Reinvestigation of the Synthesis of Isoliquiritigenin: Application of Horner–Wadsworth–Emmons Reaction and Claisen–Schmidt Condensation

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Isoliquiritigenin [ILG, (*E*)-1] was readily prepared *via* the Horner–Wadsworth–Emmons reactions using β-ketophosphonates 5a, b. An improved protocol for the synthesis of (*E*)-1 *via* the Claisen–Schmidt condensation was also presented.

Key words isoliquiritigenin; chalcone; Horner–Wadsworth–Emmons reaction; Claisen–Schmidt condensation; *cis–trans* isomerization

Isoliquiritigenin [ILG, (*E*)-**1**] is a naturally occurring antioxidant that belongs to the class of chalcones,[1] and is known to exhibit a wide spectrum of biological activities.[2,3] For example, antiinflammatory, antitumor, antiatherosclerotic, antihistaminic, antidiabetic, antiplatelet aggregation, cardioprotective, estrogenic, quinone reductase-inducing, antiviral, antileishmanial, antimalarial, antiangiogenic, antibacterial, and antimitotic activities of ILG, (*E*)-**1** have recently been reported by various authors.[4—12] ILG [(*E*)-**1**] is a commercially available but quite expensive reagent. The most widely used method for the synthesis of ILG [(*E*)-**1**] is the Claisen–Schmidt condensation reaction of the corresponding aldehyde and ketone.[13—16] In 2003, Cavarischia and colleagues reported a novel method of synthesizing flavonoids *via* the Heck reaction.[17] However, this reaction has not been sufficiently optimized to furnish ILG [(*E*)-**1**]. In the present work, we describe an alternative protocol for the preparation of ILG [(*E*)-**1**] *via* Horner–Wadsworth–Emmons (HWE) reactions. In addition, improvement of the classical Claisen–Schmidt condensation is presented. As far as we know, our protocol constitutes the first report of the use of the HWE reaction for the synthesis of ILG [(*E*)-**1**].[18—22]

In our synthetic approach for ILG [(*E*)-**1**] and its *Z*-isomer [(*Z*)-**1**], several types of HWE reagents **5a**—**d** were prepared from the commercially available 2,4-dihydroxybenzoic acid (**2**) by the following procedure (Chart 1). Hydroxy and carboxy groups of benzoic acid **2** were protected as the corresponding methoxymethyl (MOM) ether and ester by methoxymethyl chloride (MOMCl) in the presence of Hünig's base in quantitative yield. The resultant MOM benzoate **3** was reacted with (diethoxyphosphoryl)methanide generated by deprotonation of diethyl methylphosphonate (**4a**) by lithium hexamethyldisilazide (LHMDS) to afford diethyl 2-[2,4-bis(methoxymethoxy)phenyl]-2-oxoethylphosphonate (**5a**) in 68% yield. Similarly, phosphonate **5b** was obtained in 70% yield by the reaction of dimethyl methylphosphonate (**4b**) and MOM benzoate **3**. However, phosphonates **4c**, **d** did not afford the corresponding HWE reagents **5c**, **d** because of the lability of **4c**, **d** under the same reaction conditions. Thus, phosphonates **4c**, **d** in tetrahydrofuran (THF) were added slowly into the mixture of **3** and LHMDS in THF at −50 °C. As a result, the HWE reagents

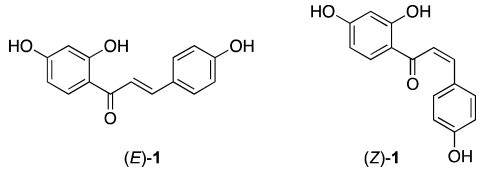

Fig. 1. Chemical Structures of ILG [(*E*)-**1**] and Its *Z*-Isomer [(*Z*)-**1**]

