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First Total Synthesis of Highly *Anti*-Inflammatory Active Licochalcone D Through Water-Accelerated [3,3]-Sigmatropic Rearrangement

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Licochalcones, derived from the dried roots of *Glycyrrhiza inflata*, have been reported to show various biological activities including antitumor, antiparasitic, antileishmanial, antioxidative, superoxide scavenging, antibacterial, and PTP1B activity. Licochalcone D has an allyl group on ring A instead of ring B, however, most other natural licochalcones possess the group on ring B. Total synthesis of licochalcone D has not been reported even possessing the strongest *anti*-inflammatory activity. Therefore, the first total synthesis of licochalcone D has been developed by using water-accelerated [3,3]-sigmatropic rearrangement method.

Key Words : Licochalcone D, *Anti*-inflammatory activity, Glycyrrhiza inflata, Water-accelerated [3,3]-sigmatropic rearrangement, Licorice

Introduction

Licorice, an herbal medicine prepared from the root of some Glycyrrhiza species containing various licochalcones, is one of the most popular folk medicine in the world.[1] Licorice has been used by human beings for over 4000 years and used for treatment of inflammation and gastric ulcer. It is well known that licochalcones separated from licorice has various activities, such as chemopreventive,[2] antibacterial,[3] antimalarial,[4] antispasmodic activities.[5] *anti*-inflammatory,[6] vascular,[7] cytotoxic,[8] *anti*-proliferative,[9] inhibitor of topoisomerase I,[10] and protein tyrosine phosphatase 1B.[11] Although licorice is widely used in medicine, it is still not fully elucidated which components in licorice are responsible for its various activities.

In recent studies, the *anti*-inflammatory activities of chalcones such as licochalcone A (Lico A), licochalcone B (Lico B), licochalcone C (Lico C), licochalcone D (Lico D), echinatin and isoliquiritigenin were examined (Fig. 1), and Lico D significantly inhibited the mast cell degranulation, play a key role in allergic inflammation, in RBL (rat basophilic leukemia)-2H3 cells with low cytotoxicity compare with the other licochalcones.[12] The 50% inhibitory concentration (IC_{50}) against degranulation and 30% cytotoxicity (CC_{30}), respectively, of each chalcones are as follows; Lico A: 17 & 24 μM, Lico C: 24 & >30 μM, Lico D: 21 & >30 μM. On the other hand, Lico B, echinatin and isoliquiritigenin showed no significant inhibitory effects. Since Lico A, Lico C and Lico D exhibited similar inhibitory effects on the degranulation with the IC_{50} at 17, 24 and 21 μM, Lico D was regarded as the best among those compounds considering its lower cytotoxicity over 30 mM. Also, Lico D was reported to have significant inhibition effect of LPS-induced activation of PKA, which is required for the phosphorylation of NF-κB p65 at serine 276.[13] It is well known that NF-κB activation induces the expression of inducible NO synthase (iNOS) leading to NO production in inflammatory regions.[14] Precise IC_{50} of LPS-induced NO production of each compound is as follows; Lico A: 5.6 μM, Lico B: 2.3 μM, Lico D: 2.2 μM. On the other hand, Lico C, echinatin and isoliquiritigenin failed to induce the potent reduction of LPS-induced NF-κB activation. Both inhibitory results indicated that Lico D has the most potent *anti*-inflammatory effects among the chalcones as shown in Figure 1.

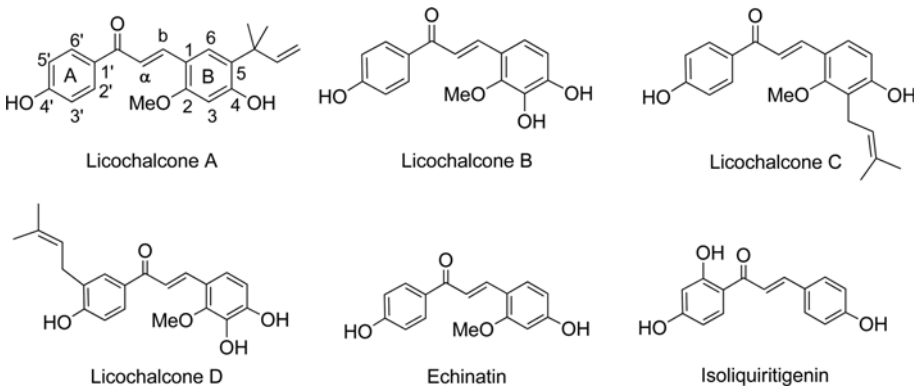


Figure 1. Structures of licochalcones A-D, echinatin and isoliquiritigenin.

