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# Total Synthesis of Licochalcone E

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Total synthesis of (±)-licochalcone E (**1**), an allyl retrochalcone isolated from roots of *Glycyrrhiza inflata*, has been achieved from 4-tetrahydropyranyloxyacetophenone (**7**) with (*E*)-2-methoxy-4-(2-methyl-2-butenyloxy)benzaldehyde (**6**) or (*Z*)-2-methoxy-4-(2-methyl-2-butenyloxy)-benzaldehyde (**11**) through a convergent strategy involving aldol condensation and Claisen rearrangement as key steps.

**Key Words**: Licochalcone E, Aldol condensation, Claisen rearrangement, Synthesis

## Introduction

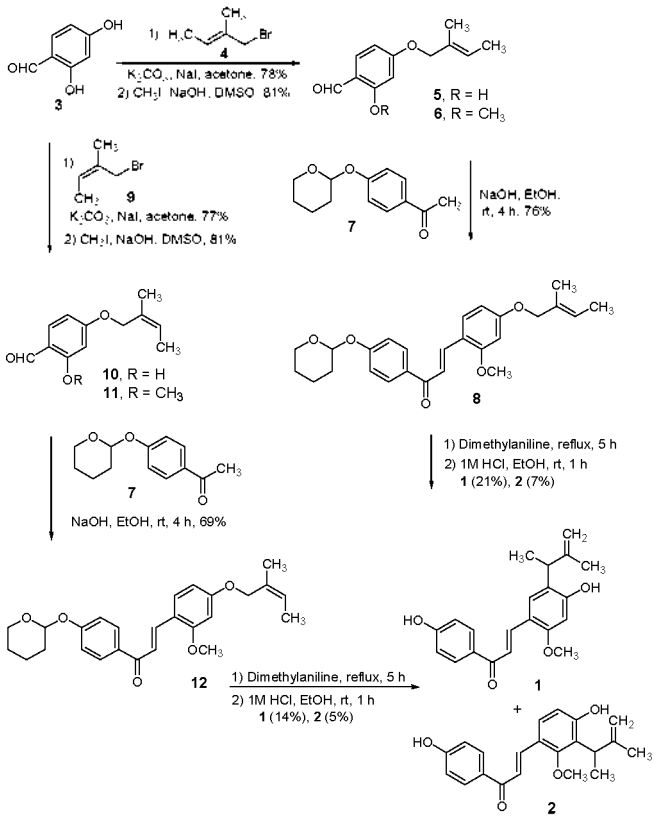
Licochalcone A-D and echinatin, isolated from the roots of *Glycyrrhiza inflata*, are well known retrochalcones[1,2] with diverse biological activities.[3-10] Recently, licochalcone E was isolated from *G. inflata* during cytotoxicity-guided fractionation using the HT1080 cell line, and its structure was elucidated as (-)-4,4'-dihydroxy-2-methoxy-5-(1,2-dimethylallyl)chalcone (**1**) on the basis of spectral data.[11] The biological activities of licochalcone E have been intensively studied since its discovery. It inhibits topoisomerase 1, and induces endothelial cell apoptosis by modulating NF-*k*B and the Bcl-2 family.[12,13] Licochalcone A and E also inhibit protein tyrosine phosphatase 1B.[14] Further biological studies of licochalcone E have been hampered by the inadequate supply, as is true for many other natural products. Herein, we report a facile synthesis of licochalcone E from readily available 2,4-dihydroxybenzaldehyde (**3**) compared to recent synthesis.[15]

## Results and Discussion

The synthesis began with protection of 4-hydroxyacetophenone with 3,4-dihydro-2*H*-pyran in the presence of pyridinium *p*-toluenesulfonate to give 4-tetrahydropyranyloxyacetophenone (**7**) in quantitative yield. The synthetic pathway is outlined in Scheme 1.