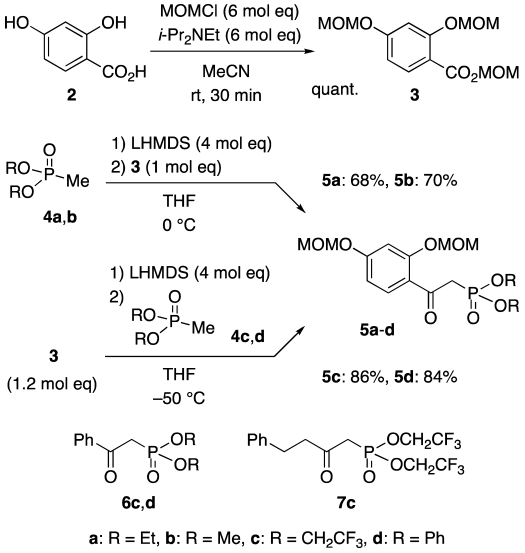

Chart 1. Synthesis of HWE Reagents **5a**—**d**

5c, **d** were successfully obtained in 86% and 84% yields, respectively. Recently, Milburn *et al.*[23] and Maloney *et al.*[24] independently reported the preparation of β-ketophosphonates by the condensation of alkyl phosphonates with various esters. However, phosphonates **4c**, **d** have not been tolerated under their reaction conditions, and the corresponding β-ketophosphonates **6c**, **d** and **7c** have not been obtained at all.

The synthesis of ILG [(*E*)-**1**] was performed *via E*-selective HWE reaction of phosphonates **5a**, **b** with 4-formylpheny benzoate (**8**) utilizing NaH as a base. The reaction of **5b** and **8** proceeded smoothly to furnish the desired *E*-olefin (*E*)-**9** in 91% yield. In order to simplify the reaction procedure, with-

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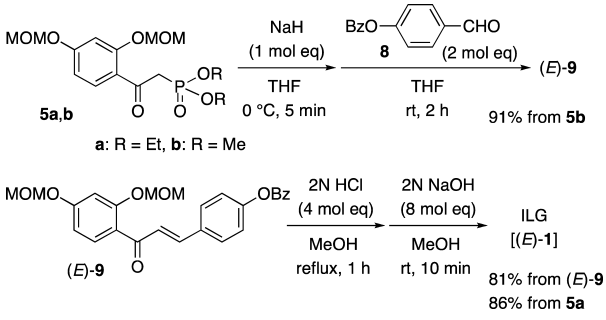

Chart 2. Synthesis of ILG [(*E*)-**1**] *via* Horner–Wadsworth–Emmons Reactions

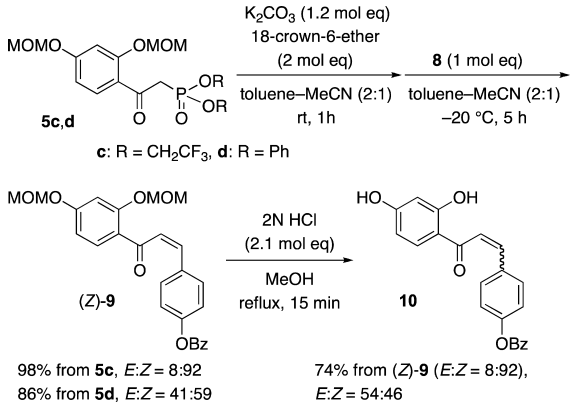

Chart 3. Synthetic Approach for (*Z*)-**10** *via* Horner–Wadsworth–Emmons Reactions

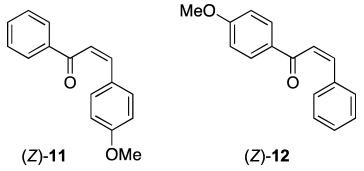

Fig. 2. Chemical Structures of (*Z*)-**11**, **12**

out the need to purify (*E*)-**9**, continuous deprotection by acidic and basic treatment afforded ILG [(*E*)-**1**] in 86% yield from **5a**, as shown in Chart 2.