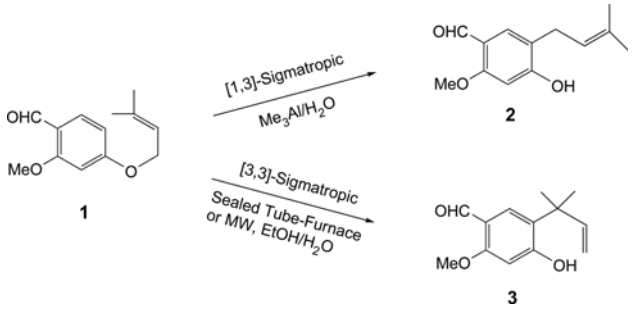


Figure 2. The chemoselectivity between [1,3] *vs* [3,3]-sigmatropic rearrangements.

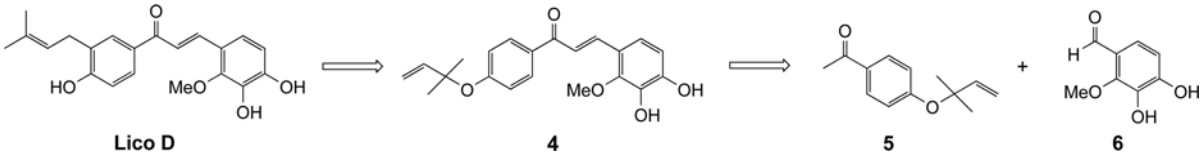
When we compared the chemical structures of chalcones based on the reported activities, we assumed that the position of the allyl group at chalcone ring is important, since only Lico D has an allyl group on ring A, however, Lico A and Lico C have the group on ring B. Interestingly, the total synthesis of Lico D has not been reported yet to the best of our knowledge. The chloroform extract of *G. inflata* root (3 kg) afforded Lico A (9.5 g), Lico B (260 mg), Lico C (190 mg), Lico D (125 mg) and echinatin (200 mg),[15] which required the total synthesis of Lico D. As we had needed sizable amounts of Lico D for *in vivo* tests, we required to develop an efficient synthetic method for this compound through water-accelerated [3,3]-sigmatropic rearrangement reaction of corresponding aryl prenyl ether system.

The chemoselectivity between [1,3]- or [3,3]-sigmatropic rearrangement reaction was demonstrated by using Me_3Al/H_2O or $Me_3Al/PhB(OH)_2$ to give [1,3]-sigmatropic rearranged product with deprenylated phenol as a by-product or by using water-accelerated [3,3]-sigmatropic rearrangement with EtOH/water (4/1, v/v) (Fig. 2) which was utilized for the Lico A synthesis.[16] Herein we report the water-accelerated [3,3]-sigmatropic rearrangement reaction method for the Lico D synthesis.

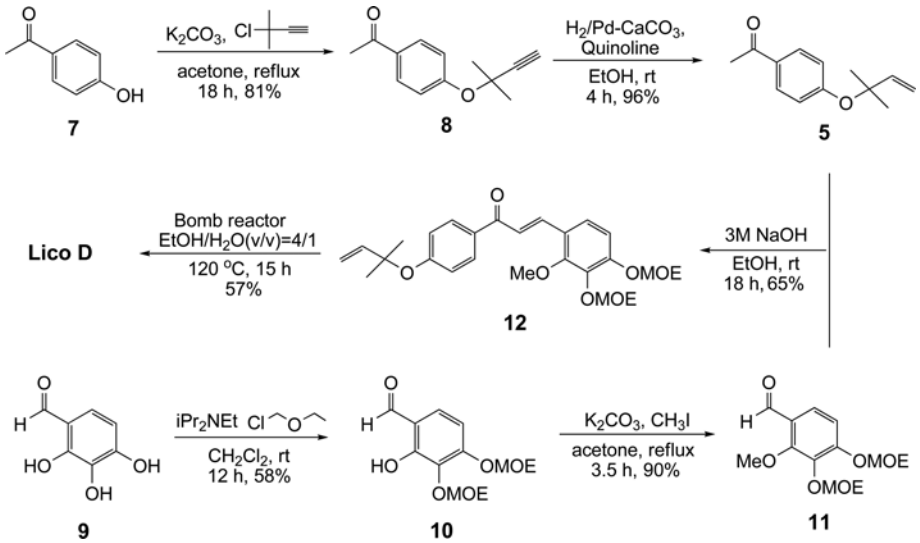
Results and Discussion

The retrosynthetic approaches for Lico D was illustrated in Scheme 1. Chalcone **4** could be an appropriate intermediate for Lico D synthesis through the water-accelerated [3,3]-sigmatropic rearrangement without any side reaction such as deprenylation. The chalcone **4** could be easily obtained from the acetophenone **5** with the benzaldehyde **6** by using conventional Claisen-Schmidt condensation.

