

Facile Synthesis of Licochalcone C

Cheol Gi Kim, Jae-Ho Jeon, Young Hwa Seo, and Jong-Gab Jun*

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

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

Received January 10, 2014, Accepted March 8, 2014

Licochalcone C was synthesized from commercially available 2,4-dihydroxybenzaldehyde by using regioselective Al_2O_3 -mediated C-prenylation followed by conventional Claisen-Schmidt condensation in basic condition.

Key Words : Licochalcone C, Water-accelerated [3,3]-sigmatropic rearrangement, Al_2O_3 , Prenylation, Claisen-Schmidt condensation

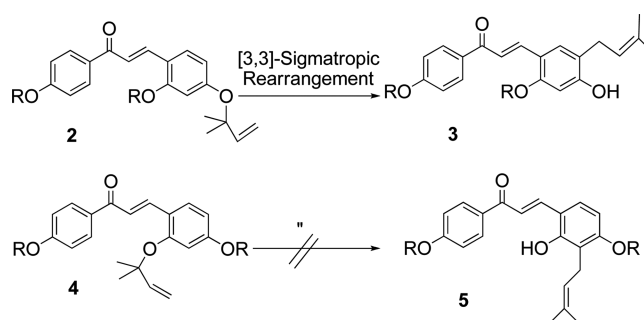
Introduction

Glycyrrhiza inflata is the main species in licorice and contains several licochalcones showing various biological properties, including antibacterial,¹ antitumor,² anti-inflammatory,³ and antioxidative⁴ activities. Of which licochalcone C (**1**) has been known as antioxidant based on the results that it reduces the production of superoxide radicals and consequently reduces the activity of inducible nitric oxide synthase (iNOS) via inhibition of nuclear factor kappa B (NF- κ B) activation.⁵ Licochalcone C also has been known as strong inhibitor against PTP1B enzyme.⁶ However, the study of biological activities for licochalcone C has not been fully elucidated because of the low isolated yield (15 mg) from 2 kg of powdered *Glycyrrhiza glabra*.⁵ Also, the chemical synthesis of licochalcone C in the literature has been reported by only two, but one procedure⁷ used commercially unavailable starting material and the other synthesis⁸ showed a low total yield (6% with 4 steps).

Water-accelerated [3,3]-sigmatropic rearrangement reaction has been introduced in the licochalcone A synthesis⁹ in our group, and also utilized for the synthesis of licochalcone D¹⁰ and E.¹¹ As long as the necessity of large quantities of licochalcone C for its biological studies, the synthetic challenge is required by using water-accelerated [3,3]-sigmatropic rearrangement reaction or other methods.

Results and Discussion

Water-accelerated [3,3]-sigmatropic rearrangement of chalcone **2** produced regioselectively only **3** in licochalcone A synthesis,⁹ however, chalcone **4** failed to give the desired product **5** for licochalcone C synthesis in every efforts with different conditions and protecting groups (Scheme 1). It is



Scheme 1. Regioselective prenylation in water-accelerated [3,3]-sigmatropic rearrangement reaction.

noteworthy that only the MOE protected **4** produced the desired product **5** in the [3,3]-sigmatropic rearrangement condition, but it was also decomposed in the course of the deprotection step.

Regioselective C-prenylation of phenol **6** is a key step in the licochalcone C synthesis, and several attempts instead of sigmatropic rearrangement were applied with prenylating agent **7** in various conditions as shown in Table 1. *n*-BuLi (entry 1)¹² or DBU condition (entry 2)¹³ showed no expected product, however prenylation promoted by aluminum oxide (entry 3)¹⁴ produced the desired product **8** in 21% yield. Aluminum oxide complex with BaO (entry 4) or ZnO (entry 5) also gave the same product in similar yield. Friedel-Crafts reaction using Lewis acids (entries 6-8)¹⁵ did not give the prenylated product. Strong base condition using KOH (entries 9-10)¹⁶ gave only undesired regioisomer **9**.