Next we investigated the HWE reaction of phosphonate **5c** with 4-formylpheny benzoate (**8**) utilizing K_2CO_3 in the presence of 18-crown-6-ether. As expected, (*Z*)-**9** was obtained in a *Z*-selective manner ($E:Z=8:92$) in 98% yield. However, similar treatment of phosphonate **5d** afforded (*Z*)-**9** in 86% yield with low stereoselectivity ($E:Z=41:59$). In addition, *cis–trans* isomerization was caused by the deprotection of phenolic MOM ethers of (*Z*)-**9** ($E:Z=8:92$) with 2 N HCl under reflux conditions in methanol.[25] As a result, deprotected product **10** was obtained as a mixture of *E*/*Z* isomers ($E:Z=54:46$) in 74% yield as shown in Chart 3. In the convenient stereoselective synthesis of (*Z*)-chalcone derivatives from 1,3-diaryl-2-propynyl silyl ethers, Yoshizawa and Shioiri have warned about the potential for the facile isomerization of (*Z*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one [(*Z*)-**11**].[26] Interestingly, however, (*Z*)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one [(*Z*)-**12**], the positional isomer, was successively obtained as a major product by the same synthetic procedure (Fig. 2).

While numerous similar methods utilizing the classical

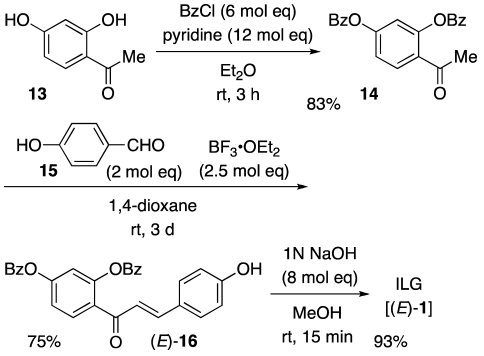

Chart 4. Synthesis of ILG [(*E*)-**1**] *via* Claisen–Schmidt Condensation under Acidic Conditions

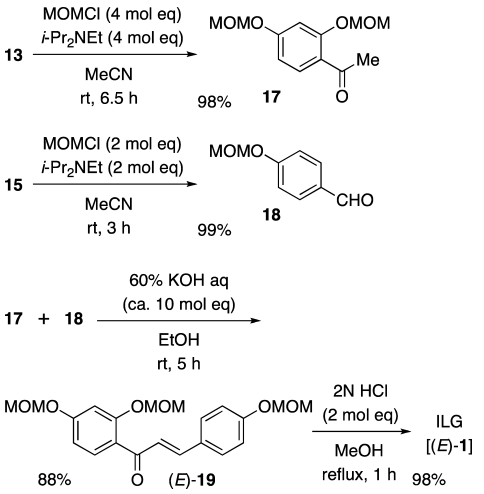

Chart 5. Synthesis of ILG [(*E*)-**1**] *via* Claisen–Schmidt Condensation under Basic Conditions

Claisen–Schmidt condensation have been reported for the synthesis of ILG [(*E*)-**1**],[13—16] these reactions have not yet been fully optimized. Thus, we reinvestigated this condensation to assess its utility for the construction of ILG [(*E*)-**1**]. Our results showed that the Claisen–Schmidt condensation of ketone **14**, which was readily available from 1-(2,4-dihydroxyphenyl)ethanone (**13**), and 4-hydroxybenzaldehyde (**15**) in the presence of $BF_3 \cdot OEt_2$ afforded (*E*)-**16** in 75% yield.[27] Following alkaline hydrolysis of (*E*)-**16**, ILG [(*E*)-**1**] was obtained in 93% yield as shown in Chart 4. In addition, ILG [(*E*)-**1**] was obtained *via* Claisen–Schmidt condensation of ketone **17** and aldehyde **18** under aqueous KOH conditions in fairly good yields.[28] Purification by column chromatography was required only once in this concise protocol (Chart 5).

