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Gram-scale synthesis of anti-pancreatic flavonoids (±)-8-[1-(4′-hydroxy-3′-methoxyphenyl)prop-2-en-1-yl]-chrysin and -galangin

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ABSTRACT

Gram-scale total synthesis of (±)-8-[1-(4′-hydroxy-3′-methoxyphenyl)prop-2-en-1-yl]-galangin (**1**) and -chrysin (**2**) has been accomplished in eight steps from commercially available phloroglucinol and three steps from commercially available chrysin, respectively, featuring an efficient introduction of C(8) (1-prop-2-en-1-yl)phenyl moiety in the natural products through chemo- and regioselective cinnamylation and regioselective aromatic Claisen rearrangement.

1. Introduction

Pancreatic cancer has had a markedly increased incidence during the past several decades and ranks as the fourth leading cause of cancer death in the US. According to the *American Cancer Society's 2013 Cancer Facts and Figures*, pancreatic cancer accounts for about 7% of all cancer deaths and is the 10th most common cancer diagnosis among men and the 9th most common among women in the US.[1]

Recently, Kadota and co-workers reported the isolation and structural elucidation of anti-pancreatic agents (7″*R*)-8-[1-(4′-hydroxy-3′-methoxyphenyl)prop-2-en-1-yl]galangin (**1**) and (7″*R*)-8-[1-(4′-hydroxy-3′-methoxyphenyl)prop-2-en-1-yl]chrysin (**2**) from propolis, collected from Brazil and Myanmar[2a] (Fig. 1).

The structure of **1** and **2** was determined by extensive NMR spectroscopic analysis to reveal that structurally, **1** and **2** are the first cases possessing unusual C(8) 1-phenyl-prop-2-en-1-yl appendage in flavone or flavonol skeletal, which of structures have not been found in any natural source.[3] Their absolute configuration was assigned based on their structural similarities to the known compounds (7*R*)-2-hydroxy-4,5-dimethoxydalbergiquinol (**3**), (7*S*)-2,4-dihydroxydalbergiquinol (**4**), and (7*S*)-3,4-dihydroxydalbergiquinol (**5**) isolated from Nepalese propolis utilizing Cotton effect and $[\alpha]_D$ values (specific optical rotation).[2a]

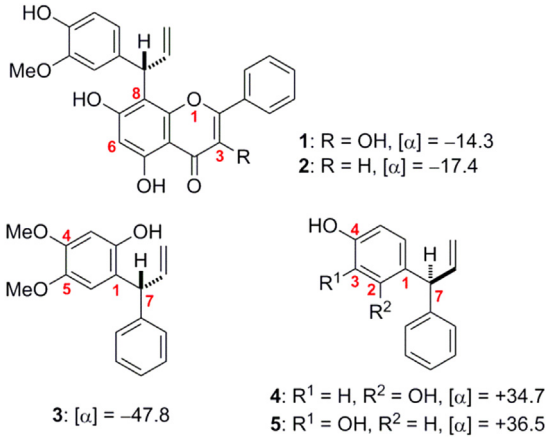

Fig. 1. Anti-pancreatic flavonoids **1** and **2** and their structurally related compounds.

Compounds **1** and **2** exhibited a potent preferential cytotoxicity (PC_{50}) (4.6 and 12.7 μM for **1** and **2**, respectively) against human pancreatic cancer cells (PANC-1) in a nutrient-deprived medium (NDM), but **1** was noncytotoxic up to 100 μM against normal TIG-3 human fetal lung fibroblast cells indicating its selectivity against PANC-1 cells.[2] Due to the great potential as a promising anti-pancreatic compound, the scarcity (0.0025% and 0.005% isolated yield for **1** and **2**, respectively, from crude propolis) and a need for further biological evaluation of **1** and **2**, we sought to develop an efficient

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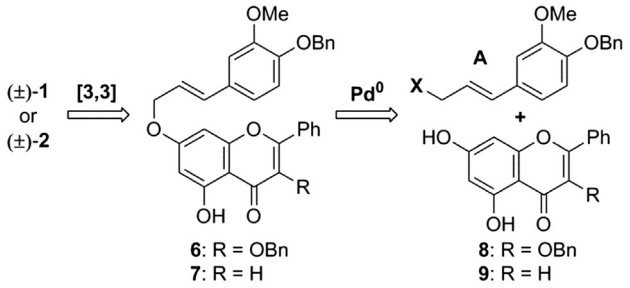
and facile synthetic route that would be amenable to provide sufficient (gram-quantity) quantities of **1** and **2** for further biological studies as potential new drug candidate. Herein, we report a concise and efficient route to gram-scale first total synthesis of (±)-**1** and (±)-**2** highlighted by a Pd^0-catalyzed chemo- and regioselective cinnamylation and regioselective aromatic Claisen rearrangement.[4–6]

Our retrosynthetic plan for (±)-**1** and (±)-**2** is outlined in Scheme 1. Structurally, (±)-**1** and (±)-**2** consist of flavone or flavonol core and unusual C(8) 1-phenyl-prop-2-en-1-yl appendage. Therefore, it would be desirable that two key fragments flavone or flavonol core were coupled with latent 1-phenyl-prop-2-en-1-yl moiety by appropriate methods that could allow for analogs of C(8)-appendage. Keeping this protocol in mind, we envisioned that (±)-**1** and (±)-**2** could be completed from flavonol **6** and flavone **7**, respectively, by regioselective aromatic Claisen rearrangement at C(8). Cinnamyl ethers (units) in flavonol **6** and flavone **7** would be accessible by a cinnamylation of C(7)-hydroxyl in bis-phenol **8** or commercially available chrysin (**9**) with electrophilic cinnamyl units **A** by appropriate coupling methodologies even though the issues on the chemo- and regioselectivity should be considered.

