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Facile Synthesis of Licochalcone C

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

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

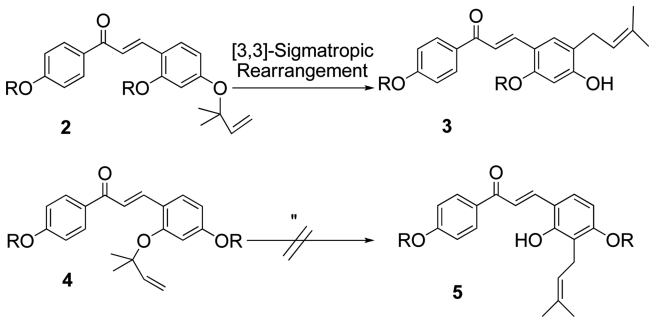
Introduction

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 antioxidative[4] 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 facor kappa B (NF-kB) 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 procedure[7] used commercially unavailable starting material and the other synthesis[8] showed a low total yield (6% with 4 steps).

Water-accelerated [3,3]-sigmatropic rearrangement reaction has been introduced in the licochalcone A synthesis[9] in our group, and also utilized for the synthesis of licochalcone D[10] 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 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.



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

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-

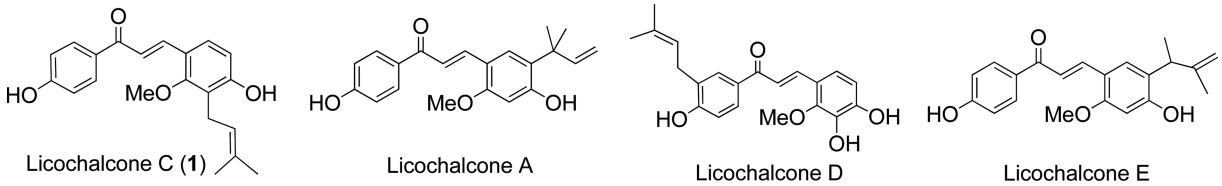
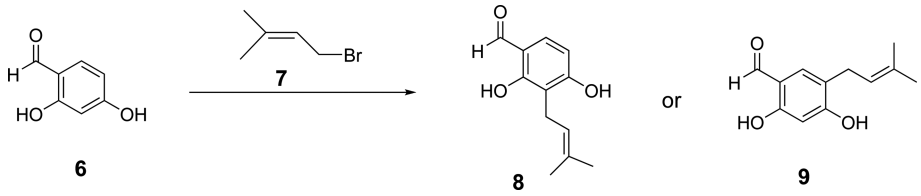
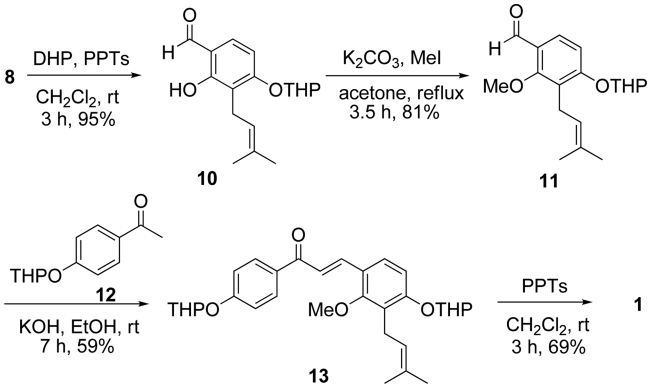


Figure 1. Structure of licochalcones C, A, D and E.

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



Entry	Reaction condition	Solvent	Temp (time)	Product (%yield)
1	*n*-BuLi	cyclohexane → Et_2O	rt (1 h) → reflux (3 h)	-
2	DBU	THF	rt (48 h)	-
3	Al_2O_3	Et_2O	rt (72 h)	**8** (21%)
4	BaO-Al_2O_3(1:1)	Et_2O	rt (72 h)	**8** (20%)
5	ZnO-Al_2O_3(1:1)	Et_2O-hexane(1:3)	rt (72 h)	**8** (18%)
6	$ZnCl_2$	CH_2Cl_2	rt (20 h)	-
7	$TiCl_4$	CH_2Cl_2	rt (20 h)	-
8	$SnCl_2$	CH_2Cl_2	rt (20 h)	-
9	KOH	H_2O	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 ^{1}H NMR data of the product were well matched with the references,[5,8] but the ^{13}C 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 ^{13}C NMR data.

In summary, we prepared licochalcone C by using Al_2O_3-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 Al_2O_3 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 ^{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. 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, F_{254} (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), Al_2O_3 (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. Al_2O_3 was filtered by glass filter. The reaction mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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-2*H*-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 CH_2Cl_2 (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 CH_2Cl_2, dried over anhydrous $MgSO_4$, 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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-2*H*-pyran-2-yl)oxy]benzaldehyde (11). To a 2-hydroxy-3-(3-methylbut-2-en-1-yl)-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-benzaldehyde (**10**) (540 mg, 1.86 mmol) in acetone (15 mL) was added slowly K_2CO_3 (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 CH_2Cl_2, dried over anhydrous Na_2SO_4, 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); ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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-2*H*-pyran-2-yl)oxy]phenyl}-1-{4-[(tetrahydro-2*H*-pyran-2-yl)oxy]phenyl}prop-2-en-1-one (13). To a 2-methoxy-3-(3-methylbut-2-en-1-yl)-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-benzaldehyde (**11**) (80 mg, 0.26 mmol), 1-[4-(teterahydro-2*H*-pyran-2-yloxy)pheneyl]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 CH_2Cl_2, dried over anhydrous $MgSO_4$, 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); ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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-[(tetrahydro-2*H*-pyran-2-yl)oxy]phenyl}-1-{4-[(tetrahydro-2*H*-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 CH_2Cl_2, dried over anhydrous $MgSO_4$, 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{21}H_{22}O_4$ M^+ 338.1518, found 338.1519.

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