In conclusion, we have demonstrated a convenient synthesis of ILG [(*E*)-**1**] *via* *E*-selective HWE reaction of HWE reagents **5a**, **b** and aldehyde **8**. Further, novel HWE reagents **5c**, **d** were synthesized successfully, though the stereoselective synthesis of (*Z*)-**10** was unsuccessful. In addition, the classical Claisen–Schmidt condensation reaction was reinvestigated and improved concise protocols of the reaction under acidic and basic conditions for the synthesis of ILG [(*E*)-**1**] were presented.

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were obtained using a JASCO

FT/IR-420 IR Fourier transform spectrometer. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on JEOL JNM-AL400 and JEOL JNM-AL300 spectrometers, respectively. Chemical shifts are given in δ values (parts per million) using tetramethylsilane (TMS) as an internal standard. Electron spray ionization mass spectra (ESI-MS) were recorded on a Waters LCT Premier spectrometer. All reactions were monitored by TLC employing 0.25-mm silica gel plates (Merck 5715; 60 F_{254}). Column chromatography was carried out on silica gel [Kanto Chemical 60N (spherical, neutral); 63—210 μm]. Anhydrous THF, toluene, 1,4-dioxane, and Et_2O were used as purchased from Kanto Chemical. Anhydrous MeCN was commercially obtained from Nacalai Tesque, Inc. All other reagents were used as purchased. The usual workup refers to washing an organic portion with brine, drying it over anhydrous Na_2SO_4, filtration, and concentration *in vacuo*. The diastereomer ratios of **9**, **10** were confirmed on the basis of integration of the appropriate proton absorptions determined by ^{1}H-NMR (400 MHz, $CDCl_3$) analysis.

Typical Procedure for the Preparation of *E*-Selective HWE Reagents 5a, b To a stirred solution of diethyl methylphosphonate (**4a**) (144 μl, 1.0 mmol) in anhydrous THF (1 ml) was added LHMDS (1.07 mol/l in *n*-hexane, 3.74 ml, 4.0 mmol) at 0 °C under an atmosphere of argon. The reaction mixture was stirred at 0 °C for 1 h, and a solution of MOM benzoate **3** (286.3 mg, 1.0 mmol) in anhydrous THF (1 ml) was slowly added to the solution. After being stirred at 0 °C for 20 h under an atmosphere of argon, the resultant mixture was treated with an aqueous saturated solution of NH_4Cl (30 ml) and then extracted with $CHCl_3$ (30 ml×3). The extract was submitted to the usual workup to give a crude product, which was purified by chromatography on a silica gel column [*n*-hexane–acetone (2 : 1)] to give **5a** (255.9 mg, 68%).

Diethyl 2-[2,4-Bis(methoxymethoxy)phenyl]-2-oxoethylphosphonate (**5a**): Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.26 (6H, t, $^3J_{H,H}$=7.1 Hz), 3.48 (3H, s), 3.54 (3H, s), 3.80 (2H, d, $^2J_{H,P}$=22.0 Hz), 4.10 (4H, m), 5.20 (2H, s), 5.29 (2H, s), 6.73 (1H, dd, $^3J_{H,H}$=8.8 Hz, $^4J_{H,H}$=2.2 Hz), 6.85 (1H, d, $^4J_{H,H}$=2.2 Hz), 7.77 (1H, d, $^3J_{H,H}$=8.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 16.3 (d, $^3J_{C,P}$=6.9 Hz), 42.4 (d, $^1J_{C,P}$=130.8 Hz), 56.3 (s), 56.6 (s), 62.2 (d, $^2J_{C,P}$=6.9 Hz), 94.2 (s), 94.9 (s), 102.9 (s), 109.1 (s), 122.0 (d, $^3J_{C,P}$=2.5 Hz), 132.8 (s), 158.5 (s), 162.3 (s), 191.4 (d, $^2J_{C,P}$=7.8 Hz); IR (neat) 3646, 2983, 2829, 2360, 1664, 1601, 1574, 1493, 1437, 1398, 1254, 1155 cm^{-1}; ESI-MS Calcd for $C_{16}H_{25}NaO_8P$ MW 399.1185, Found *m/z* 399.1185 (M^++Na).

