A Short and Efficient Synthesis of Licochalcone E

Jizhen Li,*[a] Yuhua Mi,[a] Jianghua He,[a] Xuming Deng*[b]

[a] College of Chemistry, Jilin University, 2519 Jiefang Road, Changchun 130023, P. R. of China
Fax +86(431)88499179; E-mail: ljz@jlu.edu.cn

[b] College of Animal Science and Veterinary Medicine, Jilin University, 5333 Xi'an Road, Changchun 130062, P. R. of China
Fax +86(431)87836160; E-mail: xumingdeng@jluhp.edu.cn

Received 18 June 2010

Abstract: Licochalcone E was synthesized concisely via an abnormal Claisen rearrangement and Claisen–Schmidt condensation as the key reactions in a three-step sequence. The overall yield is 20% starting from prenyl bromide and 4-hydroxy-2-methoxybenzaldehyde.

Key words: licochalcone E, abnormal Claisen rearrangement, Claisen–Schmidt condensation, total synthesis

Licorice is a traditional medicine used in the Northeast Asia for the treatment of gastric and peptic ulcers, bronchial asthma, inflammation and other diseases.[1,2] Six retrochalcones, licochalcone A–E and echinatin (Figure 1) have been isolated and characterized from the roots of *G. inflata*, which is the main species in Chinese Xinjiang licorice.[3–6] These retrochalcones are comprised of two benzene rings joined by an α,β-unsaturated carbonyl system, structurally distinguishable from normal chalcones by the lack of oxygen functionalities at C-2′ and C-6′ positions of A ring. In particular, among many constituents, retrochalcones, chalcones, flavonoids are responsible for the yellow color of licorice. The series of retrochalcones family have shown various biological properties, including antitumor,[3,7] antiparasitic,[8] antileishmanial,[9] antibacterial activities.[10] They also display antioxidative and superoxide scavenging property.[11]

Among the reported retrochalcones, licochalcone E, as a member of this family, was isolated in 2005 by Cheon's group.[6] The initial biological activity study showed that this compound exhibited a higher cytotoxicity compared to the analogous licochalcone A and isoliquiritigenin.[6] Furthermore, licochalcone E has also been reported to modulate the nuclear factor (NF)-KB and Bc1-2 families and to induce endothelial cell apoptosis.[12] Recently, research revealed that licochalcone E inhibited protein tyrosine phosphatase 1B (PTP1B) which played crucial role in negative regulation of insulin and leptin signaling pathways.[13]

Due to the demand of large amount of licochalcone E for further biological activity studies and the low isolated yield from natural product (yield: 0.0005% from 1 kg of *G. inflate*), chemical synthesis of licochalcone E was highly desirable. Several routes to the semi-synthesis or total synthesis of licochalcone E have been reported by Cheon and Na independently in 2009 and 2010.[14] These methods, however, suffered from limitations such as tedious protection and deprotection procedure of phenolic hydroxy group, by employing Claisen rearrangement and Claisen–Schmidt condensation reaction as the key steps. For example, as depicted in Scheme 1, licochalcone E was obtained in 15% overall yield via at least five steps from the starting material 1-bromo-2-methyl-2*E*-butene (**2**), as well as the formation of a side product which was tentatively called licochalcone F was observed.[14a]

Our goal was to search for a shorter and more efficient protocol for the synthesis of licochalcone E, and we suspected that this may be achieved by overcoming the shortcoming of the above mentioned synthesis strategies.[14a] To our best knowledge, an abnormal Claisen rearrangement as the special rearrangement reaction usually happens after normal Claisen rearrangement of certain allyl vinyl ether without protection of phenolic hydroxy group.[15–17] Thus, functional allyl groups could be introduced into suitable position directly by the utilization of this reaction. Recently, its contribution to naturally occurring products or relative compounds was explored.[18] Additionally, even though Claisen–Schmidt condensation was usually performed under basic conditions, the greater advantage of running the reaction under acidic conditions had been demonstrated in the construction of retrochalcone such as licochalcone A without hydroxy group protection.[19,20] Therefore, we envisaged that a shorter route may be secured through abnormal Claisen rearrangement and the utilization of acidic conditions in the Claisen–Schmidt condensation.

