An Efficient First Synthesis of Licochalcone G

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Chalcones (1,3-diarylpropenones) constitute one of the major classes of flavonoids with widespread distribution in plant kingdom.[1] Prehistoric therapeutic applications of these small and nonchiral molecules can be associated with the 1000-year-old use of plants and herbs for the treatment of different medical disorders. Chalcones have a conjugated double bond and an entirely delocalized π-electron system on both benzene rings which attributes nonlinear optical properties to them.[2] Several natural and nonnatural chalcones have been investigated as anti-inflammatory,[3] anti-oxidant,[4] antimicrobial,[5] antiprotozoal (antileishmanial and antitrypanosomal),[6] anticancer,[7] antibacterial,[8] antiviral,[9] antihyperglycemic,[10] antiplatelet,[11] anti-ulcerative,[12] antitubercular,[13] anti-angiogenic,[14] and antiplasmodial[15] agents. They have also shown inhibitory effects on several enzymes.[16] Chalcones are important precursors in the biosynthesis of flavones and flavanones. The chemistry and therapeutic applications of chalcones have triggered extensive and enduring efforts toward the syntheses of these important compounds throughout the world.

Licochalcone G (**7**, Figure 1) was isolated from the acetone extract of *Glycyrrhiza inflata*.[17] *G. inflata* is the main species in licorice, contains numerous retrochalcones and showed various biological properties. Licorice has been used by human beings for over 4000 years and it appears as a component herb in about 60% of traditional Chinese medicine prescriptions. Licochalcone G (**7**) showed anti-influenza (H1N1 swine influenza) activity.[17] To date, synthesis of this important chalcone was not reported in the literature.

Previously, we have reported the synthesis of licochalcones A–E (**1–5**).[18] In continuation of our work on the synthesis of these bioactive natural products and their derivatives, herein we wish to describe the first synthesis of licochalcone G (**7**) using water-accelerated [3,3]-sigmatropic rearrangement and Claisen–Schmidt condensation as key steps.

Retrosynthetic approach for licochalcone G (**7**) synthesis is depicted in Scheme 1. We envisaged that the target molecules could be achieved from intermediate **8** by deprotection. Compound **8** could easily be prepared from compounds **9** and **10** by means of Claisen–Schmidt condensation. Compound **9** could be obtained from 2,4,-dihydroxyacetophenone (**11**) whereas compound **10** could be prepared from 4-hydroxy-2-methoxy benzaldehyde (**12**).

Accordingly, we commenced the synthesis from 2,4,-dihydroxyacetophenon (**11**). As shown in Scheme 2, allyl protection of compound **11** using K_2CO_3/NaI system in DMF at 60 °C afforded the diallyl protected 2,4-dihydroxyacetophenone **9** in 98% yield. Next, treatment of 4-hydroxy-2-methoxy benzaldehyde (**12**) with 1-bromo-3-methyl-2-butene (prenyl bromide) in the presence of K_2CO_3 in acetone under reflux condition gave compound **13** in 97% yield. The aryl prenyl ether **13** was then subjected to water-accelerated [3,3]-sigmatropic rearrangement reaction using EtOH/H_2O (v/v = 4/1) in pressure tube afforded the product **14** in 53% yield. The phenolic ─OH group of compound **14** was protected as ethoxymethyl aryl ether (EOM─O─Ar). The choice of protecting group is quite important in the chalcone synthesis in many aspects such as yield, migration, deprotection, etc. Treatment of compound **14** with chloromethyl ethyl ether (EOM─Cl) using K_2CO_3 in DMF at room temperature resulted the compound **10** in 81% yield. Claisen–Schmidt condensation of compound **9** and **10** using ethanolic KOH at room temperature in 15 h produced the protected chalcone **8** in 52% yield. The *trans*-configuration was confirmed with coupling constant (J = 16.2 Hz) between the two doublet signals at δ 7.98 and 7.56, a presentative coupling pattern for the protons in the conjugated alkene system. Treatment of compound **8** with Dowex resin in anhydrous methanol at room temperature gave the EOM-free chalcone in 60% yield. Finally, allyl group deprotection was achieved using K_2CO_3 and catalytic amount of $Pd(PPh_3)_4$ (2 mol %) in anhydrous MeOH at 60 °C to furnish the desired natural chalcone licochalcone G in 85% yield.

In conclusion, we have developed an efficient approach for the first synthesis of licochalcone G. Water-accelerated [3,3]-sigmatropic rearrangement and Claisen–Schmidt condensation are the key transformations of the present method. We feel, the present synthetic route may find application for the construction of different natural and nonnatural chalcones of this kind.