Dimethyl 2-[2,4-Bis(methoxymethoxy)phenyl]-2-oxoethylphosphonate (**5b**): Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.48 (3H, s), 3.54 (3H, s), 3.77 (6H, d, $^3J_{H,P}$=11.2 Hz) 3.81 (2H, d, $^2J_{H,P}$=21.7 Hz), 5.21 (2H, s), 5.30 (2H, s), 6.73 (1H, dd, $^3J_{H,H}$=8.8 Hz, $^4J_{H,H}$=2.2 Hz), 6.86 (1H, d, $^4J_{H,H}$=2.2 Hz), 7.81 (1H, d, $^3J_{H,H}$=8.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 41.5 (d, $^2J_{C,P}$=132.0 Hz), 52.8 (d, $^2J_{C,P}$=6.2 Hz), 56.4 (s), 56.6 (s), 94.2 (s), 94.9 (s), 102.9 (s), 109.2 (s), 121.6 (d, $^3J_{C,P}$=3.1 Hz), 132.9 (s), 158.8 (s), 162.5 (s), 190.9 (d, $^2J_{C,P}$=6.9 Hz); IR (neat) 3465, 2958, 2852, 2360, 1664, 1601, 1402, 1255, 1155, 1032 cm^{-1}; ESI-MS Calcd for $C_{14}H_{21}NaO_8P$ MW 371.0872, Found *m/z* 371.0877 (M^++Na).

Typical Procedure for the Preparation of *Z*-Selective HWE Reagents 5c, d To a solution of MOM benzoate **3** (687.1 mg, 2.4 mmol) in anhydrous THF (10 ml) was added LHMDS (1.07 mol/l in *n*-hexane, 7.48 ml, 8.0 mmol) at −50 °C, and then a solution of bis(2,2,2-trifluoroethyl)methyl phosphonate (**4c**, 396 μl, 2.0 mmol) in anhydrous THF (10 ml) was slowly added to the reaction mixture at −50 °C under an atmosphere of argon. After being stirred at −50 °C for 2 min, the solution was treated with a saturated aqueous solution of NH_4Cl (30 ml) and then extracted with Et_2O (30 ml×3). The extract was submitted to the usual workup to give a crude product, which was purified by chromatography on a silica gel column [*n*-hexane–acetone (4 : 1)] to give **5c** (833.3 mg, 86%).

Bis(2,2,2-trifluoroethyl) 2-[2,4-Bis(methoxymethoxy)phenyl]-2-oxoethylphosphonate (**5c**): Colorless needles ($CHCl_3$–*n*-hexane): mp 69—70 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.48 (3H, s), 3.53 (3H, s), 3.94 (2H, d, $^2J_{H,P}$=19.5 Hz), 4.44—4.51 (4H, m), 5.21 (2H, s), 5.30 (2H, s), 6.75 (1H, dd, $^3J_{H,H}$=8.8 Hz, $^4J_{H,H}$=2.2 Hz), 6.85 (1H, d, $^4J_{H,H}$=2.2 Hz), 7.83 (1H, d, $^3J_{H,H}$=8.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 42.4 (d, $^1J_{C,P}$=142.6 Hz), 56.4 (s), 56.7 (s), 62.3 (qd, $^2J_{C,F}$=38.0 Hz, $^2J_{C,P}$=5.6 Hz), 94.2 (s), 94.8 (s), 102.7 (s), 109.5 (s), 120.6 (d, $^3J_{C,P}$=5.6 Hz), 122.7 (qd, $^1J_{C,F}$=277.4 Hz, $^3J_{C,P}$=8.7 Hz), 132.9 (d, $^4J_{C,P}$=1.0 Hz), 158.9 (s), 163.2 (s), 190.1 (d, $^2J_{C,P}$=7.5 Hz); IR (KBr) 2968, 1670, 1601, 1574, 1487, 1163, 1076 cm^{-1}; ESI-MS Calcd for $C_{16}H_{19}F_6NaO_8P$ MW 507.0619, Found *m/z* 507.0620 (M^++Na); *Anal.* Calcd for $C_{16}H_{19}F_6O_8P$: C, 39.68; H, 3.95. Found: C, 39.57; H, 4.14%.