Licochalcone C is synthesized from the C-prenylated product **8** prepared using Al_2O_3 , thus regioselective protection of **8** to **10** in 95% yield followed by methylation using K_2CO_3 with MeI to give **11** in 81% yield, and base-mediated Claisen-Schmidt condensation with acetophenone **12** allow-

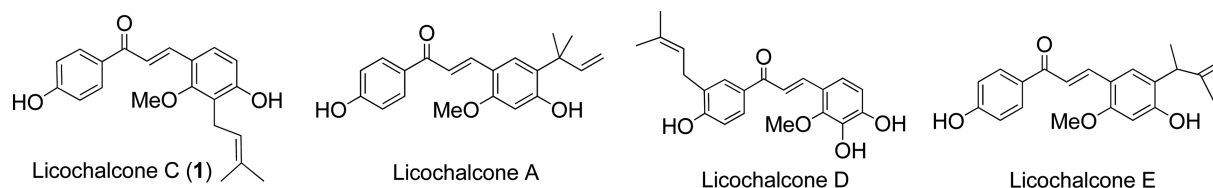
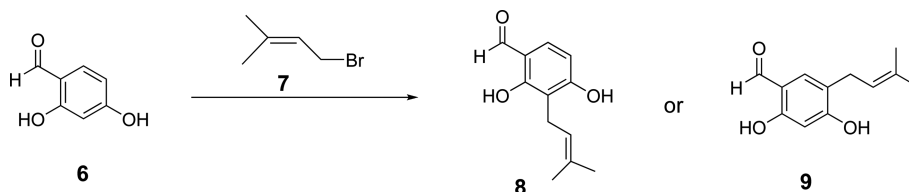
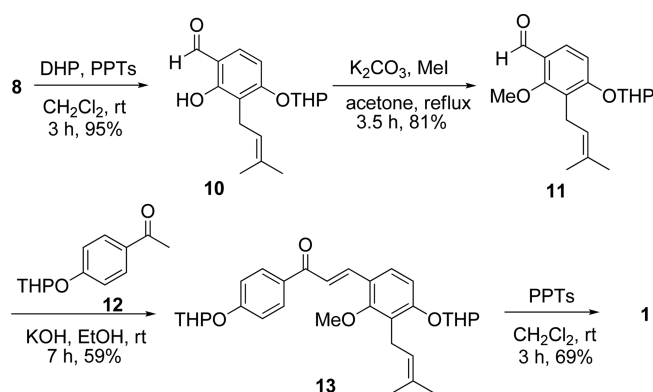


Figure 1. Structure of licochalcones C, A, D and E.

Table 1. C-Prenylation reaction of phenol **6**

Entry	Reaction condition	Solvent	Temp (time)	Product (%yield)
1	<i>n</i> -BuLi	cyclohexane → Et ₂ O	rt (1 h) → reflux (3 h)	-
2	DBU	THF	rt (48 h)	-
3	Al ₂ O ₃	Et ₂ O	rt (72 h)	8 (21%)
4	BaO-Al ₂ O ₃ (1:1)	Et ₂ O	rt (72 h)	8 (20%)
5	ZnO-Al ₂ O ₃ (1:1)	Et ₂ O-hexane(1:3)	rt (72 h)	8 (18%)
6	ZnCl ₂	CH ₂ Cl ₂	rt (20 h)	-
7	TiCl ₄	CH ₂ Cl ₂	rt (20 h)	-
8	SnCl ₂	CH ₂ Cl ₂	rt (20 h)	-
9	KOH	H ₂ O	rt (4 h)	9 (30%)
10	KOH	MeOH	rt (24 h)	-

**Scheme 2.** Synthesis of licochalcone C (**1**).

ed the chalcone **13** in 59% yield (Scheme 2). Finally, pyridinium *p*-toluenesulfonate (PPTs)-mediated deprotection produced the licochalcone C in 69% yield, without having any decomposed problems. The synthetic licochalcone C was crystallized as yellow needles and mp was 197–199 °C, which was never reported in the previous reports. Even though ¹H NMR data of the product were well matched with the references,^{5,8} but the ¹³C NMR data were quite different with those in the reference.⁸ There are 14 *sp*² with 5 *sp*³ carbons in the reference, while we reports 15 *sp*² with 4 *sp*³ carbons in the ¹³C NMR data.

In summary, we prepared licochalcone C by using Al₂O₃-mediated C-prenylation, regioselective protection and methylation, followed by conventional Claisen-Schmidt condensation in basic condition. Direct water-accelerated [3,3]-sigmatropic rearrangement reaction of chalcones could not be employed in the licochalcone C synthesis due to the decomposition problems, however we found the regioselective C-prenylation using Al₂O₃ for a new additional licochalcone C synthesis.