Experimental

All chemicals were purchased from Sigma-Aldrich (Munich, Germany) and Alfa Aesar Chemicals (Karlsruhe, Germany) and were used without further purification unless noted

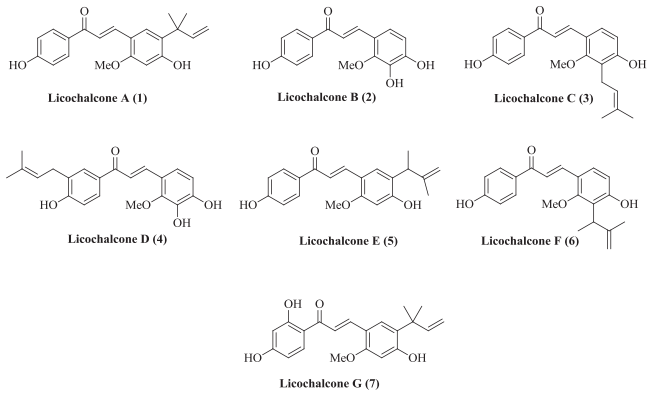
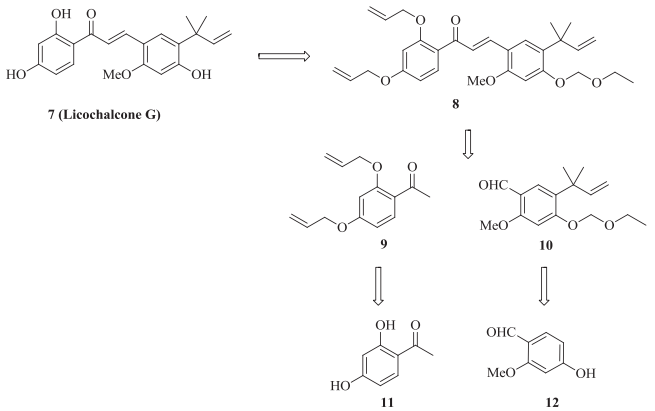


Figure 1. Structures of licochalcones A–G (**1–7**).



Scheme 1. Retrosynthetic analysis for the synthesis of licochalcone G (**7**).

otherwise. ^{1}H-NMR spectra were recorded at Varian Mercury-300 MHz FT-NMR (Varian Inc., Palo Alto, CA, USA) and 75 MHz for ^{13}C, with the chemical shift (δ) reported in parts per million (ppm) relative to tetramethylsilane (TMS) and the coupling constants (*J*) quoted in Hz. $CDCl_3$ was used as a solvent and an internal standard. Mass spectra were recorded using a JMS-700 (JEOL. Ltd, Tokyo, Japan) spectrometer. Melting points were measured on a MEL-TEMP II apparatus and were uncorrected. Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F_{254} (layer thickness 0.2 mm; Merck, Darmstadt, Germany) plastic-backed silica gel plates and visualized by UV light (254 nm) or staining with *p*-anisaldehyde.