2,4-Dihydroxybenzaldehyde (**3**) reacted with tiglic bromide[7] (**4**) in the presence of $K_2CO_3$ and NaI gave (*E*)-2-hydroxy-4-(2-methyl-2-butenyloxy)benzaldehyde (**5**) selectively in 78% yield. None of the 2-alkylated isomer was detected. Methylation of 2-phenol with methyliodide and NaOH in DMSO afforded (*E*)-2-methoxy-4-(2-methyl-2-butenyloxy)benzaldehyde (**6**) in 81% yield. Aldol condensation of **6** and **7** in the presence of NaOH in ethanol provided **8** in 76% yield. The final key Claisen rearrangement was carried out in boiling *N,N*-dimethylaniline solvent followed by acid hydrolysis of the tetrahydropyran group to afford the desired licochalcone E (**1**) and its isomer (**2**) in 21% and 7% yield, respectively.

Angelic bromide, a regioisomer of tiglic bromide, reacted in the same fashion as tiglic bromide with 2,4-dihydroxybenzaldehyde (**3**) in the presence of $K_2CO_3$ and NaI gave (*Z*)-2-hydroxy-4-(2-methyl-2-butenyloxy)benzaldehyde (**10**) selectively in 77% yield. Methylation of **10** followed by aldol condensation provided **12** which was subjected to the key Claisen rearrangement and acid hydrolysis to yield the desired licochalcone E (**1**) and its isomer (**2**) in 14% and 5% yield, respectively. Spectral and analytical data for **1** and **2** were identical to those reported.[11,15] This result proved that the regiochemistry of the γ-methyl substituent of the allyl group has minimal effect on the Clai-




**Scheme 1**

sen rearrangement. The (*Z*)-allyl isomer (**12**) gave lower yield than the (*E*)-allyl isomer (**8**) possibly due to steric hindrance between the γ-methyl substituent of the allyl ether and the ortho hydrogen of the benzene in the (*Z*)-allyl isomer.

## Experimental

**Synthesis of (*E*)-2-hydroxy-4-(2-methylbut-2-enyloxy)benzaldehyde (5) from 2,4-dihydroxybenzaldehyde (3).** To a solution of 2,4-dihydroxybenzaldehyde (**3**, 2.79 g, 20.2 mmol) and sodium iodide (1.37 g, 9.1 mmol) in acetone (100 mL) was added potassium carbonate (7.57 g, 54.8 mmol) followed by (*E*)-2-methyl-2-butenyl bromide (3.14 g, 21.1 mmol) and the mixture was refluxed overnight. After being cooled to room temperature, the reaction mixture was filtered and the filter cake was washed with acetone. The combined acetone solution was evaporated *in vacuo* and the residue was dissolved in ethyl acetate (200 mL), washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The crude product was purified by flash chromatography ($SiO_2$, hexane : ethyl acetate = 10 : 1) to give **5** as an oil (3.25 g, 78%). $^1$H-NMR (300 MHz, $CDCl_3$) δ 11.46 (s, 1H), 9.70 (s, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 6.54 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 5.64 (m, 1H), 4.43 (s, 2H), 1.72 (s, 3H), 1.67 (d, *J* = 6.6 Hz, 3H). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ 194.3, 166.2, 164.4, 135.2, 130.6, 124.4, 115.1, 108.9, 101.4, 74.4, 13.5, 13.3.

**Synthesis of (*E*)-2-methoxy-4-(2-methylbut-2-enyloxy)benzaldehyde (6) from (*E*)-2-hydroxy-4-(2-methylbut-2-enyloxy) benzaldehyde (5).** To a suspension of (*E*)-2-hydroxy-4-(2-methylbut-2-enyloxy)benzaldehyde (**5**, 1.6 g, 7.76 mmol), and sodium hydroxide (0.62 g, 15.5 mmol) in DMSO (10 mL) was added iodomethane (1.32 g, 9.33 mmol) and the mixture was stirred for 60 min at room temperature. The reaction mixture was poured into ice-cold water (30 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The product was purified by flash chromatography ($SiO_2$, hexane : ethyl acetate = 10 : 1) to give 1.38 g (81%) of **6** as an oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 10.3 (s, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 6.54 (dd, *J* = 2.1, 8.7 Hz, 1H), 6.48 (d, *J* = 2.1 Hz, 1H), 5.65 (m, 1H), 4.45 (s, 2H), 3.89 (s, 3H), 1.74 (s, 3H), 1.68 (d, *J* = 5.7 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 188.3, 165.6, 163.6, 130.9, 130.7, 124.4, 119.0, 106.5, 98.6, 74.4, 55.6, 13.6, 13.3.

