

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

Si-Jun Kim, Jae Jun Lee, Hyun-Ho Yoon, and Jong-Gab Jun*

Department of Chemistry and Institute of Applied Chemistry, Hallym University, Chuncheon 200-702, Korea

*E-mail: jgjun@hallym.ac.kr

Received April 30, 2013, Accepted June 15, 2013

Key Words : 4-Hydroxyderricin, Claisen-Schmidt condensation, Water-accelerated [3,3]-sigmatropic rearrangement, *Angelica keiskei*, Chalcone

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 chemopreventive⁹ 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 synthesis¹² and showed advantages promising higher yield and preventive effect to abnormal rearrangement which was known disadvantage¹³ 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

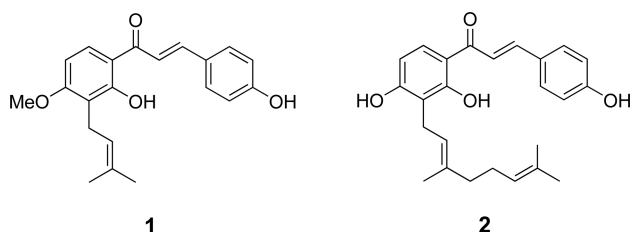
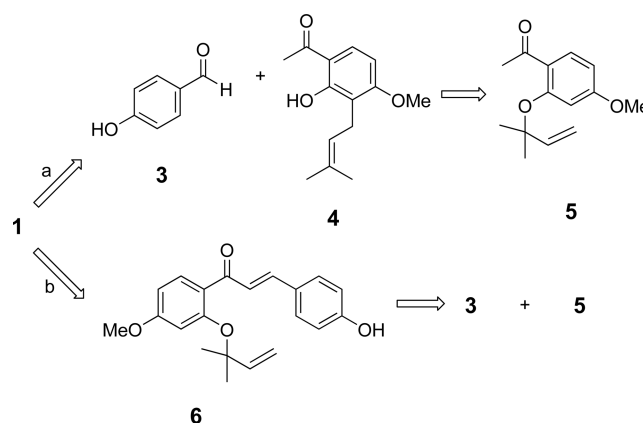
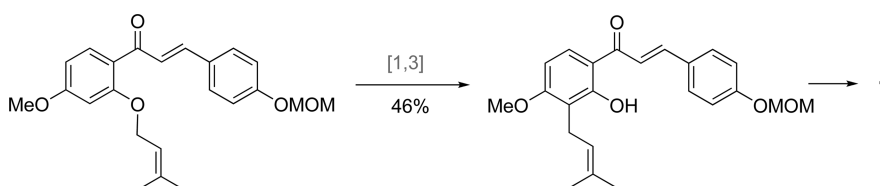


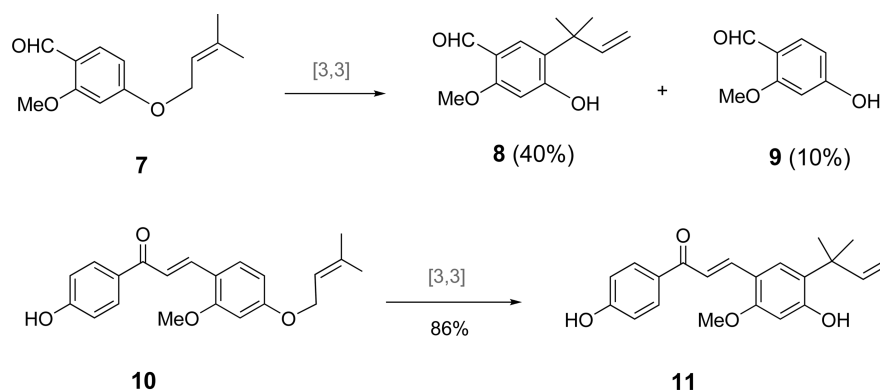
Figure 1. Structures of 4-hydroxyderricin (**1**) and xanthoangelol (**2**).