Diphenyl 2-[2,4-Bis(methoxymethoxy)phenyl]-2-oxoethylphosphonate (**5d**): Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.44 (3H, s), 3.49 (3H, s), 4.09 (2H, d, $^2J_{H,P}$=22.2 Hz), 5.17 (2H, s), 5.20 (2H, s), 6.75 (1H, dd, $^3J_{H,H}$=8.8 Hz, $^4J_{H,H}$=2.2 Hz), 6.84 (1H, d, $^4J_{H,H}$=2.2 Hz), 7.13—7.17 (6H, m), 7.27—7.31 (4H, m), 7.85 (1H, d, $^3J_{H,H}$=8.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 42.0 (d, $^1J_{C,P}$=132.0 Hz), 56.4 (s), 56.6 (s), 94.1 (s), 94.9 (s), 102.8 (s), 109.3 (s), 120.7 (d, $^3J_{C,P}$=4.4 Hz), 121.5 (d, $^3J_{C,P}$=1.9 Hz), 125.2 (s), 129.7 (s), 133.0 (s), 150.2 (d, $^2J_{C,P}$=8.7 Hz), 158.7 (s), 162.6 (s), 189.7 (d, $^2J_{C,P}$=7.5 Hz); IR (neat) 2956, 2829, 1664, 1601, 1491, 1277, 1215, 1188, 1157 cm^{-1}; ESI-MS Calcd for $C_{24}H_{25}NaO_8P$ MW 495.1185, Found *m/z* 495.1185 (M^++Na); Anal. Calcd for $C_{24}H_{25}O_8P$: C, 61.02; H, 5.33. Found: C, 60.72; H, 5.41%.

Typical Procedure for the Preparation of Isoliquilitigenin [(*E*)-1] by *E*-Selective HWE Reaction To a solution of **5a** (106.5 mg, 0.283 mmol) in anhydrous THF (3 ml) was added NaH (50% dispersion in oil, 13.6 mg, 0.283 mmol) at 0 °C under an atmosphere of argon. After being stirred at 0 °C for 5 min, 4-formylphenyl benzoate (**8**, 128.0 mg, 0.566 mmol) was added to the resultant solution, and then the temperature was raised to room temperature. After being stirred at room temperature for 2 h, the reaction mixture was treated with a saturated aqueous solution of NH_4Cl (15 ml) and extracted with AcOEt (20 ml×3). To a solution of the resultant crude (*E*)-**9** in MeOH (15 ml) was added 2 N HCl (0.556 ml, 1.132 mmol), and the solution was refluxed for 1 h. The reaction mixture was cooled to room temperature and 2 N NaOH (1.132 ml, 2.264 mmol) was added. After being stirred at room temperature for 10 min, the reaction mixture was treated with 2 N HCl (0.5 ml) and then extracted with AcOEt (20 ml×3). The combined extract was submitted to the usual workup to give a crude product, which was purified by chromatography on a silica gel column [*n*-hexane–AcOEt (4 : 1)] to give (*E*)-**1** (62.2 mg, 86%) as yellow needles (acetone–*n*-hexane): mp 201—202 °C; ^{1}H-NMR (400 MHz, CD_3OD) δ: 6.28 (1H, d, $^4J_{H,H}$=2.4 Hz), 6.40 (1H, dd, $^3J_{H,H}$=8.8 Hz, $^4J_{H,H}$=2.4 Hz), 6.83 (2H, d, $^3J_{H,H}$=8.8 Hz), 7.60 (1H, d, $^3J_{H,H}$=15.4 Hz), 7.61 (2H, d, $^3J_{H,H}$=8.8 Hz), 7.78 (1H, d, $^3J_{H,H}$=15.4 Hz), 7.96 (1H, d, $^3J_{H,H}$=8.8 Hz); ^{13}C-NMR (75 MHz, CD_3OD) δ: 103.8 (s), 109.2 (s), 114.7 (s), 116.9 (s), 118.3 (s), 127.9 (s), 131.9 (s), 133.4 (s), 145.7 (s), 161.6 (s), 166.4 (s), 167.6 (s), 193.5 (s); IR (KBr) 3288, 1630, 1543, 1514, 1369, 1292, 1225, 1167, 1144, 1032 cm^{-1}; ESI-MS Calcd for $C_{15}H_{12}NaO_4$ MW 279.0633, Found *m/z* 279.0635 (M^++Na); *Anal.* Calcd for $C_{15}H_{12}O_4 \cdot 1/2\ H_2O$: C, 67.92; H, 4.94. Found: C, 67.99; H, 4.96%.