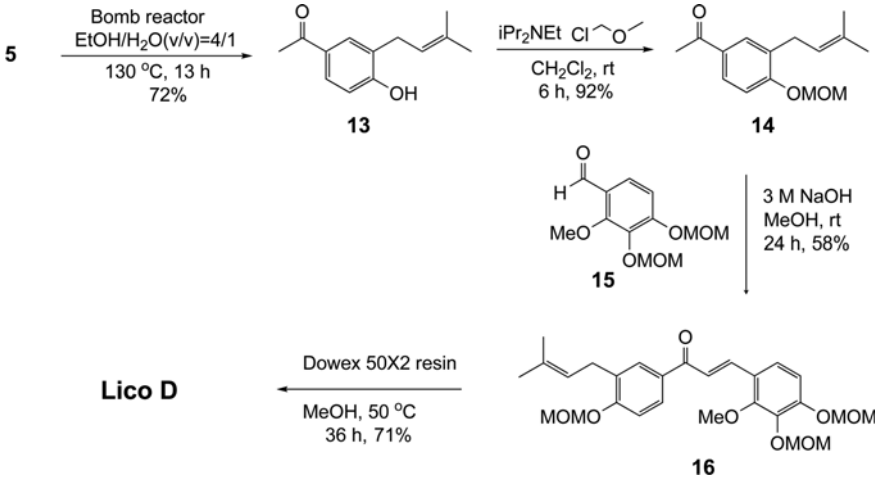
4-Hydroxyacetophenone (**7**) with 3-chloro-3-methyl-1-butyne in basic reflux produced 81% yield of **8** and following reduction with Lindlar catalyst produced the acetone **5** in 96% yield (Scheme 2). 2,3,4-Trihydroxybenzaldehyde (**9**) was selectively protected by using 1.8 equiv each of diisopropylethylamine (DIPEA) and chloromethylethylether (ClMOE) to give 3,4-diethoxymethyletherbenzaldehyde **10** in 58% yield, which was then methylated with CH_3I in basic condition to produce methoxybenzaldehyde **11** in 90% yield. The use of 2 equiv each of DIPEA and ClMOE in the protection step gave the mixture of di- and tri-MOE protected products which was not possible to separate since having same TLC R_f values. Claisen-Schmidt condensation of the acetophenone **5** and the aldehyde **11** with 3 M NaOH in EtOH smoothly produced the chalcone **12** in 65% yield. The water-accelerated [3,3]-sigmatropic rearrangement of chal-



Scheme 1. Retrosynthetic analysis of Licochalcone D.



Scheme 2. Total Synthesis of Licochalcone D.



Scheme 3. Alternative synthesis of Lico D.

cone **12** successfully transformed to a desired Lico D in bomb reactor at 120 °C with EtOH/water (4/1, v/v) solvent system in 57% yield without any deprenylated by-product**.** It is noteworthy that the both protecting groups (MOE) were removed quantitatively during the rearrangement step, which allowed one-step shorter than planned synthetic sequences.

When we applied the [3,3]-sigmatropic rearrangement step on the acetophenone **5**, the rearranged acetophenone **13** was produced in 72% yield without deprenylation, which was then protected to **14** in 92% yield (Scheme 3). Claisen-Schmidt condensation of **14** with methoxybenzaldehyde **15** produced MOM-protected chalcone **16** in 58% yield, which was required for deprotection with Dowex 50X2 resin to give the final product in 71% yield. Lico D synthesis as shown in Scheme 2 involving 15% total yield in 6 steps is more effective than the Scheme 3 synthesis involving 4% in 8 steps.

In summary, we report herein the first total synthesis of Lico D by using conventional Claisen-Schmidt condensation and water-accelerated [3,3]-sigmatropic rearrangement reactions. This method could overcome the limited supply of sizable amount of Lico D for the growing request of diverse *in vivo* tests.

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 ^{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. 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.