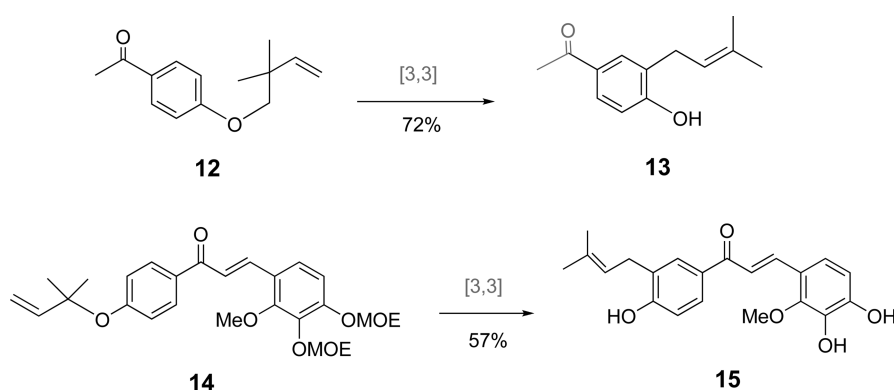
Scheme 2. Retrosynthetic approach to 4-hydroxyderricin.



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.

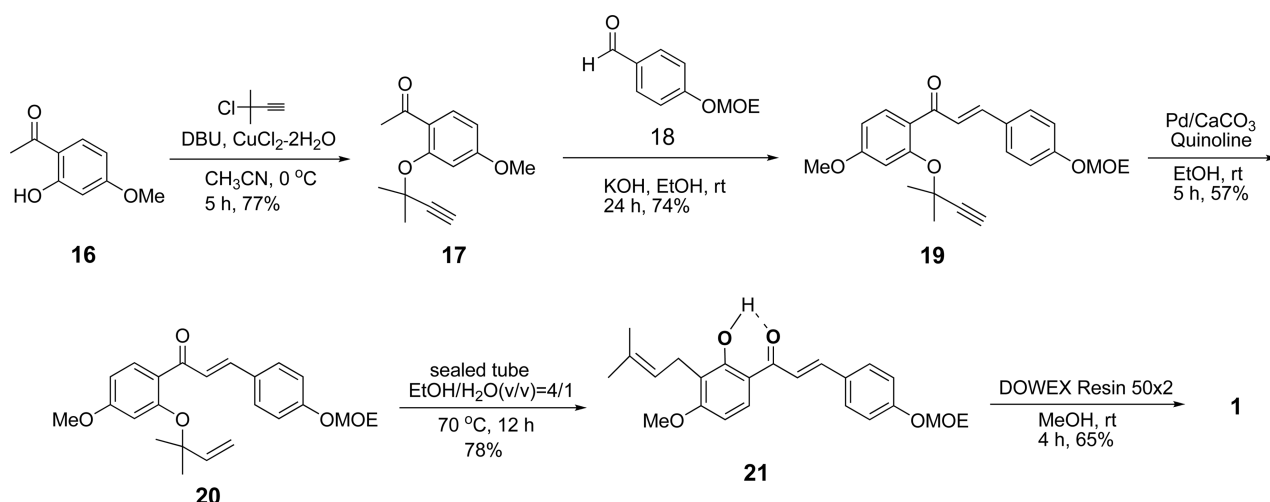
The synthetic methods of 4-hydroxyderricin employing water-accelerated [3,3]-sigmatropic rearrangement as a key step are depicted in Scheme 5. Commercially available 2-hydroxy-4-methoxyacetophenone (**16**) was coupled with 3-chloro-3-methyl-1-butyne in the presence of DBU (1,8-diazabicycloundec-7-ene) and CuCl₂·2H₂O 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* sp² protons respectively.