**Synthesis of (*E*)-3-[2-methoxy-4-(2-methylbut-2-enyloxy) phenyl]-1-[4-(tetrahydropyran-2-yloxy)-phenyl]propenone (8) from (*E*)-2-methoxy-4-(2-methylbut-2-enyloxy)benzaldehyde (6).** A solution of (*E*)-2-methoxy-4-(2-methylbut-2-enyloxy)benzaldehyde (**6**, 657 mg, 2.98 mmol), 4-tetrahydropyranyloxyacetophenone (7, 657 mg, 2.98 mmol), and sodium hydroxide (240 mg, 5.98 mmol) in ethanol (10 mL) was stirred for 4 h at room temperature. The reaction mixture was added to water and extracted with ethyl acetate. The combined organic phases were washed with water, dried, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (hexane : ethyl acetate = 5 : 1) to give **8** (964 mg, 76%). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 15.6 Hz, 1H, H-β), 8.00 (d, *J* = 9.0 Hz, 2H), 7.55 (d, *J* = 15.6 Hz, 1H, H-α), 7.54 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 9.0 Hz, 2H), 6.53 (dd, *J* = 2.7, 8.4 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 5.66 (m, 1H), 5.52 (m, 1H, H-2′), 4.43 (s, 2H), 3.89 (s, 3H), 3.85 (m, H-6a′), 3.63 (m, H-6e′), 1.75 (s, 3H), 1.69 (d, *J* = 7.8 Hz, 3H), 2.07-1.57 (m, 6H, H3′~H5′). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.6, 162.3, 160.5, 160.3, 139.8, 132.4, 131.3, 130.8, 130.5, 124.1, 120.3, 117.2, 115.9, 106.2, 99.2, 96.1, 74.3, 62.0, 55.5, 30.2, 25.1, 18.5, 13.6, 13.3.

