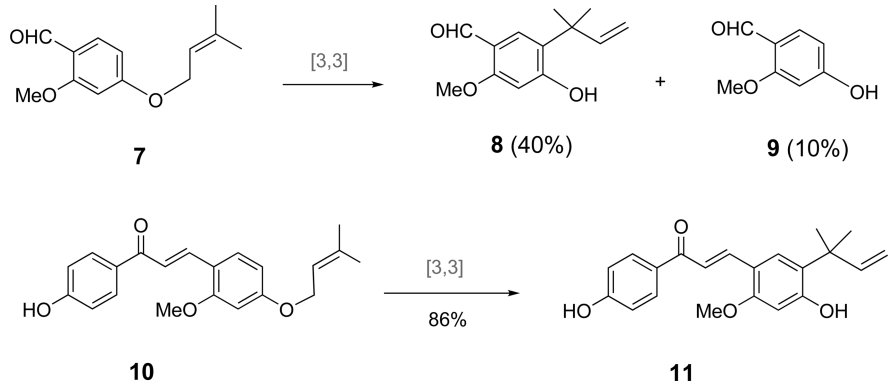
Figure 1. Structures of 4-hydroxyderricin (**1**) and xanthoangelol (**2**).



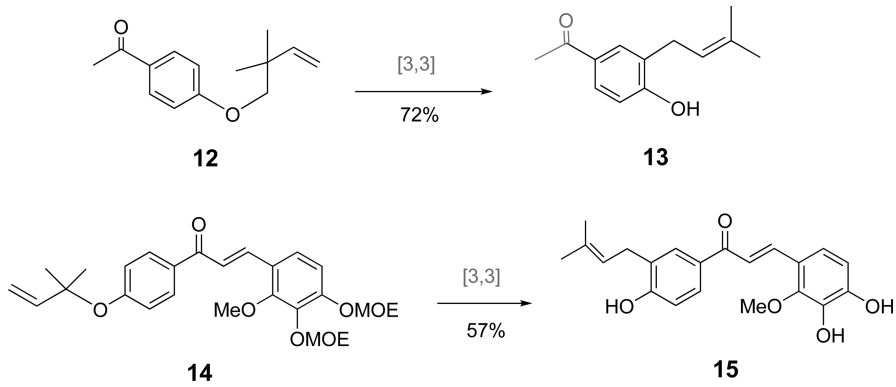
Scheme 2. Retrosynthetic approach to 4-hydroxyderricin.



Scheme 1. [1,3]-Sigmatropic rearrangement in Sugamoto's 4-hydroxyderricin synthesis.



Scheme 3. [3,3]-Sigmatropic rearrangement reactions in licochalcone A synthesis.



Scheme 4. [3,3]-Sigmatropic rearrangement reactions in licochalcone D synthesis.

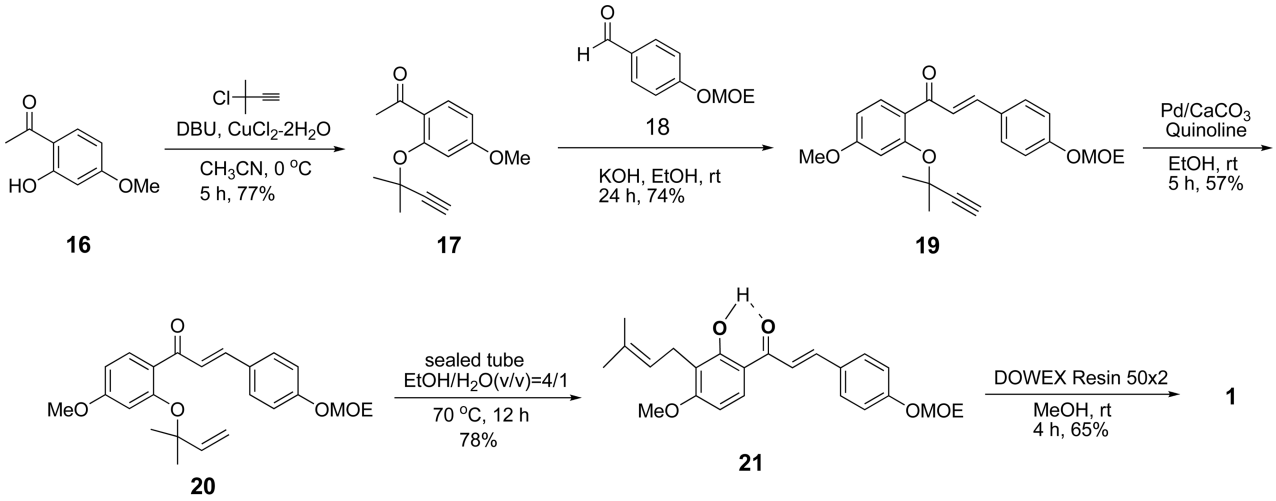
reaction (Scheme 4).[14] These results lead us to choose the method b, which involves the Claisen-Schmidt condensation of the two phenolic units **3** and **5** to chalcone **6** and the [3,3]-sigmatropic rearrangement of **6** to install the *m*-prenyl unit for the synthesis of 4-hydroxyderricin.