Experimental

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. Mass spectra were recorded using a JMS-700 (JEOL) spectrometer. Melting points were measured on a MEL-TEMP II apparatus and were uncorrected. Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F₂₅₄ (Merck, layer thickness 0.2 mm) plastic-backed *silica* gel plates and visualized by UV light (254 nm) or staining with *p*-anisaldehyde.

2,4-Dihydroxy-3-(3-methylbut-2-en-1-yl)benzaldehyde (8). To a 2,4-dihydroxybenzaldehyde (**6**) (100 mg, 0.66 mmol), Al₂O₃ (5 g, 49 mmol) in diethyl ether (50 mL) was added 1-bromo-3-methyl-2-butene (**7**) under nitrogen atmosphere and stirred for 72 h at rt. Al₂O₃ was filtered by glass filter. The reaction mixture was extracted with CH₂Cl₂, dried over anhydrous Na₂SO₄, concentrated *in vacuo*, and purified by *silica* gel flash column chromatography (EtOAc/hexane = 1/5) to give a clean white solid (30 mg, 21%). R_f 0.42 (EtOAc/hexane = 1/3); mp 119–121 °C; ¹H NMR (300 MHz, CDCl₃) δ 11.70 (1H, s), 9.64 (1H, s), 7.28 (1H, d, *J* = 9.0 Hz), 6.65 (1H, br s), 6.47 (1H, d, *J* = 9.0 Hz), 5.25 (1H, t, *J* = 6.3 Hz), 3.42 (2H, d, *J* = 6.0 Hz), 1.82 (3H, s), 1.75 (3H, s). ¹³C NMR (75 MHz, CDCl₃) δ 194.4, 162.3, 161.6, 135.5, 133.4, 120.7, 115.0, 114.0, 108.8, 25.8, 21.5, 18.0.

2-Hydroxy-3-(3-methylbut-2-en-1-yl)-4-[(tetrahydro-2H-pyran-2-yl)oxy]benzaldehyde (10). To a 2,4-dihydroxy-3-(3-methylbut-2-en-1-yl)benzaldehyde (**8**) (34 mg, 0.16 mmol), PPTs (4 mg, 0.02 mmol) in CH₂Cl₂ (3 mL) was added slowly DHP (16 mg, 0.19 mmol) under nitrogen atmos-

phere and stirred for 4 h at rt. The reaction mixture was extracted with CH₂Cl₂, dried over anhydrous MgSO₄, concentrated *in vacuo*, and purified by silica gel flash column chromatography (EtOAc/hexane = 1/3) to give a yellow solid (47 mg, 95%). R_f 0.70 (EtOAc/hexane = 1/3); mp 40 °C; ¹H NMR (300 MHz, CDCl₃) δ 11.45 (1H, s), 9.68 (1H, s), 7.30 (1H, d, *J* = 8.7 Hz), 6.77 (1H, d, *J* = 8.7 Hz), 5.23 (1H, t, *J* = 6.9 Hz), 4.94 (1H, t, *J* = 4.8 Hz), 3.81 (1H, d, t, *J* = 11.1, 2.7 Hz), 3.61 (2H, d, *J* = 7.2 Hz), 3.39 (1H, t, *J* = 7.8 Hz), 1.78 (3H, s), 1.71 (6H, m), 1.67 (3H, s). ¹³C NMR (75 MHz, CDCl₃) δ 194.6, 161.3, 160.9, 133.0, 131.6, 121.8, 117.7, 115.7, 106.4, 95.8, 61.9, 30.1, 25.8, 25.1, 21.8, 18.4, 17.9.