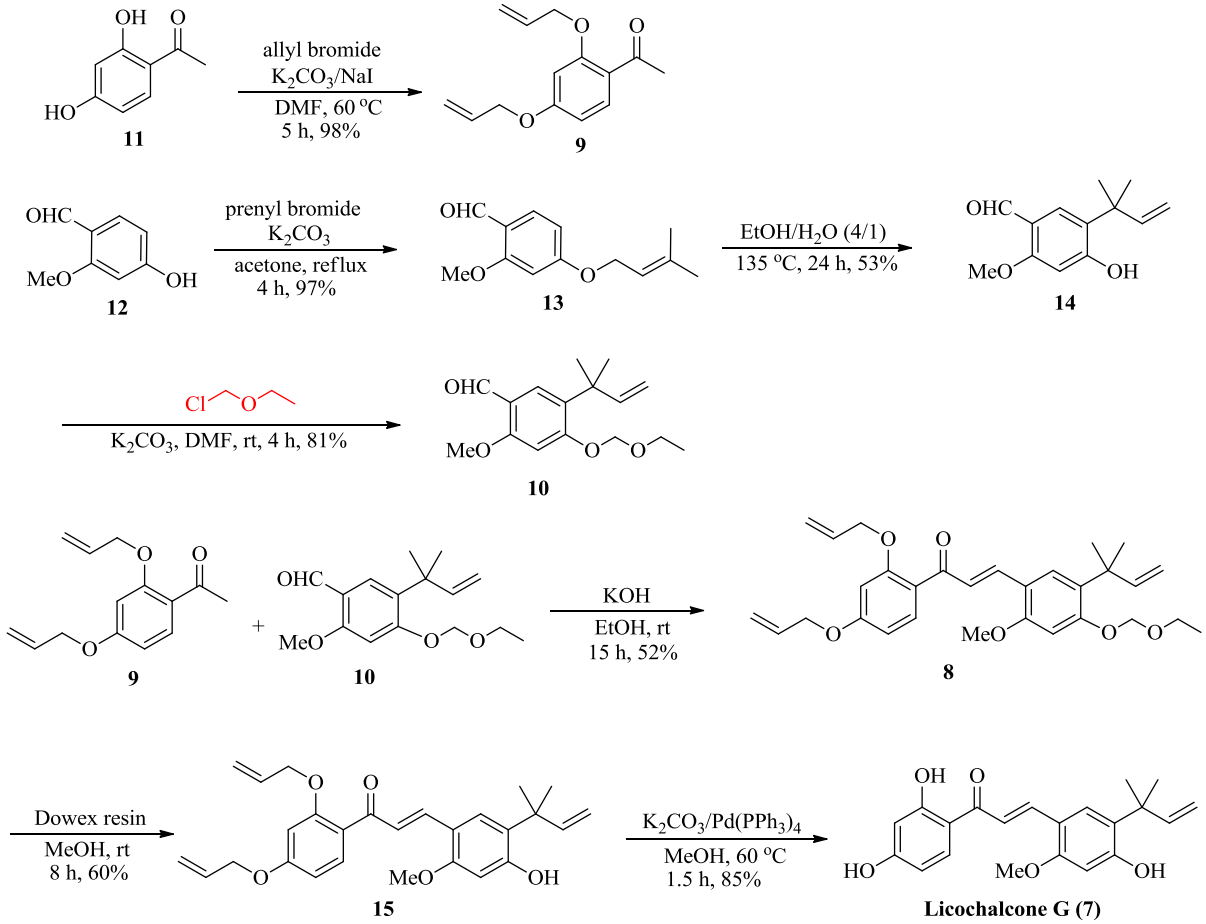
1-(2,4-Bis(allyloxy)phenyl)ethanone (9): To a suspension of 2,4-dihydroxyacetophenone (0.30 g, 2.0 mmol), K_2CO_3 (0.69 g, 5 mmol), and NaI (0.09 g, 0.6 mmol) in anhydrous DMF (10 mL) was added allyl bromide (0.42 mL, 4.8 mmol) dropwise at room temperature under nitrogen atmosphere. The mixture was then stirred at 60 °C for 5 h. After completion of the reaction, the mixture was cooled to room temperature and water (20 mL) was added. The mixture was then extracted with ether (3 × 40 mL), and the combined organic layer was washed with water (2 × 40 mL), brine (2 × 40 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by column chromatography (EtOAc/hexane = 1/8) to yield the compound **9** (0.45 g, 98%) as white solid. R_f = 0.4 (EtOAc/hexane = 1/5); mp = 40–42 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (1H, d, *J* = 8.7 Hz), 6.52 (1H, dd, *J* = 8.7, 1.8 Hz), 6.46 (1H, d, *J* = 1.8 Hz), 6.12–5.97 (2H, m), 5.46–5.38 (2H, m), 5.34–5.29 (2H, m), 4.61–4.55 (4H, m), 2.60 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 163.0, 159.7, 132.4, 132.3, 132.2, 121.2, 118.1, 118.0, 105.9, 99.8, 69.3, 68.8, 32.0.

2-Methoxy-4-[(3-methylbut-2-en-1-yl)oxy] benzaldehyde (13): To a stirred suspension of 4-hydroxy-2-metoxybenzaldehyde **12** (0.50 g, 3.29 mmol) and K_2CO_3 (1.26 g, 9.86 mmol) in acetone (15 mL) was added 1-bromo-3-methyl-2-butene (0.42 mL, 3.62 mmol) dropwise at room temperature under nitrogen atmosphere. The mixture was then refluxed for 4 h. After completion of the reaction, the mixture was cooled to room temperature, filtered through celite pad and washed with acetone (30 mL). The filtrate was concentrated *in vacuo*. EtOAc (30 mL) and H_2O (20 mL) were added to the residue and two layers were separated. The aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layer was washed with brine (2 × 40 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/4) to yield the compound **13** (0.70 g, 97%) as white solid.