The synthetic methods of 4-hydroxyderricin employing water-accelerated [3,3]-sigmatropic rearrangement as a key step are depicted in Scheme 5. Commercially available 2-hydroxy-4-methoxyacetophenone (**16**) was coupled with 3-chloro-3-methyl-1-butyne in the presence of DBU (1,8-diazabicycloundec-7-ene) and $CuCl_2 \cdot 2H_2O$ in acetonitrile to give *O*-alkynylated compound **17** in 77% yield. In the ^1H NMR spectrum, we observed a singlet peak of methyne proton at δ 2.67 and two new methyl protons at δ 1.75 as a singlet. Claisen-Schmidt condensation of the methyl ketone **17** with MOE-protected 4-hydroxybenzaldehyde **18** in KOH-EtOH basic condition produced chalcone **19** in 74% yield. The *trans* configuration was confirmed with coupling constant (J = 15.6 Hz) between two doublet signals at δ 7.60 and 7.39, are presentative coupling pattern for *trans* protons in the conjugated alkene system. Partial reduction of triple bond in chalcone **19** using Lindlar catalyst yielded chalcone **20** in 57% yield. The structure was confirmed by the disappearance of the methyne proton and the appearance of vinylic protons at δ 6.14 (dd, J = 17.7 and 10.8 Hz), 5.19 (d, J = 17.7 Hz) and 5.15 (d, J = 10.8 Hz), indicating C-2', C-3'$_{trans}$ and C-3'$_{cis}$ sp^2 protons respectively.

Water-accelerated [3,3]-sigmatropic rearrangement reaction of aryl prenyl ether **20** using EtOH/H_2O (v/v = 4/1) smoothly produced expected product **21** in 78% yield without any abnormal rearrangement or deprenylation at 70 °C in sealed tube within 12 h. In Sugamoto synthesis, the [1,3]-sigmatropic rearrangement reaction of aryl prenyl ether using montmorillonite K10 yielded only 46% yield.[11] The structure of **21** showed a hydrogen bonded phenol O-H proton at δ 13.7 as a sharp singlet, and allylic protons at δ 3.38 (d, J = 6.9 Hz), vinylic proton at δ 5.22 (br t, J = 6.9 Hz), and terminal two methyls at δ 1.80 (br s) and 1.68 (br s) in rearranged butenyl side chain. The MOE protecting group survived in this reaction although it was deprotected at 120 °C as shown in the licochalcone D synthesis.[13]

We found that the reaction temperature was critical in water-accelerated [3,3]-sigmatropic rearrangement, and that undesirable deprenylation product was obtained at higher temperature. It has been also reported that the deprenylation was unavoidable at higher temperature in normal [3,3]-sigmatropic rearrangement of aryl prenyl ether systems.[15] The optical reaction temperature for the [3,3]-sigmatropic rearrangement without deprenylation was quite dependent upon the structure. This could be a limitation of water-accelerated [3,3]-sigmatropic rearrangement reaction, even though it has the advantages such as higher yield and preventive effect to abnormal rearrangement.

Finally, deprotection of MOE group of **21** using DOWEX resin 50 × 2 in MeOH at rt produced 4-hydroxyderricin in 65% yield, and the spectral data for this compound agreed



Scheme 5. Total synthesis of 4-hydroxyderricin *via* [3,3]-sigmatropic rearrangement.

well with the literature values.[11b]

In summary, we report herein the practical and effective total synthesis of biologically active 4-hydroxyderricin, a poly-phenolic chalcone compound containing *m*-prenyl group at ring A. The key steps of the synthesis are Claisen-Schmidt condensation of the the two phenolic units **17** and **18** to chalcone **19** and the water-accelerated [3,3]-sigmatropic rearrangement of 1,1-dimethyl-2-propenyl aryl ether **20** to introduce the *m*-prenyl unit in 4-hydroxyderricin.