Herein, we present one short and efficient synthesis route to licochalcone E, the reagents and reaction conditions for which are depicted in Scheme 2. Our journey towards the synthesis of licochalcone E began with prenyl bromide (**8**) and 4-hydroxy-2-methoxybenzaldehyde (**1**), and the O-alkenelated ether **9** was formed at room temperature using K_2CO_3 and anhydrous acetone as solvent in 86% yield. The abnormal Claisen rearrangement reaction proceeded by heating ether **9** to 185 °C for 26 hours in anhydrous *N*,*N*-dimethylaniline under nitrogen. After cooling to room temperature, the reaction system was neutralized by diluted HCl. The crude product was then extracted with diethyl ether and purified via silica gel chromatography to obtain the key intermediate 5-(1,2-dimethyl-2-propenyl)-4-hydroxy-2-methoxy benzaldehyde (**5**) in 32% yield, ac-

SYNLETT 2010, No. 15, pp 2289–2292
Advanced online publication: 12.08.2010
DOI: 10.1055/s-0030-1258029; Art ID: W09910ST

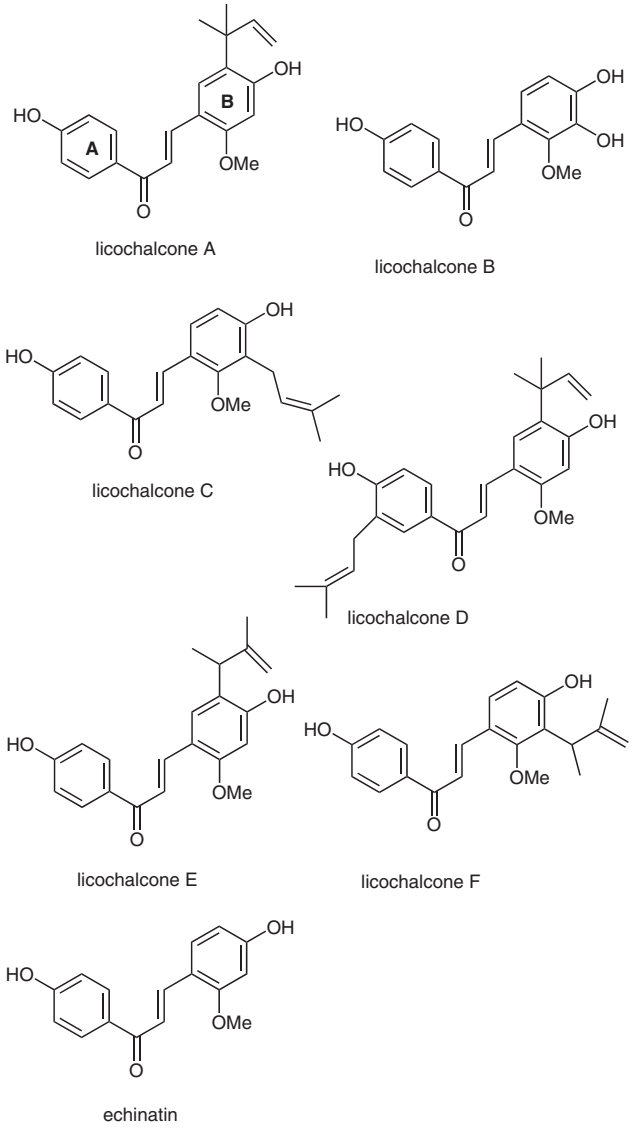
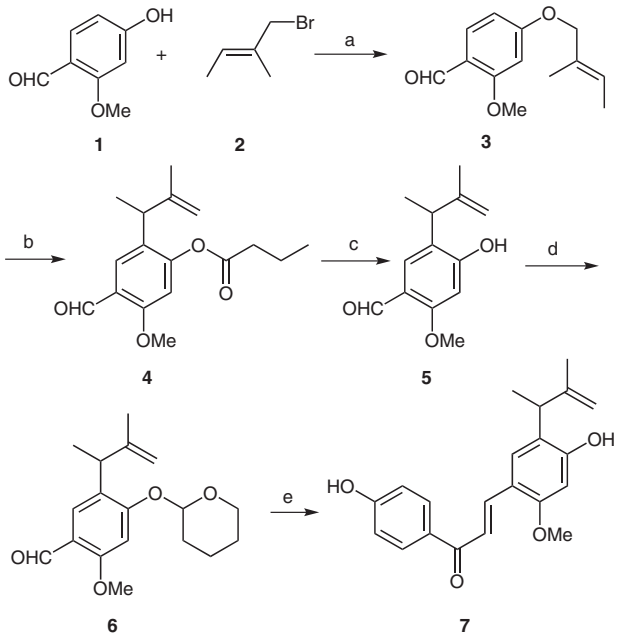