Water-accelerated [3,3]-sigmatropic rearrangement reac-

tion of aryl prenyl ether **20** using EtOH/H₂O (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 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 ¹³C, with the chemical shift (δ) reported in parts per million (ppm) relative to TMS and the coupling constants (*J*) quoted in Hz. CDCl₃ 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, F₂₅₄ (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-propenyloxy)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), CuCl₂·2H₂O (5.0 mg, 0.03 mmol) and 1,8-diazabicycloundec-7-ene (0.49 mL, 3.31 mmol) in acetonitrile (10 mL) under N₂ atmosphere, and stirred for 5 h at 0 °C. The solvent was evaporated *in vacuo* and the residue was extracted with CH₂Cl₂. The organic phase was dried over anhydrous Na₂SO₄ 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, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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-propenyloxy)]prop-2-en-1-one (14). To a solution of 4-methoxy-2-(1,1-dimethyl-2-propenyloxy)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 Na₂SO₄ 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, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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-propenyloxy)]prop-2-en-1-one (**14**) (188 mg, 0.48 mmol) in EtOH (5 mL) was added 5 wt % Pd-CaCO₃ (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, CDCl₃) 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). ^1H 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 \times 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). ^1H 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 $\text{C}_{21}\text{H}_{22}\text{O}_4$ M^+ 338.1518, found 338.1519.

Acknowledgments. This research was financially supported by Priority Research Centers Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (NRF-2009-0094071), and by Hallym University Research Fund, 2012 (HRF-201209-016).

References and Notes

1. Takaoka, S.; Hibasami, H.; Ogasawara, K.; Imai, N. *J. Herbs Spices Med. Plants* **2008**, *14*, 166-174.
2. Nakata, K.; Taniguchi, M.; Baba, K. *Nat. Med.* **1999**, *53*, 329-332.
3. Li, L.; Aldini, G.; Carini, M.; Chen, C.-Y. O.; Chun, H.-K.; Cho, S.-M.; Park, K.-M.; Correa, C. R.; Russell, R. M.; Blumberg, R. M.; Yeuma, K.-J. *Food Chem.* **2009**, *115*, 227-232.
4. Enoki, T.; Ohnogi, H.; Nagamine, K.; Kudo, Y.; Sugiyama, K.; Tanabe, M.; Kobayashi, E.; Sagawa, H.; Kato, Y. *J. Agric. Food Chem.* **2007**, *55*, 6013-6017.
5. Kishiro, S.; Nunoura, S.; Nagai, H.; Akihisa, T.; Ra, C. *Biol. Pharm. Bull.* **2008**, *31*, 442-448.
6. Kimura, Y.; Baba, K. *Intl. J. Cancer* **2003**, *106*, 429-437.
7. Baba, K.; Taniguchi, M.; Nakata, K. *Foods Food Ingredients J. Jpn.* **1998**, *178*, 52-60.
8. Ogawa, H.; Ohno, M.; Baba, K. *Clin. Exp. Pharm. Physiol.* **2005**, *32*, 19-23.
9. Akihisa, T.; Tokuda, H.; Hasegawa, D.; Ukiya, M.; Kimura, Y.; Enjo, F.; Suzuki, T.; Nishino, H. *J. Nat. Prod.* **2006**, *69*, 38-42.
10. Akihisa, T.; Kikuchi, T.; Nagai, H.; Ishii, K.; Tabata, K.; Suzuki, T. *J. Oleo Sci.* **2011**, *60*, 71-77.
11. (a) Sugamoto, K.; Kurogi, C.; Matsushita, Y.-i.; Matsui, T. *Tetrahedron Lett.* **2008**, *49*, 6639-6641. (b) Sugamoto, K.; Matsushita, Y.-i.; Matsui, K.; Kurogi, C.; Matsui, T. *Tetrahedron* **2011**, *67*, 5346-5359.
12. Jeon, J.-H.; Kim, M. R.; Jun, J.-G. *Synthesis* **2011**, 370-376.
13. Fukuyama, T.; Li, T.; Peng, G. *Tetrahedron Lett.* **1994**, *35*, 2145-2148.
14. Kim, S.-J.; Jun, J.-G. *Bull. Korean Chem. Soc.* **2013**, *34*, 54-58.
15. Coombers, C. L.; Moody, C. J. *J. Org. Chem.* **2008**, *73*, 6758-6762.