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Synthesis of 4-hydroxyderricin and related derivatives

Kazuhiro Sugamoto *, Chiaki Kurogi, Yoh-ichi Matsushita, Takanao Matsui

Faculty of Engineering, University of Miyazaki, Gakuen-Kibanadai, Miyazaki 889-2192, Japan

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ABSTRACT

Naturally occurring chalcones, namely 4-hydroxyderricin (**1**), xanthoangelol H (**2**), deoxyxanthoangelol H (**3**), and deoxydihydroxanthoangelol H (**4**), were first synthesized and evaluated for antibacterial activities.

4-Hydroxyderricin (**1**) was isolated from *Lonchocarpus neuroscapha*[1] and *Angelica keiskei*[2] (Fig. 1). Xanthoangelol H (**2**),[3] deoxyxanthoangelol H (**3**),[4] and deoxydihydroxanthoangelol H (**4**)[4] were isolated from *Angelica keiskei*. Compound **1** exhibited various biological activities, such as antibacterial activity against gram-positive pathogenic bacteria,[5] antitumor promoting activity in mouse skin carcinogenesis using DMBA and TPA,[6] phenylephrine-induced vasoconstriction in vivo,[7] hypotensive and lipid regulatory actions in hypertensive rats,[8] antitumor and antimetastatic activities,[9] and inhibitory effect on induction of EBV-EA by TPS in Raji cells.[10] Compounds **1** and **2** exhibited cytotoxicity against neuroflastoma cells.[11] Compound **3** exhibited inhibitory effect on induction of EBV-EA by TPS in Raji cells.[4] Compound **1** is one of the major components of *Angelica keiskei*, on the other hand, **2–4** are minor components. For example, **1** (13.5 g) and **2** (30 mg) were isolated from air-dried roots (19.5 kg),[3] and **3** (17 mg) and **4** (3 mg) were isolated from stem exudates (300 g).[4] It is difficult to isolate **2–4** from *Angelica keiskei*. Therefore, few reports have been published on the biological activities of **2–4**.[4,10,11] To our knowledge, no work has been done on total synthesis of **1–4**. It seems to be important to develop synthetic routes of these chalcones for elucidation of the relationship between their structures and promising activities.

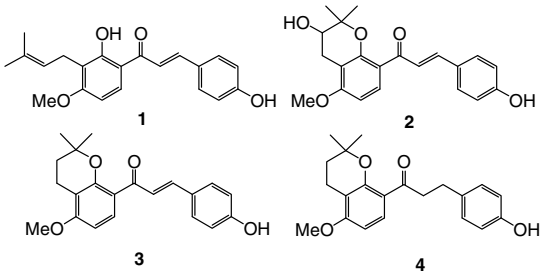
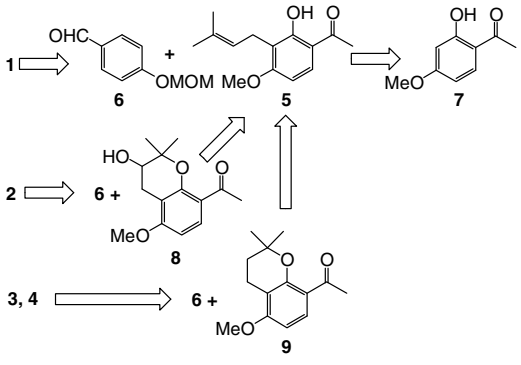


Figure 1.

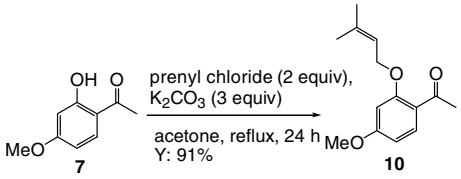
Herein, we report the synthesis of these chalcones **1–4** and evaluation of their antibacterial activity.

4-Hydroxyderricin (**1**) would be prepared by Claisen–Schmidt condensation of the key intermediate **5** with 4-methoxymethoxybenzaldehyde (**6**) (Scheme 1). Compound **5** could be converted from accessible 2′-hydroxy-4′-methoxyacetophenone (**7**). Xanthoangelol H (**2**), deoxyxanthoangelol H (**3**), and deoxydihydroxanthoangelol H (**4**) also would be prepared via **5**.