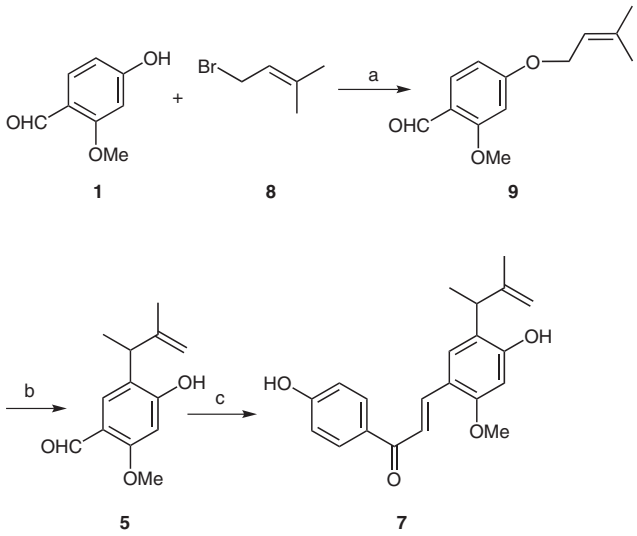
Figure 1 Structure of the retrochalcones

companied by the recovery of starting material **1** formed from the decomposition of **9** in 4% yield. Finally, 1.5–2.0 M HCl in anhydrous ethanol was added slowly to a mixture of **5** and 4-hydroxyacetophenone at 0–5 °C to promote the Claisen–Schmidt condensation. After workup, the orange-colored title product licochalcone E (**7**) was obtained in 72% yield after silica gel chromatography.

In comparison to reported literature,[14a] herein licochalcone E was synthesized efficiently by a three-step sequence from starting material prenyl bromide and 4-hydroxy-2-methoxybenzaldehyde. The spectral data of intermediate **5** and licochalcone E (**7**) were consistent with the reported literature values.[6,14] The *trans* configuration of licochalcone E could also be confirmed by the large coupling constant (J = 15.9 Hz) observed for the olefinic proton signals in its ^{1}H NMR spectrum.