4-(1,1-Dimethylprop-2-ynyloxy)acetophenone (8). To a dissolved solution of 4-hydroxyacetophenone (**7**) (700 mg, 5.14 mmol) and K_2CO_3 (1.78 g, 12.85 mmol) in acetone (25 mL) was added slowly 3-chloro-3-methyl-1-butyne (0.69 mL, 6.17 mmol) and refluxed for 18 h. After completion of the reaction, K_2CO_3 was filtered and the resulting solution was concentrated *in vacuo* and the residue was extracted with methylene chloride. The organic layer was dried with Na_2SO_4, filtered, concentrated and purified by *silica* gel flash column chromatography (EtOAc/hexane = 1/4) to give a clear liquid; yield: 839 mg (81%). R_f 0.52 (EtOAc/Hexane = 1/4); ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (2H, dd, *J* = 8.7, 3.0 Hz), 7.25 (2H, dd, *J* = 8.7, 3.0 Hz), 2.64 (1H, s), 2.56 (3H, s), 1.70 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 159.8, 131.1, 129.8, 119.2, 85.1, 74.7, 72.3, 29.6, 26.5.

4-(1,1-Dimethylprop-2-enyloxy)acetophenone (5). Acetophenone **8** (160 mg, 0.79 mmol), Pd-$CaCO_3$ (8 mg, 5% of the weight) and quinoline (3 mg, 0.023 mmol) under hydrogen atmosphere were dissolved in EtOH (3 mL) and stirred for 4 h at rt. The reaction mixture was filtered, washed with methanol, evaporated *in vacuo* and extracted with methylene chloride. The organic solvent was dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated *in vacuo*. The residue was purified by *silica* gel flash column chromatography (EtOAc/Hexane = 1/7) to give an orange colored liquid; yield: 154 mg (96%). R_f 0.56 (EtOAc/hexane = 1/4). ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (2H, dd, *J* = 9.0, 2.1 Hz), 6.99 (2H, dd, *J* = 9.0, 2.1 Hz), 6.12 (1H, dd, *J* = 17.4, 10.8 Hz), 5.21 (1H, br d, *J* = 17.4 Hz), 5.19 (1H, br d, *J* = 10.8 Hz), 2.54 (3H, s), 1.52 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 160.6, 143.6, 130.5, 129.7, 119.4, 113.9, 80.3, 27.3, 26.4.

3,4-Diethoxymethoxy-2-hydroxybenzaldehyde (10). 2,3,4-Trihydroxybenzaldehyde (**9**) (500 mg, 3.24 mmol) and diisopropylethylamine (1 mL, 5.84 mmol) were stirred for 10 min at rt in methylene chloride (25 mL) as a solvent. To the reaction mixture was added slowly chloromethylethylether (0.5 mL, 5.84 mmol) and stirred for 12 h at rt. The reaction mixture was extracted with methylene chloride, washed with saturated $NaHCO_3$, NaCl solution, concentrated *in vacuo*, and purified by *silica* gel flash column chromatography (EtOAc/Hexane = 1/6) to give the titled compound as a clear liquid; yield: 508 mg (58%). R_f 0.48 (EtOAc/hexane = 1/3).

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.24 (1H, s), 9.74 (1H, s), 7.26 (1H, d, *J* = 8.7 Hz), 6.84 (1H, d, *J* = 8.7 Hz), 5.32 (2H, s), 5.21 (2H, s), 3.92 (2H, q, *J* = 6.9 Hz), 3.74 (2H, q, *J* = 6.9 Hz), 1.23 (3H, t, *J* = 6.9 Hz), 1.22 (3H, t, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 157.3, 156.1, 133.3, 130.0, 116.8, 107.2, 96.4, 93.4, 65.1, 65.0, 15.1, 15.0.

3,4-Diethoxymethoxy-2-methoxybenzaldehyde (11). To a benzaldehyde **10** (614 mg, 4.44 mmol) in acetone (18 mL) was added methyl iodide (0.1 mL, 1.63 mmol) under nitrogen atmosphere and refluxed for 3.5 h. The reaction mixture was filtered, extracted with methylene chloride, concentrated *in vacuo*, and purified by *silica* gel flash column chromatography (EtOAc/hexane = 1/6) to give a yellow liquid; yield: 381 mg (90%). R_f 0.48 (EtOAc/hexane = 1/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.22 (1H, s), 7.57 (1H, d, *J* = 8.7 Hz), 7.02 (1H, d, *J* = 8.7 Hz), 5.30 (2H, s), 5.18 (2H, s), 3.99 (3H, s), 3.88 (2H, q, *J* = 6.9 Hz), 3.74 (2H, q, *J* = 6.9 Hz), 1.24 (3H, t, *J* = 6.9 Hz), 1.23 (3H, t, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 157.3, 156.9, 139.1, 124.4, 124.1, 111.1, 97.1, 93.5, 65.4, 64.9, 62.7, 31.0, 15.1