Treatment of **7** with prenyl chloride in the presence of K_2CO_3 gave prenyloxyacetophenone (**10**) in 91% yield (Scheme 2). The rearrangement of **10** was first attempted in the presence of solid



Scheme 1.



Scheme 2.

* Corresponding author. Tel.: +81 985 58 7390; fax: +81 985 58 7323.
E-mail address: sugamoto@cc.miyazaki-u.ac.jp (K. Sugamoto).

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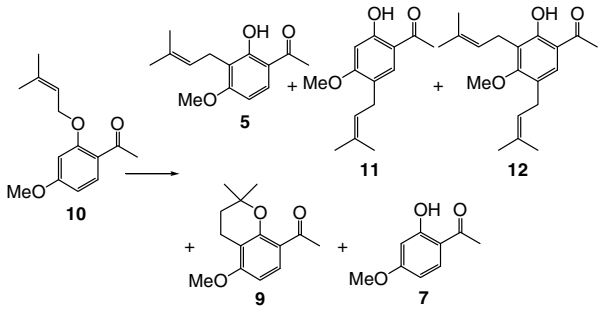
Table 1
Rearrangement of **10** in the presence of solid acid catalyst

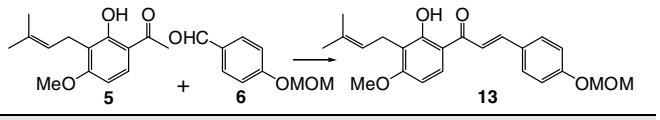


Entry	Conditions	Yield (%)				
		5	**11**	**12**	**9**	**7**
1	Montomorillonite K10 (1 wt equiv), CH_2Cl_2, 0 °C, 0.5 h	53	25	7	0	4
2	Florisil® (10 wt equiv), toluene, reflux, 2 h	27	32	0	8	10

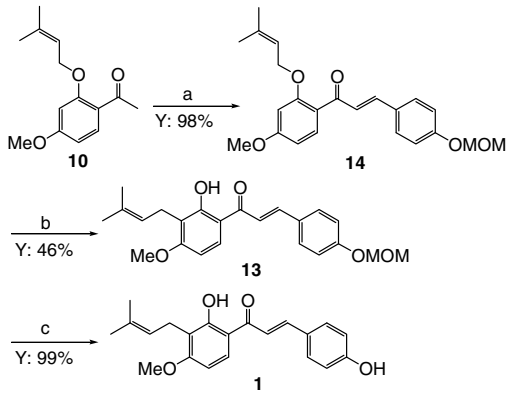
acid catalyst in a procedure similar to that described in the previous reports (Table 1).[12,13] The treatment of **10** in the presence of montmorillonite K10 in CH_2Cl_2 at 0 °C gave desired compound **5** in 53% yield, along with **11** (25%), **12** (7%), and **7** (4%). The rearrangement of **10** using Florisil® in toluene at 110 °C gave **5** as well, but only provided **5** in 27% yield, along with **11** (32%), **7** (8%), and chroman **9** (10%).

Table 2 shows the Claisen–Schmidt condensation of **5** with **6** under several conditions. The yield of chalcone **13** was low in all cases. The low yield is presumably caused by secondary cyclization of 2′-hydroxychalcone to flavanone as reported in the literature.[14] In contrast, condensation of **10** with **6** in the presence of 3 M NaOH afforded the chalcone **14** in good yield (Scheme 3). The rearrangement of **14** using montmorillonite K10 at 0 °C gave the desired

Table 2
Claisen–Schmidt condensation of **5** with **6**



Entry	Conditions	Yield of **13** (%)
1	3 M KOH, EtOH, rt, 24 h	38
2	50% KOH, EtOH, rt, 35 h	33
3	$Ba(OH)_2{\cdot}8H_2O$ (2.5 equiv), EtOH, 50 °C, 1 h	23



Scheme 3. Reagents and conditions: (a) **6** (1.2 equiv), 3 M NaOH, EtOH, rt, 12 h; (b) montmorillonite K10 (1 wt equiv), CH_2CH_2, 0 °C, 1.5 h; (c) *p*-TsOH–H_2O (1 equiv), MeOH, 30 °C, 24 h.

product **13** in 46% yield. 4-Hydroxyderricin (**1**) was synthesized by deprotection of **13** using *p*-toluenesulfonic acid monohydrate at 30 °C in high yield. Compound **1** was prepared in 41% yield over 4 steps from **7** via **14**. Physical and spectral data of synthetic **1** were consistent with those reported for natural **1**.[1]