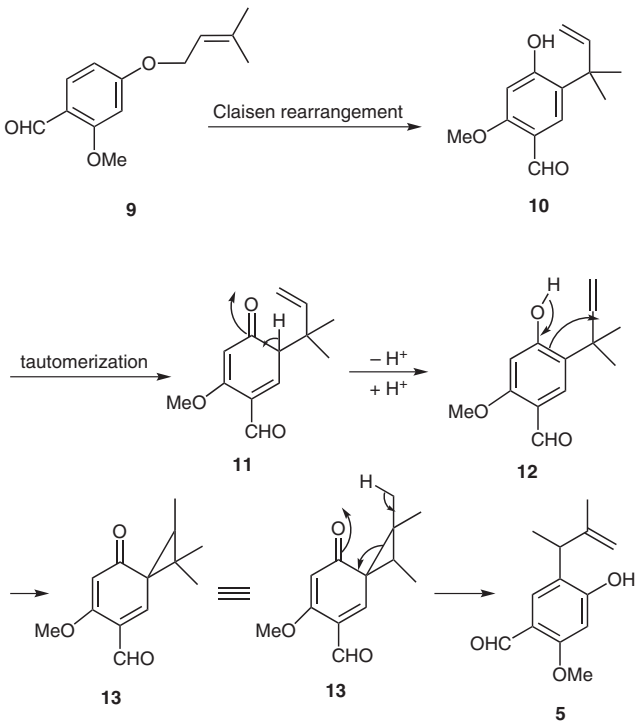


Scheme 1 Synthesis route of licochalcone E from 1-bromo-2-methyl-2*E*-butene as reported in the literature.[14a] *Reagents and conditions*: (a) K_2CO_3, acetone; (b) *N*,*N*-dimethylaniline, *n*-butyric anhydride; (c) (1) 10% NaOH–EtOH; (2) 2 M HCl; (d) THP, PTSA, CH_2Cl_2; (e) (1) 4-hydroxyacetophenone, NaOH–EtOH; (2) 4 M HCl.



Scheme 2 Total synthesis route of licochalcone E from prenyl bromide. *Reagents and conditions*: (a) K_2CO_3, acetone; (b) *N*,*N*-dimethylaniline; (c) 4-hydroxyacetophenone, HCl–EtOH.

A plausible reaction mechanism of the abnormal Claisen rearrangement is shown in Scheme 3. The initial [3,3]-sigmatropic reaction process produces the normal Claisen rearrangement compound **10** which is not isolable but undergoes tautomerization to form quinone **11**. Compound **11** then undergoes an intramolecular oxy-ene reaction to form cyclopropane **13**. Subsequently, retro oxy-ene reaction leads to the formation of the abnormal rearrangement product **5**.



Scheme 3 The mechanism of abnormal Claisen rearrangement reaction

In summary, we have developed an efficient and short access to licochalcone E via a three-step procedure with an overall yield of 20%.[21] This simple and efficient route makes the synthesis of licochalcone E in large scale possible. Furthermore, our result presented herein implies that the synthesis of other analogues of this family may also be carried out via the abnormal Claisen rearrangement reaction. Further biological study of licochalcone E and the synthesis of other modified analogues and derivatives are currently underway in our group.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This research was supported by funding from the Scientific Forefront and Interdisciplinary Innovation Project, JiLin University (Grant, No 421031531412), P. R. of China.