(*E*)-3-(2,3,4-Triethoxymethoxyphenyl)-1-[4-(1,1-dimethylprop-2-enyloxy)phenyl]prop-2-en-1-one (12). 4-(1,1-Dimethylprop-2-enyloxy)acetophenone (**5**) (204 mg, 0.10 mmol) and 3,4-diethoxymethoxy-2-methoxybenzaldehyde (**11**) (218 mg, 0.77 mmol) were dissolved in EtOH (8 mL) at rt. NaOH (3 M, 0.5 mL) was added and stirred for 18 h at rt. After completion of reaction, EtOH was concentrated *in vacuo* and the reaction mixture was adjusted to pH 7 by addition of saturated aqueous sodium hydrosulfite solution and extracted with methylene chloride. 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 (Acetone/hexane = 1/7) to give a yellow liquid; yield: 234 mg (65%). R_f 0.28 (Acetone/hexane = 1/5). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (1H, d, *J* = 15.6 Hz), 7.92 (2H, dd, *J* = 9.0, 2.7 Hz), 7.52 (1H, d, *J* = 15.6 Hz), 7.36 (1H, d, *J* = 8.7 Hz), 7.04 (2H, dd, *J* = 9.0, 2.7 Hz), 6.98 (1H, d, *J* = 8.7 Hz), 6.14 (1H, dd, *J* = 17.4, 10.8 Hz), 5.28 (2H, s), 5.21 (1H, br d, *J* = 17.4 Hz), 5.19 (1H, br d, *J* = 10.8 Hz), 5.18 (2H, s), 3.89 (3H, s), 3.88 (2H, q, *J* = 6.9 Hz), 3.75 (2H, q, *J* = 6.9 Hz), 1.53 (6H, s), 1.24 (6H, t, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.0, 160.4, 153.9, 153.2, 143.7, 139.9, 138.7, 131.7, 129.9, 123.7, 123.3, 121.6, 119.5, 113.9, 111.6, 97.1, 93.7, 80.3, 65.2, 64.6, 61.5, 27.3, 15.2, 15.1.

(*E*)-3-(3,4-Dihydroxy-2-methoxyphenyl)-1-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]prop-2-en-1-one (Licochalcone D). Chalcone **12** (63 mg, 0.13 mmol) was dissolved in EtOH/H_2O (4/1, v/v; 4 mL) and reacted for 15 h at 120 °C in bomb reactor. After completion of reaction, solvent was concentrated *in vacuo* and extracted with EtOAc/Acetone (2:1) mixure. 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 = 1/2) to give a pale brown needle; yield: 27 mg (57%). The spectral data of this compound was nicely matched to the literature value.[15] R_f 0.22 (EtOAc/hexane = 1/1). mp 112-114 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 7.92 (1H, d, *J* = 15.6 Hz), 7.81 (1H, d, *J* = 2.1 Hz), 7.79 (1H, dd, *J* = 8.7, 2.1 Hz), 7.61 (1H, d, *J* = 15.6 Hz), 7.18 (1H, d, *J* = 8.7 Hz), 6.85 (1H, d, *J* = 8.7 Hz), 6.64 (1H, d, *J* = 8.7 Hz), 5.34 (1H, br t, *J* = 7.5 Hz), 3.84 (3H, s), 3.39 (2H, d, *J* = 7.5 Hz), 1.76 (3H, br s), 1.73 (3H, br s). ^{13}C NMR (75 MHz, acetone-d_6) δ 189.1, 160.9, 150.4, 150.0., 139.9, 139.7, 133.8, 132.5, 132.1, 129.9, 129.9, 124.0, 122.3, 121.7, 120.8, 116.4, 113.3, 62.5, 30.0, 26.9, 18.9.