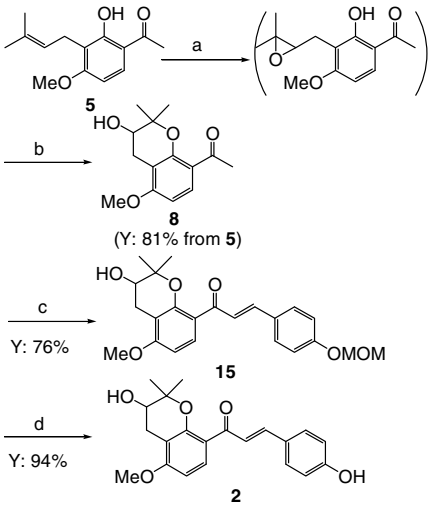
The epoxidation of **5** with *m*-CPBA proceeded at room temperature to afford the epoxide as an intermediate, which was immediately converted into the chroman **8** (Scheme 4). Condensation of **8** with **6** gave chalcone **15** in 76% yield. Xanthoangelol H (**2**) was synthesized by deprotection of **15** using *p*-toluenesulfonic acid monohydrate under reflux in good yield. Physical and spectral data of synthetic **2** were consistent with those reported for natural **2**.[3]

Treatment of **5** in the presence of montmorillonite K10 at 50 °C provided the chroman **9** in high yield (Scheme 5).[15]

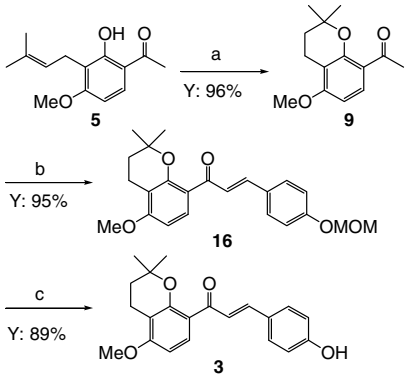
Condensation of **9** with **6** gave the chalcone **16** in 95% yield. Deoxyxanthoangelol H (**3**) was synthesized by deprotection of **16** under similar conditions described above in good yield.

Hydrogenation of **16** in the presence of Pd/C catalyst gave **17** in 94% yield (Scheme 6). Deoxydihydroxanthoangelol H (**4**) was synthesized by deprotection of **17** under similar conditions described above in good yield. Physical and spectral data of synthetic **3** and **4** were consistent with those reported for natural **3**[2] and **4**.[4]

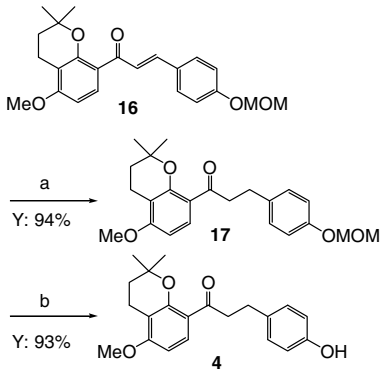
Antibacterial activities of synthesized chalcones **1–4** were investigated against both Gram-negative (*Escherichia coli, Proteus*



Scheme 4. Reagents and conditions: (a) *m*-CPMA (1.2 equiv), CH_2CH_2, rt, 0.5 h; (b) montmorillonite K10 (1 wt equiv), CH_2CH_2, rt, 1 h; (d) **6** (1.2 equiv), 3 M NaOH, EtOH, rt, 20 h; (d) *p*-TsOH–H_2O (1 equiv), MeOH, reflux, 2 h.



Scheme 5. Reagents and conditions: (a) montmorillonite K10 (1 wt equiv), Toluene, 50 °C, under N_2, 40 h; (b) **6** (1.2 equiv), 3 M NaOH, EtOH, rt, 20 h; (c) *p*-TsOH–H_2O (1 equiv), MeOH, reflux, 2 h.



Scheme 6. Reagents and conditions: (a) Pd/C (0.1 wt equiv), under H_2, (1 atm), EtOH, rt, 0.5 h; (b) *p*-TsOH–H_2O (1 equiv), MeOH, reflux, 1 h.