2-Methoxy-3-(3-methylbut-2-en-1-yl)-4-[(tetrahydro-2H-pyran-2-yl)oxy]benzaldehyde (11). To a 2-hydroxy-3-(3-methylbut-2-en-1-yl)-4-[(tetrahydro-2H-pyran-2-yl)oxy]benzaldehyde (**10**) (540 mg, 1.86 mmol) in acetone (15 mL) was added slowly K₂CO₃ (514 mg, 3.72 mmol) under nitrogen atmosphere and stirred for 10 min at rt. MeI (0.13 mL, 2.23 mmol) was added slowly to this reaction mixture and stirred for 3.5 h at rt. After completion of reaction, the solvent was evaporated. The reaction mixture was extracted with CH₂Cl₂, dried over anhydrous Na₂SO₄, concentrated *in vacuo*, and purified by silica gel flash column chromatography (EtOAc/hexane = 1/7) to give a yellow liquid (459 mg, 81%). R_f 0.70 (EtOAc/hexane = 1/3); ¹H NMR (300 MHz, CDCl₃) δ 10.18 (1H, s), 7.69 (1H, d, *J* = 9.0 Hz), 6.99 (1H, d, *J* = 9.0 Hz), 5.19 (1H, t, *J* = 6.9 Hz), 4.94 (1H, t, *J* = 4.8 Hz), 3.87 (3H, s), 3.63 (2H, d, *J* = 7.2 Hz), 3.49 (3H, m), 1.79 (3H, s), 1.73 (5H, m), 1.69 (3H, s). ¹³C NMR (75 MHz, CDCl₃) δ 188.9, 162.3, 161.0, 131.5, 128.3, 124.3, 123.2, 122.5, 110.3, 95.9, 62.9, 62.0, 30.7, 25.5, 25.1, 22.8, 18.5, 18.0.

3-{2-Methoxy-3-(3-methylbut-2-en-1-yl)-4-[(tetrahydro-2H-pyran-2-yl)oxy]phenyl}-1-{4-[(tetrahydro-2H-pyran-2-yl)oxy]phenyl}prop-2-en-1-one (13). To a 2-methoxy-3-(3-methylbut-2-en-1-yl)-4-[(tetrahydro-2H-pyran-2-yl)oxy]benzaldehyde (**11**) (80 mg, 0.26 mmol), 1-[4-(tetrahydro-2H-pyran-2-yloxy)phenyl]ethanone (**12**) (64 mg, 0.31 mmol) in EtOH (5 mL) was added KOH (59 mg, 1.05 mmol), and stirred for 6 h at rt. After completion of reaction, the solvent was evaporated. The reaction mixture was extracted with CH₂Cl₂, dried over anhydrous MgSO₄, concentrated *in vacuo*, and purified by silica gel flash column chromatography (EtOAc/hexane = 1/4) to give a yellow liquid (75.5 mg, 59%). R_f 0.73 (EtOAc/hexane = 1/3); ¹H NMR (300 MHz, CDCl₃) δ 7.99 (2H, d, *J* = 9.0 Hz), 7.98 (1H, d, *J* = 15.3 Hz), 7.51 (1H, d, *J* = 8.4 Hz), 7.50 (1H, d, *J* = 16.5 Hz), 7.10 (2H, d, *J* = 9.0 Hz), 6.95 (1H, d, *J* = 8.1 Hz), 5.52 (1H, t, *J* = 3.0 Hz), 5.49 (1H, t, *J* = 3.0 Hz), 5.21 (1H, t, *J* = 6.9 Hz), 3.85 (2H, m), 3.76 (3H, s), 3.61 (2H, d, *J* = 7.2 Hz), 3.41 (2H, m), 1.89 (6H, m), 1.79 (3H, s), 1.72 (6H, m), 1.68 (3H, s). ¹³C NMR (75 MHz, CDCl₃) δ 189.0, 160.5, 158.9, 157.7, 139.6, 132.0, 131.1, 130.4, 126.8, 124.7, 123.0, 121.9, 120.9, 115.9, 110.4, 96.0, 95.9, 62.3, 62.0, 61.9, 30.3, 30.2, 25.8, 25.3, 25.1, 23.3, 18.6, 18.0.

3-[4-Hydroxy-2-methoxy-3-(3-methylbut-2-en-1-yl)phenyl]-1-(4-hydroxyphenyl)prop-2-en-1-one; Licochalcone C (1). To a 3-{2-Methoxy-3-(3-methylbut-2-en-1-yl)-4-[(tetra-