R_f = 0.30 (EtOAc/hexane = 1/3); mp = 47–49 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.26 (1H, s), 7.79 (1H, d, *J* = 8.7 Hz), 6.54 (1H, dd, *J* = 8.7, 2.4 Hz), 6.45 (1H, d, *J* = 2.4 Hz), 5.48 (1H, t, *J* = 6.9 Hz), 4.57 (2H, d, *J* = 6.9 Hz), 3.88 (3H, s), 1.79 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.1, 165.3, 163.3, 139.2, 130.6, 118.8, 118.6, 106.1, 98.6, 65.2, 55.6, 26.0, 18.4.

4-Hydroxy-2-methoxy-5-(2-methylbut-3-en-2-yl)benzaldehyde (14): Compound **13** (0.60 g, 2.72 mmol) was dissolved in EtOH–H_2O (4:1 v/v, 10 mL) in a 35-mL Ace pressure tube with Polytetrafluoroethylene (PTFE) bushes and an Fluoroelastomer with TFE addotives (FETFE) O-ring seal. The tube was then placed in an electric furnace at 135 °C for 24 h. When the tube had cooled to room temperature, the screw-cap was loosened, and the mixture was transferred to a 100-mL round-bottom flask. The solvent was then evaporated *in vacuo*. EtOAc (30 mL) was added and the organic phase was washed with deionized distilled H_2O (20 mL) and brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane = 1/4) to give compound **14** (0.30 g, 53%) as white solid. R_f = 0.2 (EtOAc/hexane = 1/3); mp = 194–196 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.27 (1H, s), 7.77 (1H, s), 6.60 (1H, s), 6.42 (1H, s), 6.17 (1H, dd, *J* = 17.7, 10.8 Hz), 5.38 (1H, dd, *J* = 17.7, 1.0 Hz), 5.35 (1H, dd, *J* = 10.8, 1.0 Hz), 3.87 (3H, s), 1.44 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.3, 162.7, 161.9, 147.5, 127.2, 124.8, 118.3, 114.4, 100.6, 55.7, 39.8, 27.1.

4-(Ethoxymethoxy)-2-methoxy-5-(2-methylbut-3-en-2-yl)benzaldehyde (10): To a stirred suspension of compound



Scheme 2. Synthesis of licochalcone G (**7**).

14 (0.24 g, 1.08 mmol) and K_2CO_3 (0.45 g, 3.28 mmol) in DMF (8 mL) was added chloromethyl ethyl ether (EOM—Cl) (0.15 mL, 1.62 mmol) dropwise at room temperature under nitrogen atmosphere. The mixture was stirred for 4 h at this temperature. After completion of the reaction, water (10 mL) was added. The mixture was then extracted with ether (2 × 30 mL), the combined organic layer was washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. The crude residue was purified by column chromatography (EtOAc/hexane = 1/7) to yield the compound **10** (0.24 g, 81%) as colorless liquid. R_f = 0.48 (EtOAc/hexane = 1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.30 (1H, s), 7.79 (1H, s), 6.76 (1H, s), 6.09 (1H, dd, J = 17.4, 10.5 Hz), 5.30 (2H, s), 4.93 (1H, dd, J = 17.4, 0.9 Hz), 4.87 (1H, dd, J = 10.5, 0.9 Hz), 3.91 (3H, s), 3.73 (2H, q, J = 6.9 Hz), 1.46 (6H, s), 1.26 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.4, 162.4, 162.3, 147.3, 129.2, 127.3, 118.0, 110.1, 98.0, 92.6, 64.6, 55.7, 40.1, 27.5, 15.1.

(*E*)-1-(2,4-Bis(allyloxy)phenyl)-3-(4-(ethoxymethoxy)-2-methoxy-5-(2-methylbut-3-en-2-yl)phenyl)prop-2-en-1-one (8): To a stirred solution of compound **9** (0.07 g, 0.3 mmol) and compound **10** (0.1 g, 0.36 mmol) in EtOH (5 mL) was added KOH (0.25 g, 4.52 mmol) at room temperature. The mixture was stirred at room temperature for 15 h. After completion of the reaction, deionized water (15 mL) was added, and the solution was extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by column chromatography (EtOAc/hexane = 1/7) to yield the compound **8** (0.07 g, 52%) as pale yellow color viscous oil.