**Synthesis of (*E*)-3-(4-hydroxy-2-methoxy-5-(3-methylbut-3-en-2-yl)phenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (1) and (*E*)-3-(4-hydroxy-2-methoxy-3-(3-methylbut-3-en-2-yl) phenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (2) from (*E*)-3-[2-methoxy-4-(2-methylbut-2-enyloxy)phenyl]-1-[4-(tetrahydropyran-2-yloxy)-phenyl]propenone (8).** Oxygen free argon was passed for 1 h through a solution of crude (*E*)-3-[2-methoxy-4-(2-methylbut-2-enyloxy)phenyl]-1-[4-(tetrahydropyran-2-yloxy)-phenyl]propenone (**8**, 800 mg, 1.89 mmol) in dimethylaniline (5 mL). After refluxing 5 h, the mixture was cooled and dimethylaniline was removed by silica gel chromatography (hexane : ethyl acetate = 2 : 1). The crude product was dissolved in anhydrous ethanol (5 mL) containing 1 mL of 1 M HCl and the mixture was stirred for 1 h, extracted with ethyl acetate, dried, and concentrated *in vacuo*. The residue was purified by column chromatography with eluent system of hexane: ethyl acetate = 2 : 1 to give (*E*)-3-(4-Hydroxy-2-methoxy-5-(3-methylbut-3-en-2-yl)phenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (**1**, 134 mg) and (*E*)-3-(4-hydroxy-2-methoxy-3-(3-methylbut-3-en-2-yl)phenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (**2**, 45 mg) in 21% and 6% yield, respectively. Compound **1** $[\alpha]^D$ = -10.4 (c = 0.2, acetone). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 15.3 Hz, 1H, H-β), 7.92 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 15.3 Hz, 1H, H-α), 7.31 (s, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.51 (s, 1H), 4.91 (s, 2H), 3.84 (s, 3H), 3.74 (m, 1H), 1.67 (s, 3H), 1.33 (d, *J* = 6.9 Hz, 3H). $^1$H NMR (300 MHz, acetone-$d_6$) δ 8.01 (d, *J* = 15.3 Hz, 1H, H-β), 7.97 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 15.3 Hz, 1H, H-α), 7.48 (s, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.66 (s, 1H), 4.91 (s, 1H), 4.87 (s, 1H), 3.86 (m, 1H), 3.83 (s, 3H), 1.67 (s, 3H), 1.35 (d, *J* = 7.2 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 188.7, 163.9, 160.4, 159.7, 150.1, 140.1, 131.6, 131.0, 129.3, 125.3, 119.2, 116.5, 116.0, 110.1, 100.1, 56.0, 38.7, 22.5, 19.8. Compound **2** $[\alpha]^D$ = -15.0 (c = 0.2, EtOH). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 15.5 Hz, 1H, H-β), 7.99 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.51 (d, *J* = 15.5 Hz, 1H, H-α), 6.98 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 8.9 Hz, 1H), 5.24 (s, 1H), 5.21 (s, 1H), 4.00 (m, 1H), 3.80 (s, 3H), 1.76 (s, 3H), 1.45 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.8, 161.7, 159.0, 149.9, 139.9, 131.2, 130.3, 127.6, 123.4, 121.0, 120.4, 115.9, 113.9, 112.0, 63.0, 50.8, 36.3, 22.9, 17.3.

**Synthesis of (*Z*)-2-hydroxy-4-(2-methylbut-2-enyloxy)benzaldehyde (10) from 2,4-dihydroxybenzaldehyde (3).** To a solution of 2,4-dihydroxybenzaldehyde (**3**, 2 g, 14.5 mmol) and sodium iodide (1 g, 6.7 mmol) in acetone (100 mL) was added potassium carbonate (5.45 g, 39.4 mmol) followed by (*Z*)-2-methyl-2-butenyl bromide (**9**, 2.35 g, 15.8 mmol) and the mixture was refluxed overnight. After being cooled to room temperature, the reaction mixture was filtered and the filter cake was washed with acetone. The combined acetone solution was evaporated *in vacuo* and the residue was dissolved in ethyl acetate (200 mL), washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The crude product was purified by flash

chromatography ($SiO_2$, hexanes : ethyl acetate = 10 : 1) to give an oil (2.31 g, 77%). $^1$H-NMR (300 MHz, $CDCl_3$) δ 11.48 (s, 1H), 9.70 (s, 1H), 7.42 (d, $J$ = 8.7 Hz, 1H), 6.56 (dd, $J$ = 2.4, 8.7 Hz, 1H), 6.44 (d, $J$ = 2.4 Hz, 1H), 5.49 (m, 1H), 4.57 (s, 2H), 1.80 (m, 3H), 1.71 (dm, $J$ = 6.9 Hz, 3H). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ 194.3, 166.3, 164.4, 135.2, 130.5, 124.9, 115.1, 108.8, 101.2, 67.1, 21.1, 13.4.