Typical Procedure of *Z*-Selective HWE Reaction for the Preparation of (*Z*)-9 A solution of **5c** (242.1 mg, 0.5 mmol), K_2CO_2 (82.9 mg, 0.6 mmol), and 18-crown-6-ether (264.3 mg, 1.0 mmol) in anhydrous toluene (3 ml) and MeCN (1.5 mL) was stirred at room temperature for 1 h under an atmosphere of argon. After being cooled to −20 °C, aldehyde **8** (113.1 mg, 0.5 mmol) was added to the solution, and then the stirring was continued for 5 h. The reaction mixture was treated with a saturated aqueous solution of NH_4 (30 mL) and then extracted with $CHCl_3$ (30 ml×3). The combined extract was submitted to the usual workup to give a crude product, which was purified by chromatography on a silica gel column [*n*-hexane–AcOEt (3 : 1)] to give (*Z*)-**9** (219.5 mg, 98%, *E* : *Z*=8 : 92) as a yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.45 (3H, s), 3.50 (3H, s), 5.20 (2H, s), 5.23 (2H, s), 6.71 (1H, d, $^3J_{H,H}$=12.7 Hz), 6.73 (1H, dd, $^3J_{H,H}$=8.7 Hz, $^4J_{H,H}$=2.2 Hz), 6.80 (1H, d, $^3J_{H,H}$=12.7 Hz), 6.80 (1H, d, $^4J_{H,H}$=2.2 Hz), 7.13 (2H, d, $^3J_{H,H}$=8.7 Hz), 7.49—7.53 (2H, m), 7.59 (2H, d, $^3J_{H,H}$=8.7 Hz), 7.62—7.66 (1H, m), 7.76 (1H, d, $^3J_{H,H}$=8.7 Hz), 8.17—8.19 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 56.3 (s), 56.5 (s), 94.2 (s), 94.8 (s), 103.2 (s), 109.1 (s), 121.3 (s), 123.2 (s), 128.6 (s), 129.4 (s), 130.2 (s), 130.4 (s), 130.8 (s), 132.8 (s), 133.3 (s), 133.6 (s), 136.5 (s), 151.0 (s), 158.2 (s), 161.9 (s), 164.9 (s), 192.2 (s); IR (neat) 2956, 2827, 2360, 1738, 1649, 1601, 1504, 1252, 1205, 1169 cm^{-1}; ESI-MS Calcd for $C_{26}H_{24}NaO_7$ MW 471.1420, Found *m/z* 471.1442 (M^++Na); *Anal.* Calcd for $C_{26}H_{24}O_7$: C,69.63; H, 5.39. Found: C, 69.37; H, 5.40%.