References and Notes

(1) Huang, K. C. *The Pharmacology of Chinese Herbs*; CRC Press: Florida, **1993**, 277.
(2) Asl, M. N.; Hosseinzadeh, H. *Phytother. Res.* **2008**, *22*, 709.
(3) Saitoh, T.; Shibata, S. *Tetrahedron Lett.* **1975**, 4461.
(4) Ayabe, S. I.; Kobayashi, M.; Hikichi, M.; Matsumoto, K.; Furuya, T. *Phytochemistry* **1980**, *19*, 2179.
(5) Kajiyama, K.; Demizu, S.; Hiraga, Y.; Kinoshita, K.; Koyama, K.; Takahashi, K.; Tamura, Y.; Okada, K.; Kinoshita, T. *Phytochemistry* **1992**, *31*, 3229.
(6) Yoon, G.; Jung, Y. D.; Cheon, S. H. *Chem. Pharm. Bull.* **2005**, *53*, 694.
(7) Park, E. J.; Park, H. R.; Lee, J. S.; Kim, J. W. *Planta Med.* **1998**, *64*, 464.
(8) Nielsen, S. F.; Chen, M.; Theander, T. G.; Kharazmi, A.; Christensen, S. B. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 449.
(9) Nielsen, S. F.; Christensen, S. B.; Cruciani, G.; Kharazmi, A.; Liljefors, T. *J. Med. Chem.* **1998**, *41*, 4819.
(10) Haraguchi, H.; Tanimoto, K.; Tamura, Y.; Mizutani, K.; Kinoshita, T. *Phytochemistry* **1998**, *48*, 125.
(11) Haraguchi, H.; Ishikawa, H.; Mizutani, K.; Tamura, Y.; Kinoshita, T. *Bioorg. Med. Chem.* **1998**, *6*, 339.
(12) Chang, H. J.; Yoon, G.; Park, J. S.; Kim, M. H.; Back, M. K.; Kim, N. H.; Shin, B. A.; Ahn, B. W.; Cheon, S. H.; Jung, Y. D. *Biol. Pharm. Bull.* **2007**, *30*, 2290.
(13) Yoon, G.; Lee, W. J.; S, N.; Cheon, S. H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5155.
(14) (a) Na, Y.; Cha, J. H.; Yoon, H. G.; Kwon, Y. J. *Chem. Pharm. Bull.* **2009**, *57*, 607. (b) Yoon, G.; Liu, Z.; Jeong, H. J.; Cheon, S. H. *Bull. Korean Chem. Soc.* **2009**, *30*, 2959. (c) Liu, Z.; Yoon, G.; Cheon, S. H. *Tetrahedron* **2010**, *66*, 3165. (d) Yoon, G.; Oak, M.; Lee, J.; Cheon, S. H. *Bull. Korean Chem. Soc.* **2010**, *31*, 1085.
(15) Schobert, R.; Siegfried, S.; Gordon, G.; Mulholland, D.; Nieuwenhuyzen, M. *Tetrahedron Lett.* **2001**, *42*, 4561.
(16) Roberts, R. M.; Landolt, R. G. *J. Org. Chem.* **1966**, *31*, 2699.
(17) Coombes, C. L.; Moody, C. J. *J. Org. Chem.* **2008**, *73*, 6758.
(18) Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131.
(19) Xu, R. S.; Wen, G. L.; Jiang, S. F.; Wang, C. G.; Jiang, F. X.; Xie, Y. Y.; Gao, Y. S. *Acta Chim. Sinica* **1979**, *37*, 289.
(20) Kromann, H.; Larsen, M.; Boesen, T.; Schonning, K.; Nielsen, S. F. *Eur. J. Med. Chem.* **2004**, *39*, 993.
(21) **Procedures for the Preparation of Licochalcone E and Selected Spectral Data**: At r.t., K_2CO_3 (2.8 g, 20.3 mmol) which had been grinded carefully was added to the stirred solution of 4-hydroxy-2-methoxybenzaldehyde (2.0 g, 13.2 mmol) in anhyd acetone. Then after 10 min, prenyl bromide (1.80 mL, 15.3 mmol) was added to the reaction mixture by pipette. The reaction was stirred for 24 h, until it was complete (checked by TLC). K_2CO_3 was removed by filtration, and the solvent was evaporated under vacuum. The crude residue was recrystallized from PE to generate the white-colored solid compound **9** (2.4 g, yield 86%). R_f 0.41 (PE–acetone = 10:2). MS: m/z = 243.2 $[M + Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.76 (s, 3 H), 1.81 (s, 3 H), 3.89 (s, 3 H), 4.57–4.59 (d, J = 6.9 Hz, 2 H), 5.46–5.51 (t, J = 6.9 Hz, 1 H), 6.46–6.47 (d, J = 2.1 Hz, 1 H), 6.54–6.57 (dd, J = 2.1, 8.7 Hz, 1 H), 7.79–7.82 (d, J = 8.7 Hz, 1 H), 10.29 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.20, 25.79, 55.52, 65.11, 98.56, 106.20, 118.62, 118.86, 130.66, 139.25, 163.50, 165.45, 188.28. IR (KBr): 2970, 2940, 1680, 1620, 1580, 1500, 1450, 1420, 1390, 1310, 1290, 1270, 1200, 1120, 1030, 928, 818, 787, 642, 602 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.82; H, 7.29. A solution of compound **9** (1.0 g, 4.54 mmol) in freshly distilled *N*,*N*-dimethylaniline (5 mL) under nitrogen atmosphere protection was stirred for 26 h at about 185 °C in sealed tube. Then after cooling to r.t., the reaction mixture was neutralized by dilute 10% HCl solution until its pH changed to 5–7. The solution was extracted with Et_2O. The Et_2O layer was washed with sat. $NaHCO_3$ and NaCl solution separately, and then dried with anhyd $MgSO_4$. The residue obtained after evaporation of the solvent was separated via silica gel column chromatography using mixtures of PE and acetone (30:1) as eluent to give the key intermediate **5** as a white solid (0.32 g, 32%), accompanied by decomposed starting material 4-hydroxy-2-methoxybenzaldehyde (**1**; 40 mg, yield: 4%).