R_f = 0.51 (EtOAc/hexane = 1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (1H, d, J = 16.2 Hz), 7.71 (1H, d, J = 8.7 Hz), 7.56 (1H, d, J = 16.2 Hz), 7.51 (1H, s), 6.75 (1H, s), 6.55 (1H, dd, J = 8.7, 2.1 Hz), 6.50 (1H, d, J = 2.1 Hz), 6.16–5.98 (3H, m), 5.46–5.16 (6H, m), 4.94 (2H, s), 4.61–4.56 (4H, m), 3.84 (3H, s), 3.73 (2H, q, J = 6.9 Hz), 1.44 (6H, s), 1.24 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 162.3, 158.8, 158.7, 158.4, 148.0, 147.7, 137.8, 132.5, 132.4, 128.7, 127.5, 125.0, 123.2, 118.0, 117.4, 116.5, 109.8, 106.0, 100.3, 98.7, 92.7, 69.2, 68.9, 64.3, 55.6, 40.1, 27.5, 15.2.

(*E*)-1-(2,4-Bis(allyloxy)phenyl)-3-(4-hydroxy-2-methoxy-5-(2-methylbut-3-en-2-yl)phenyl)prop-2-en-1-one (15): To a stirred solution of compound **8** (30.0 mg, 0.06 mmol) in anhydrous MeOH (5 mL) was added Dowex® 50X2-100 (Sigma-Aldrich, Munich, Germany) resin (0.03 g)

at room temperature under nitrogen atmosphere. The mixture was stirred for 8 h at room temperature. After completion of the reaction, resin was filtered and washed with EtOAc (15 mL). The filtrate was concentrated *in vacuo*. Crude residue was purified by column chromatography (EtOAc/hexane = 1/5) to yield the compound **15** (16.0 mg, 60%) as pale yellow color viscous oil. R_f 0.51 (EtOAc/hexane = 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (1H, d, J = 16.2 Hz), 7.71 (1H, d, J = 8.4 Hz), 7.55 (1H, d, J = 16.2 Hz), 7.47 (1H, s), 6.55 (1H, dd J = 8.4, 2.1 Hz), 6.49 (1H, d, J = 2.1 Hz), 6.41 (1H, s), 6.36 (1H, s), 6.17 (1H, dd J = 17.7, 10.8 Hz), 6.11–5.98 (2H, m), 5.47–5.20 (6H, m), 4.61–4.56 (4H, m), 3.80 (3H, s), 1.42 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1, 162.4, 159.1, 158.8, 157.8, 147.7, 138.1, 132.6, 132.5, 132.4, 127.4, 124.9, 124.2, 123.1, 118.1, 117.4, 116.5, 113.7, 106.0, 100.9, 100.3, 69.2, 68.9, 55.5, 39.8, 27.1.

(*E*)-1-(2,4-Dihydroxyphenyl)-3-(4-hydroxy-2-methoxy-5-(2-methylbut-3-en-2-yl)phenyl)prop-2-en-1-one (Licochalcone G) (7): To a suspension of compound **15** (16.0 mg, 0.04 mmol) and K_2CO_3 (31.0 mg, 0.22 mmol) in anhydrous MeOH (3 mL) was added $Pd(PPh_3)_4$ (1.0 mg, 0.002 mmol) at room temperature under nitrogen atmosphere. The mixture was then stirred at 60 °C for 1.5 h. After completion of the reaction, 1 N HCl (1 mL) was added and then the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with water (2 × 20 mL), brine (2 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by column chromatography (EtOAc/hexane = 1/3) to yield the compound **7** (12.0 mg, 85%) as yellow color semi solid. R_f = 0.51 (EtOAc/hexane = 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (1H, d, J = 15.0 Hz), 7.84 (1H, d, J = 8.7 Hz), 7.66 (1H, d, J = 15.0 Hz), 7.48 (1H, s), 6.48–6.42 (2H, br s), 6.45 (1H, d, J = 8.7 Hz), 6.43 (1H, s), 6.33 (1H, s), 6.21 (1H, dd, J = 17.7, 10.8 Hz), 5.82 (1H, br s), 5.42 (1H, dd, J = 17.7, 1.2 Hz), 5.38 (1H, dd, J = 10.8, 1.2 Hz), 3.92 (3H, s), 1.48 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.8, 166.4, 162.3, 161.7, 160.0, 158.7, 147.9, 141.5, 132.1, 129.6, 124.7, 118.5, 114.9, 107.7, 103.9, 101.4, 96.3, 56.1, 40.1, 27.3; Electron Impact Mass Spectrometer (EIMS) *m/z* 354 (M^+), 323 (Base), 137. HRMS calcd for $C_{21}H_{22}O_5$ M^+ 354.1467, found 354.1467.

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