Table 3
Antibacterial effect of compounds **1**–**4**

Entry	Type	Bacterium	MIC (μg/ml)				
			1	**2**	**3**	**4**	Chloramphenicol
1	Gram-negative	*Escherichia coli*	>256	>256	>256	>256	16
2	Gram-negative	*Proteus mirabilis*	>256	>256	>256	>256	02
3	Gram-negative	*Rastonia salanacearum*	2	>256	>256	>256	02
3	Gram-positive	*Bacillus subtilis*	<1	>256	>256	>256	03
4	Gram-positive	*Staphylococcus epidermidis*	1	>256	>256	>256	01

mirabilis, Rastonia salanacearum) and Gram-positive bacteria (*Bacillus subtilis, Staphylococcus epidermidis*). The MIC values are summarized in Table 3. 4-Hydroxyderricin (**1**) showed strong antibacterial activity against *R. salanacearum*, *B. subtilis,* and *S. epidermidis.* Inamori et al. reported that compound **1** have no effect against Gram-negative bacteria.[5] It is interesting to note that compound **1** exhibited strong antibacterial activity against *R. salanacearum.* On the other hand, the other chalcones **2–4** showed no activity. These results suggested that 2′-hydroxy and/or 3′-prenyl groups were important for antibacterial activity.

In conclusion, the described method allowed for the synthesis of **1** in 4 steps with 41% overall yield from commercially available **7**. Compound **2** was prepared in 28% yield at 6 steps, **3** in 39% yield at 5 steps, and **4** in 38% yield at 6 steps from **7** via the key intermediate **5**.

References and notes

1. Delle Monache, G.; de Mèllo, J. F.; Delle Monache, F.; Marini Bettolo, G. B.; Gonçaleves de Lima, O.; Coélhode de Barros, J. S. *Gazz. Chim. Ital.* **1975**, *104*, 861–865.
2. Kozawa, M.; Morita, N.; Baba, K.; Hata, K. *Yakugaku Zasshi* **1978**, *98*, 210–214.
3. Nakata, K.; Taniguchi, M.; Baba, K. *Nat. Med.* **1999**, *53*, 329–332.
4. Akihisa, T.; Tokuda, H.; Hasegawa, D.; Ukiya, M.; Kimura, Y.; Enjo, F.; Suzuki, T.; Nishino, H. *J. Nat. Prod.* **2006**, *69*, 38–42.
5. Inamori, Y.; Baba, K.; Tsujibo, H.; Taniguchi, M.; Nakata, K.; Kozawa, M. *Chem. Pharm. Bull.* **1991**, *39*, 1604–1605.
6. Okuyama, T.; Takata, M.; Takayasu, J.; Hasegawa, T.; Tokuda, H.; Nishino, A.; Nishino, H. *Planta Med.* **1991**, *57*, 242–246.
7. Matsuura, M.; Kimura, Y.; Nakata, K.; Baba, K.; Okuda, H. *Planta Med.* **2001**, *67*, 230–235.
8. Ogawa, H.; Ohno, M.; Baba, K. *Clin. Exp. Pharmacol. Physiol.* **2005**, *32*, 19–23.
9. Kimura, Y.; Taniguchi, M.; Baba, K. *Planta Med.* **2004**, *70*, 205–210.
10. Akihisa, T.; Tokuda, H.; Ukiyo, M.; Iizuka, M.; Schneider, S.; Ogasawara, K.; Mukainaka, T.; Iwatsuki, K.; Suzuki, T.; Nishimoto, H. *Cancer Lett.* **2003**, *201*, 133–137.
11. Nishimura, R.; Tabata, K.; Arakawa, M.; Ito, Y.; Kimura, Y.; Akihisa, T.; Nagai, H.; Sakuma, A.; Kohno, H.; Suzuki, T. *Biol. Pharm. Bull.* **2007**, *30*, 1878–1883.
12. Dintzner, M. R.; Morse, K. M.; McCelland, K. M.; Cologado, D. M. *Tetrahedron Lett.* **2004**, *45*, 79–81.
13. Talamás, F. X.; Smith, D. B.; Cervantes, A.; Franco, F.; Cutler, S. T.; Loughhead, D. G., ; Morgans, D. J., Jr.; Weikert, R. J. *Tetrahedron Lett.* **1997**, *38*, 4725–4728.
14. Formentín, P.; García, H.; Leyva, A. *J. Mol. Catal. A: Chem.* **2004**, *214*, 137–142.
15. Dauben, W. G.; Corgen, J. M.; Behar, V. *Tetrahedron Lett.* **1990**, *31*, 3241–3244.