R_f: 0.18 (PE–acetone = 10:2). MS: *m*/*z* = 221.3 $[M + H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41–1.44 (d, *J* = 7.2 Hz, 3 H), 1.63 (s, 3 H), 3.46–3.53 (q, *J* = 7.2 Hz, 1 H), 3.86 (s, 3 H), 5.07 (s, 1 H), 5.16 (s, 1 H), 6.40 (s, 1 H), 6.43 (s, 1 H), 7.66 (s, 1 H), 10.29 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.27, 20.66, 41.50, 55.65, 99.58, 111.96, 118.36, 122.31, 129.32, 149.64, 162.32, 162.76, 188.76. UV: λ_{max} (EtOH; log ε) = 278 (0.32), 235 (0.46), 206 (0.43) nm. IR (KBr): 3180, 1660, 1590, 1510, 1450, 1380, 1285, 1253, 1120, 1020, 891, 841, 694, 594 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.90; H, 7.33.

4-Hydroxyacetophenone (0.27 g, 2 mmol) and intermediate **5** (0.40 g, 1.82 mmol) were dissolved in anhyd EtOH (2 mL), cooled by ice-water bath, then anhyd 1.5–2.0 M HCl–EtOH (5 mL) was added slowly to the stirred solution. The mixture was continuously stirred for 2 h at 0–5 °C until the reaction was finished completely (checked by TLC). HCl and EtOH solvent were removed under vacuum; the mixture was then extracted with EtOAc, washed with H_2O, sat. $NaHCO_3$, then H_2O separately. The extracted layer was dried over $MgSO_4$, filtered, and the solvent was removed under vacuum. Then the title compound licochalcone E (**7**) was obtained as an orange solid (0.45 g, yield 72%) over silica gel column using mixtures of PE and acetone (10:1) as eluent.:

Licochalcone E also may be purified according to the following method: theg orange solid was precipitated completely after cooled H_2O was added slowly to the reaction mixture. The precipitated solid was then filtered, and recrystallized from cold EtOH–H_2O to provide the target compound.

R_f: 0.10 (PE–acetone = 10:4). MS: *m*/*z* = 337.3 $[M + H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45–1.47 (d, *J* = 7.2 Hz, 3 H), 1.69 (s, 3 H), 3.47–3.54 (q, *J* = 7.2 Hz, 1 H), 3.88 (s, 3 H), 5.09 (s, 1 H), 5.16 (s, 1 H), 5.67 (s, 1 H), 6.06 (s, 1 H), 6.43 (s, 1 H), 6.92–6.95 (d, *J* = 9.0 Hz, 2 H), 7.37 (s, 1 H), 7.53–7.59 (d, *J* = 15.9 Hz, 1 H), 7.99–8.02 (d, *J* = 9.0 Hz, 2 H), 7.99–8.04 (d, *J* = 15.9 Hz, 1 H). ^{13}C NMR (75 MHz, CD_3OD): δ = 19.79, 22.54, 38.97, 56.09, 99.59, 110.16, 116.31, 116.48, 119.29, 125.74, 129.91, 131.44, 132.07, 141.98, 150.39, 160.38, 160.51, 163.52, 191.79. UV: λ_{max} (EtOH; log ε) = 379 (1.33), 309 (0.94), 262 (0.84) nm. IR (KBr): 3400, 2970, 1640, 1600, 1560, 1500, 1450, 1410, 1340, 1290, 1210, 1170, 1120, 1040, 984, 895, 837, 756, 638, 611, 575 cm^{-1}. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.52; H, 6.56.