Claisen–Schmidt Condensation under Acidic Conditions for the Preparation of (*E*)-16 To a stirred solution of ketone **14** (180.7 mg, 0.5 mmol) and aldehyde **15** (122.1 mg, 1.0 mmol) in anhydrous 1,4-dioxane (180 μl) under an atmosphere of argon at room temperature, $BF_3 \cdot Et_2O$ (158 μl, 1.26 mmol) in anhydrous 1,4-dioxane (270 μl) was added in three portions at 24 h intervals. The resultant solution was stirred at room temperature for another 24 h, then the reaction mixture was treated with H_2O (20 ml) and extracted with AcOEt (30 ml×3). The combined extract was submitted to the usual workup to give a crude product, which was purified by chromatography on a silica gel column [*n*-hexane–AcOEt (3 : 1)] to give (*E*)-**16** (175.7 mg, 75%) as a pale yellow powder (*n*-hexane–$CHCl_3$): mp 154—156 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.60 (1H, br s), 6.73 (2H, d, $^3J_{H,H}$=8.8 Hz), 7.00 (1H, d, $^3J_{H,H}$=15.9 Hz), 7.26—7.31 (4H, m), 7.37—7.42 (2H, m), 7.51—7.58 (4H, m), 7.64—7.69 (1H, m), 7.81—7.84 (1H, m), 8.10—8.13 (2H, m), 8.20—8.22 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 116.0 (s), 117.4 (s), 119.6 (s), 122.6 (s), 126.7 (s), 128.6 (s), 128.8 (s), 130.2

(s), 130.3 (s), 130.6 (s), 131.0 (s), 134.0 (s), 134.1 (s), 146.3 (s), 149.7 (s), 153.5 (s), 158.8 (s), 164.7 (s), 164.9 (s), 191.0 (s); IR (KBr) 3406, 3051, 1741, 1709, 1672, 1601, 1577, 1516, 1277, 1130 cm^{-1}; ESI-MS Calcd for $C_{29}H_{20}NaO_6$ MW 487.1158, Found *m*/*z* 487.1156 (M^++Na).

Claisen–Schmidt Condensation under Basic Conditions for the Preparation of (*E*)-19 To a mixture of ketone **17** (240.3 mg, 1.0 mmol) and aldehyde **18** (166.2 mg, 1.0 mmol) in EtOH (2 ml) was slowly added KOH (60% in H_2O, 1.0 g, 10.7 mmol) at 0 °C, and the resultant solution was stirred at room temperature for 5 h. The reaction mixture was treated with 1 N HCl (10 ml) and then extracted with AcOEt (20 ml×3). The extract was submitted to the usual workup to give a crude product, which was purified by chromatography on a silica gel column [*n*-hexane–AcOEt (3 : 1)] to give (*E*)-**19** (341.0 mg, 88%) as a yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.49 (3H, s), 3.49 (3H, s), 3.50 (3H, s), 5.21 (2H, s), 5.22 (2H, s), 5.24 (2H, s), 6.77 (1H, dd, $^3J_{H,H}$=8.8 Hz, $^4J_{H,H}$=2.2 Hz), 6.85 (1H, d, $^4J_{H,H}$=2.2 Hz), 7.05 (2H, d, $^3J_{H,H}$=8.8 Hz), 7.35 (1H, d, $^3J_{H,H}$=15.9 Hz), 7.53 (2H, d, $^3J_{H,H}$=8.8 Hz), 7.62 (1H, d, $^3J_{H,H}$=15.9 Hz), 7.66 (1H, d, $^3J_{H,H}$=8.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 56.1 (s), 56.3 (s), 56.5 (s), 94.2 (s), 94.3 (s), 95.0 (s), 103.6 (s), 109.2 (s), 116.5 (s), 124.2 (s), 125.4 (s), 129.0 (s), 129.9 (s), 132.1 (s), 142.3 (s), 157.4(s), 158.9 (s), 161.2 (s), 191.1 (s); IR (neat) 2956, 2827, 1653, 1603, 1510, 1313, 1242, 1153, 1080 cm^{-1}; ESI-MS Calcd for $C_{21}H_{24}NaO_7$ MW 411.1420, Found *m*/*z* 411.1421 (M^++Na); *Anal.* Calcd for $C_{21}H_{24}O_7$: C, 64.94; H, 6.23. Found: C, 64.70; H, 6.19%.

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