Experimental Section

All chemicals were purchased from Sigma-Aldrich Chemicals and were used without further purification unless noted otherwise. NMR spectra were recorded at Varian Mercury-300 MHz FT-NMR and 75 MHz for ^{13}C, with the chemical shift (δ) reported in parts per million (ppm) relative to TMS and the coupling constants (*J*) quoted in Hz. $CDCl_3$ was used as a solvent and an internal standard. High-resolution mass spectra were recorded using a JMS-700 (JEOL) spectrometer. Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F_{254} (Merck, layer thickness 0.2mm) plastic-backed *silica* gel plates and visualized by UV light (254 nm) or staining with *p*-anisaldehyde.

4-Methoxy-2-(1,1-dimethyl-2-propynyloxy)acetophenone (12). 3-Chloro-3-methyl-1-butyne (0.37 mL, 3.31 mmol) in acetonitrile (4 mL) was added slowly to the reaction mixture of 2-hydroxy-4-methoxyacetophenone (**1**) (500 mg, 3.01 mmol), $CuCl_2 \cdot 2H_2O$ (5.0 mg, 0.03 mmol) and 1,8-diazabicycloundec-7-ene (0.49 mL, 3.31 mmol) in acetonitrile (10 mL) under N_2 atmosphere, and stirred for 5 h at 0 °C. The solvent was evaporated *in vacuo* and the residue was extracted with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* and the residue was purified by *silica* gel flash column chromatography (EtOAc/Hexane = 1/4) to give a yellow solid; yield: 535 mg (77%). R_f = 0.42 (EtOAc/Hexane = 1/4). ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (1H, d, *J* = 9.0 Hz), 7.17 (1H, d, *J* = 1.8 Hz), 6.58 (1H, dd, *J* = 9.0, 1.8 Hz), 3.83 (3H, s), 2.67 (1H, s), 2.57 (3H, s), 1.75 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 163.1, 156.8, 132.0, 124.6, 107.3, 104.9, 85.3, 75.1, 75.0, 73.1, 55.5, 31.9, 29.7.

(*E*)-3-[4-Ethoxymethoxyphenyl]-1-[4-methoxy-2-(1,1-dimethyl-2-propynyloxy)]prop-2-en-1-one (14). To a solution of 4-methoxy-2-(1,1-dimethyl-2-propynyloxy)acetophenone (**12**) (250 mg, 1.08 mmol) in EtOH (10 mL) was added 4-ethoxymethoxybenzaldehyde (**13**, 213 mg, 1.18 mmol) and KOH (121 mg, 2.15 mmol), and stirred for 24 h at rt. After completion of the reaction, the solvent was evaporated *in vacuo* and the residue was extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* and the residue was purified by *silica* gel flash column chromatography (EtOAc/Hexane = 1/4) to give a yellow oil; yield: 315 mg (74%). R_f = 0.25 (EtOAc/Hexane = 1/6). ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (1H, d, *J* = 8.7 Hz), 7.60 (1H, d, *J* = 15.6 Hz), 7.52 (2H, d, *J* = 8.4 Hz), 7.39 (1H, d, *J* = 15.6 Hz), 7.14 (1H, d, *J* = 2.4 Hz), 7.03 (2H, d, *J* = 8.4 Hz), 6.67 (1H, dd, *J* = 8.7, 2.4 Hz), 5.24 (2H, s), 3.85 (3H, s), 3.73 (2H, q, *J* = 6.9 Hz), 2.63 (1H, s), 1.62 (6H, s), 1.23 (3H, t, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1, 162.8, 158.9, 156.0, 141.2, 132.0, 129.7, 128.9, 126.8, 125.7, 116.4, 108.5, 106.7, 93.0, 85.7, 74.7, 73.9, 64.5, 55.5, 29.6, 15.2.

(*E*)-3-[4-Ethoxymethoxyphenyl]-1-[4-methoxy-2-(1,1-dimethyl-2-propenyloxy)]prop-2-en-1-one (15). To a solution of (*E*)-3-[4-ethoxymethoxyphenyl]-1-[4-methoxy-2-(1,1-dimethyl-2-propynyloxy)]prop-2-en-1-one (**14**) (188 mg, 0.48 mmol) in EtOH (5 mL) was added 5 wt % Pd-$CaCO_3$ (10 mg) and quinoline (2 mg, 0.02 mmol), and filled with hydrogen gas and stirred for 5 h at rt. After completion of the reaction, Pd was filtered using celite filter and the solvent was evaporated *in vacuo* and the residue was purified by *silica* gel flash column chromatography (EtOAc/Hexane = 1/10) to give a yellow oil; yield: 107 mg (57%). R_f = 0.29 (EtOAc/Hexane = 1/4). ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (1H, d, *J* = 8.1 Hz), 7.61 (1H, d, *J* = 15.6 Hz), 7.53 (2H, d, *J* = 8.7 Hz), 7.46 (1H, d, *J* = 15.6 Hz), 7.03 (2H, d, *J*