4-Hydroxy-3-(3-methylbut-2-enyl)acetophenone (13). Acetophenone **5** (142 mg, 0.70 mmol) was dissolved in EtOH/H_2O (4/1, v/v; 5.5 mL) and reacted for 13 h at 130 °C in bomb reactor. 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 white solid; yield: 102 mg (72%). R_f 0.28 (EtOAc/hexane = 1/2). mp 78-80 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (1H, d, *J* = 8.7 Hz), 7.73 (1H, d, *J* = 2.1 Hz), 6.83 (1H, dd, *J* = 8.7, 2.1 Hz), 5.98 (1H, br s), 5.31 (1H, br t, *J* = 7.2 Hz), 3.40 (2H, d, *J* = 7.2 Hz), 2.55 (3H, s), 1.79 (6H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 159.1, 134.9, 130.7, 129.8, 128.7, 127.2, 121.0, 115.3, 29.4, 26.3, 25.8, 18.0.

4-Methoxymethoxy-3-(3-methylbut-2-enyl)acetophenone (14). Acetophenone **13** (100 mg, 0.49 mmol) was dissolved in methylene chloride and diisopropylethylamine (97 mL, 0.58 mmol) were stirred for 15 min at rt. To the reaction mixture was added slowly chloromethylmethylether (0.05 mL, 0.58 mmol) and stirred for 6 h at rt. The reaction mixture was extracted with methylene chloride, dried over anhydrous Na_2SO_4,concentrated *in vacuo*, and purified by *silica* gel flash column chromatography (EtOAc/Hexane = 1/4) to give a clear liquid; yield: 112 mg (92%). R_f 0.75 (EtOAc/Hexane = 1/4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (1H, d, *J* = 6.9 Hz), 7.75 (1H, d, *J* = 3.0 Hz), 7.07 (1H, dd, *J* = 6.9, 3.0 Hz), 5.28 (1H, br t, *J* = 7.2 Hz), 5.26 (2H, s), 3.47 (3H, s), 3.36 (2H, d, *J* = 7.5 Hz), 2.54 (3H, s), 1.73 (6H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 158.6, 132.9, 130.9, 130.8, 129.9, 128.2, 121.7, 112.7, 93.9, 56.2, 28.9, 26.4, 25.9, 17.9.

(*E*)-3-(2-Methoxy-3,4-dimethoxymethoxyphenyl)-1-[4-methoxymethoxy-3-(3-methylbut-2-enyl)phenyl]prop-2-en-1-one (16). Acetophenone **14** (42 mg, 0.17 mmol) and benzaldehyde **15** (43 mg, 0.17 mmol) were dissolved in MeOH at rt. NaOH (14 mg, 0.34 mmol) was added and stirred for 24 h at rt. After completion of reaction, MeOH was concentrated *in vacuo* and the reaction mixture was neutralized by addition of 0.5 N HCl solution and extracted with methylene chloride. 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 (Acetone/hexane = 1/7) to give a reddish liquid; yield: 48 mg (58%). R_f 0.29 (Acetone/hexane = 1/4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (1H, d, *J* = 15.6 Hz), 7.86 (1H, br s), 7.84 (1H, dd, *J* = 8.7, 1.8 Hz),

7.54 (1H, d, J = 15.6 Hz), 7.37 (1H, d, J = 8.7 Hz), 7.12 (1H, d, J = 8.7 Hz), 6.97 (1H, d, J = 8.7 Hz), 5.32 (1H, br t, J = 6.9 Hz), 5.29 (2H, s), 5.25 (2H, s), 5.17 (2H, s), 3.92 (3H, s), 3.64 (3H, s), 3.53 (3H, s), 3.50 (3H, s), 3.40 (2H, d, J = 6.9 Hz), 1.75 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 158.4, 153.8, 152.9, 140.0, 138.6, 132.8, 131.9, 130.8, 130.2, 128.2, 123.8, 123.4, 121.9, 121.8, 112.7, 111.5, 98.7, 94.9, 93.9, 61.4, 57.3, 56.4, 56.2, 28.9, 25.9, 17.9.

(*E*)-3-(3,4-Dihydroxy-2-methoxyphenyl)-1-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]prop-2-en-1-one (Licochalcone D). Dowex 50X2 cation exchange resin (70 mg) was added to the protected chalcone **15** (42 mg, 0.09 mmol) in MeOH (2 mL) and stirred at 50 ºC for 36 h. The Dowex resin was filtered and MeOH was concentrated *in vacuo*, and the crude reaction mixture was purified by *silica* gel column chromatography (EtOAc/hexane = 1/1) to give a pale brown needle (21 mg, 71%). The spectral data were exactly matched with the other result as shown in Scheme 2.

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