**Synthesis of (*Z*)-2-methoxy-4-(2-methylbut-2-enyloxy)benzaldehyde (11) from (*Z*)-2-hydroxy-4-(2-methylbut-2-enyloxy) benzaldehyde (10).** To a suspension of (*Z*)-2-hydroxy-4-(2-methylbut-2-enyloxy)benzaldehyde (**10**, 0.93 g, 4.51 mmol), and sodium hydroxide (0.39 g, 9.75 mmol) in DMSO (5 mL) was added iodomethane (0.71 g, 5.01 mmol) and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into ice-cold water (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The product was purified by flash chromatography ($SiO_2$, hexane : ethyl acetate = 10 : 1) to give 0.81 g (81%) of **11** as an oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 10.3 (s, 1H), 7.80 (d, $J$ = 8.7 Hz, 1H), 6.56 (dd, $J$ = 2.1, 8.7 Hz, 1H), 6.48 (d, $J$ = 2.1 Hz, 1H), 5.56 (m, 1H), 4.60 (s, 2H), 3.90 (s, 3H), 1.81 (s, 3H), 1.73 (d, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 188.3, 165.7, 163.6, 130.9, 130.7, 124.8, 119.0, 106.4, 98.4, 67.0, 55.5, 21.2, 13.4.

**Synthesis of (*Z*)-3-[2-methoxy-4-(2-methylbut-2-enyloxy) phenyl]-1-[4-(tetrahydropyran-2-yloxy)-phenyl]propenone (12) from (*Z*)-2-methoxy-4-(2-methylbut-2-enyloxy)benzaldehyde (11).** A solution of (*Z*)-2-methoxy-4-(2-methylbut-2-enyloxy)benzaldehyde (**11**, 0.73 g, 3.31 mmol), 4-tetrahydropyranyloxyacetophenone (**7**, 0.73 g, 3.31 mmol), and sodium hydroxide (0.4 g, 10 mmol) in ethanol (15 mL) was stirred for 4 h at room temperature. The reaction mixture was poured into ice-water (20 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by flash chromatography ($SiO_2$, hexane : ethyl acetate = 5 : 1) to give an oil (0.96 g, 69%). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, $J$ = 15.9 Hz, 1H), 8.01 (d, $J$ = 8.9 Hz, 2H), 7.55 (d, $J$ = 15.9 Hz, 1H), 7.55 (d, $J$ = 8.5 Hz, 1H), 7.12 (d, $J$ = 8.9 Hz, 2H), 6.55 (dd, $J_1$ = 2.4 Hz, $J_2$ = 8.5 Hz, 1H), 6.50 (d, $J$ = 2.4 Hz, 1H), 5.54 (m, 1H), 5.52 (m, 1H), 4.57 (s, 2H), 3.88 (s, 3H), 3.86 (m, 1H), 3.62 (m, 1H), 1.82 (m, 3H), 1.72 (dd, $J_1$ = 1.2 Hz, $J_2$ = 6.9 Hz, 3H), 2.07-1.56 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.5, 162.3, 160.5, 160.2, 139.6, 132.3, 131.2, 130.7, 130.4, 124.4, 120.2, 117.2, 115.9, 106.0, 98.9, 96.0, 66.7, 62.0, 55.4, 30.1, 25.0, 21.2, 18.5, 13.3.

**Synthesis of (*E*)-3-(4-hydroxy-2-methoxy-5-(3-methylbut-3-en-2-yl)phenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (1) and (*E*)-3-(4-hydroxy-2-methoxy-3-(3-methylbut-3-en-2-yl) phenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (2) from (*Z*)-3-[2-methoxy-4-(2-methylbut-2-enyloxy)phenyl]-1-[4-(tetrahydropyran-2-yloxy)-phenyl]propenone (12).** Compound **1** and **2** were synthesized in 14% and 5% yield, respectively, following the same procedure as the preparation of **1** and **2** from-(*E*)-3-[2-methoxy-4-(2-methylbut-2-enyloxy)phenyl]-1-[4-(tetrahydropyran-2-yloxy)-phenyl]propenone (**8**).

## Conclusion

In conclusion, a facile synthesis of licochalcone E and its isomer in 10% overall yield was accomplished from readily available starting materials. Utilization of this concise synthesis of licochalcone E and its isomer could provide enough material for biological studies. Also this synthetic procedure could be applied for the preparation of diverse analogs of licochalcone E. In the Claisen rearrangement, the regiochemistry of the γ-methyl substituent of the allyl ether had minimal effect.

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