= 8.7 Hz), 6.67 (1H, d, J = 2.4 Hz). 6.59 (1H, dd, J = 8.1, 2.4 Hz), 6.14 (1H, dd, J = 17.7, 10.8 Hz), 5.24 (2H, s), 5.19 (1H, d, J = 17.7 Hz), 5.15 (1H, d, J = 10.8 Hz), 3.79 (3H, s), 3.73 (2H, q, J = 6.9 Hz), 1.46 (6H, s), 1.23 (3H, t, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.4, 162.7, 158.8, 156.8, 143.8, 140.9, 132.0, 129.7, 129.0, 126.5, 125.8, 116.4, 113.9, 107.5, 106.6, 93.0, 81.4, 64.5, 55.4, 27.0, 15.2.

(*E*)-3-[4-Ethoxymethoxyphenyl]-1-[2-hydroxy-4-methoxy-3-(3-methyl-2-butenyl)]prop-2-en-1-one (16). To a solution of (*E*)-3-[4-ethoxymethoxyphenyl]-1-[4-methoxy-2-(1,1-dimethyl-2-propenyloxy)]prop-2-en-1-one (**15**) (59 mg, 0.15 mmol) was dissolved in EtOH/H_2O (4/1, v/v; 4 mL) and reacted for 12 h at 70 °C in sealed tube. After completion of reaction, solvent was concentrated *in vacuo* and extracted with EtOAc. The organic phase was separated, dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated again and the residue was purified by *silica* gel flash column chromatography (EtOAc/Hexane = 1/4) to give a yellow oil; yield: 46 mg (78%). R_f = 0.53 (EtOAc/Hexane = 1/4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.47 (1H, s), 7.83 (1H, d, J = 15 Hz), 7.77 (1H, d, J = 8.7 Hz), 7.58 (2H, d, J = 8.7 Hz), 7.47 (1H, d, J = 15 Hz), 7.06 (2H, d, J = 8.7 Hz), 6.48 (1H, d, J = 8.7 Hz), 5.26 (2H, s), 5.22 (1H, br t, J = 6.9 Hz), 3.90 (3H, s), 3.73 (2H, q, J = 6.9 Hz), 3.38 (2H, d, J = 6.9 Hz), 1.80 (3H, br s), 1.68 (3H, br s), 1.23 (3H, t, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 163.1, 162.9, 159.3, 143.7, 131.7, 130.0, 129.0, 128.5, 122.0, 118.5, 117.5, 116.5, 114.6, 102.0, 92.9, 64.5, 55.8, 25.9, 21.8, 17.9, 15.2.

4-Hydroxyderricin (1). To a solution of (*E*)-3-[4-ethoxymethoxyphenyl]-1-[2-hydroxy-4-methoxy-3-(3-methyl-2-butenyl)]prop-2-en-1-one (**16**) (27 mg, 0.07 mmol) in MeOH (3 mL) was added activated DOWEX resin 50 × 2 (10 mg), and stirred for 4 h at rt. After completion of the reaction, resin was filtered and the solvent was evaporated *in vacuo* and the residue was purified by *silica* gel flash column chromatography (EtOAc/Hexane = 1/4) to give a yellow oil; yield: 15 mg (65%). R_f = 0.15 (EtOAc/Hexane = 1/4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.43 (1H, s), 7.80 (1H, d, J = 15.3 Hz), 7.77 (1H, d, J = 8.7 Hz), 7.52 (2H, d, J = 8.7 Hz), 7.44 (1H, d, J = 15.3 Hz), 6.86 (2H, d, J = 8.7 Hz), 6.48 (1H, d, J = 8.7 Hz), 5.90 (1H, br s), 5.22 (1H, br t, J = 7.2 Hz), 3.90 (3H, s), 3.38 (2H, d, J = 7.2 Hz), 1.79 (3H, br s), 1.68 (3H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 163.1, 162.8, 157.9, 143.9, 131.8, 130.4, 129.0, 127.7, 122.0, 118.1, 117.5, 115.9, 114.6, 102.1, 55.8, 25.9, 21.8, 17.9; HRMS (EI) calcd for $C_{21}H_{22}O_4$ M^+ 338.1518, found 338.1519.

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