hydro-2H-pyran-2-yl)oxy]phenyl}-1-{4-[(tetrahydro-2H-pyran-2-yl)oxy]phenyl}prop-2-en-1-one (**13**) (40 mg, 0.08 mmol) in MeOH (1 mL) was added PPTs (16 mg, 0.04 mmol), and stirred for 3 h at rt. After completion of reaction, the solvent was evaporated. The reaction mixture was extracted with CH₂Cl₂, dried over anhydrous MgSO₄, concentrated *in vacuo*, and purified by silica gel flash column chromatography (EtOAc/hexane = 1/3) to give a yellow needles (18 mg, 69%). R_f 0.28 (EtOAc/hexane = 1/1); mp 197-199 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.00 (1H, d, *J* = 15.6 Hz, H-β), 7.97 (2H, d, *J* = 8.1 Hz), 7.49 (1H, d, *J* = 15.6 Hz, H-α), 7.46 (1H, d, *J* = 8.7 Hz), 6.93 (2H, d, *J* = 8.1 Hz), 6.68 (1H, d, *J* = 8.7 Hz), 6.06 (2H, br s, two OHs), 5.22 (1H, t, *J* = 6.6 Hz), 3.74 (3H, s), 3.44 (2H, d, *J* = 6.6 Hz), 1.83 (3H, s), 1.75 (3H, s). ¹³C NMR (75 MHz, CDCl₃) δ 189.6, 160.3, 159.0, 158.3, 140.0, 135.4, 131.1, 130.9, 127.1, 121.3, 121.0, 120.9, 120.2, 115.4, 112.7, 62.6, 25.9, 23.2, 18.1; EIMS *m/z* 338 (M⁺), 323 (base), 308, 252, 121, 93, 65. HRMS (EI) calcd for C₂₁H₂₂O₄ 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, 2013 (HRF-201310-011).

References

- Kwon, H. S.; Park, J. H.; Kim, D. H.; Kim, Y. H.; Park, J. H.; Shin, H. K.; Kim, J. K. *J. Mol. Med. (Berl)* **2008**, *86*, 1287.
- Yoon, G.; Jung, Y. D.; Cheon, S. H. *Chem. Pharm. Bull.* **2005**, *53*, 694.
- Cho, Y.-C.; Lee, S. H.; Yoon, G.; Kim, H.-S.; Na, J. Y.; Choi, H. J.; Cho, C.-W.; Cheon, S. H.; Kang, B. Y. *Int. Immunopharmacol.* **2010**, *10*, 1119.
- Haraguchi, H.; Ishikawa, H.; Mizutani, K.; Tamura, Y.; Kinoshita, T. *Bioorg. Med. Chem.* **1998**, *6*, 339.
- Franceschelli, S.; Pesce, M.; Vinciguerra, I.; Ferrone, A.; Riccioni, G.; Patruno, A.; Grilli, A.; Felaco, M.; Speranza, L. *Molecules* **2011**, *16*, 5270.
- Yoon, G.; Lee, W.; Kim, S. N.; Cheon, S. H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5155.
- Nielsen, S. F.; Chen, M.; Theander, T. G.; Kharazmi, A.; Christensen, S. B. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 449.
- Wang, Z.; Cao, Y.; Paudel, S.; Yoon, G.; Cheon, S. H. *Arch. Pharm. Res.* **2013**, *36*, 1432.
- Jeon, J.-H.; Kim, M. R.; Jun, J.-G. *Synthesis* **2011**, *43*, 370.
- Kim, S.-J.; Jun, J.-G. *Bull. Korean Chem. Soc.* **2013**, *34*, 54.
- Jeon, J.-H.; Kim, M. R.; Kwon, E. M.; Lee, N. R.; Jun, J.-G. *Bull. Korean Chem. Soc.* **2011**, *32*, 1059.
- Simas, A. B. C.; Coelho, A. *Synthesis* **1999**, *6*, 1017.
- Lee, Y. R.; Li, X.; Lee, W. L.; Yong, C. S.; Hwang, M. R.; Lyoo, W. S. *Bull. Korean Chem. Soc.* **2008**, *29*, 1205.
- (a) Glusenkamp, K.; Buchi, G. *J. Org. Chem.* **1986**, *51*, 4483. (b) Liu, Z.; Lee, W.; Kim, S.-N.; Yoon, G.; Cheon, S. H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3755.
- Helesbeux, J.-J.; Duval, O.; Ruilet, D.; Seraphin, D.; Rondeau, D. *Tetrahedron* **2003**, *59*, 5091.
- Rao, G. V.; Swamy, B. N.; Chandregowda, V.; Reddy, G. C. *Eur. J. Med. Chem.* **2009**, *44*, 2239.