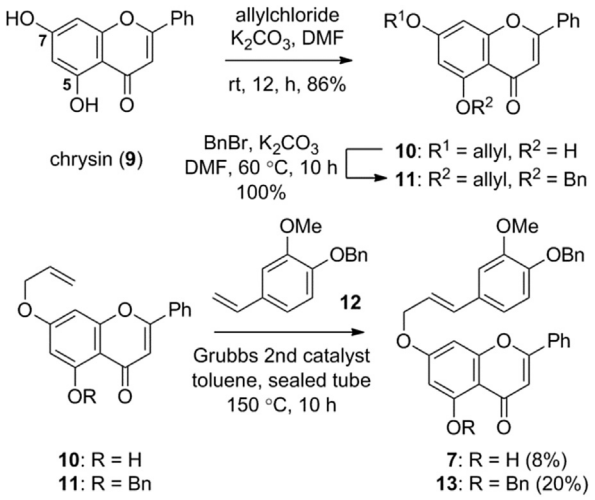


Scheme 1. Retrosynthetic plan for (±)-**1** and (±)-**2**.

2. Results and discussion

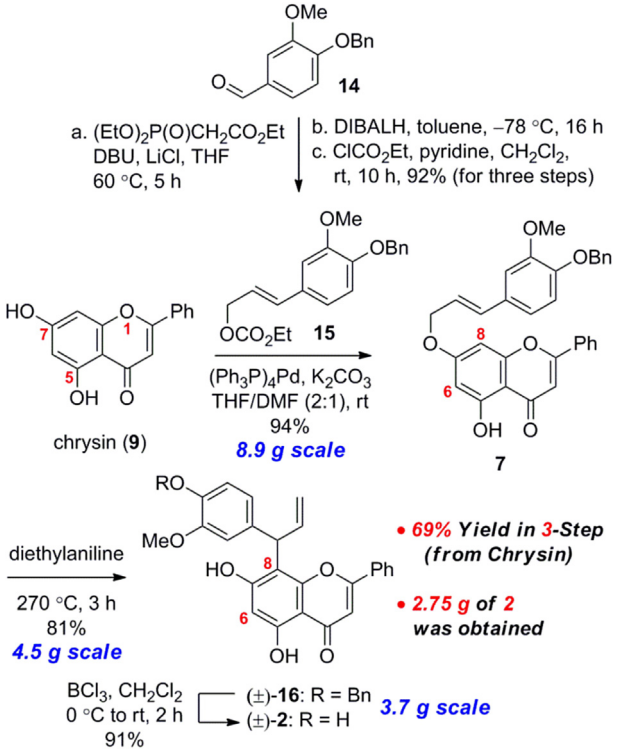
To test the possibility of an application of same protocol for synthesis of (±)-**1** and (±)-**2**, as described in our retrosynthetic plan, we embarked on the synthesis of (±)-**2**. Synthesis of (±)-**2** started with the preparation of aryl allyl ether **7** for aromatic Claisen rearrangement.[4–6] Initially, we tried to convert commercially available chrysin (**9**) to the corresponding aryl allyl ether **7** or **13** using conventional method, such as Mitsunobu reaction or Williamson ether synthesis, etc. However, to our disappointment, conventional O-alkylation with cinnamyl halide (Cl or Br) or Mitsunobu reaction with chrysin or the corresponding C(5)-Bn protected chrysin under various conditions provided desired product **13** in very poor yield (<5%), probably due to the instability of activated cinnamyl moiety (or intermediate) with electron-rich substituents in aromatic ring, such as OMe and OBn groups.

Alternatively, we adopted two-step synthesis of aryl allyl ether **7** by allylation and the cross-metathesis (CM) reaction[7] for formal cinnamylation. Thus, allyl ether **10** was prepared by direct allylation of chrysin without protecting of C(5)-hydroxyl in chrysin (**9**) (Scheme 2). CM reaction of allyl ether **10** and the known styrene **12**[8] also proved to be problematic due to low reactivity of **10** with styrene **12** and homo-CM reaction of styrene **12**. We also tried CM reaction of **11** and styrene **12** in the presence of Grubbs second-generation catalyst in refluxing CH_2Cl_2. However, in this reaction condition, aryl allyl ether **13** was obtained in poor yield (<5%) along with a large amount (~70%) of homo-CM adduct of styrene **12**. After optimization of CM reaction conditions, subjection of allyl ether **11** and styrene **12** to CM condition using Grubbs second-generation catalyst in toluene at 150 °C under sealed tube produced **13** in 20% yield, which was still unsatisfactory for scalable synthesis.



Scheme 2. Initial synthesis of aryl allyl ether **7** and **13**.

After extensive investigation on literature, we delighted to find that Pd^0-catalyzed cinnamylation of phenol could be effective for preparation of the allyl aryl ether in high yield and excellent regioselectivity demonstrated by Sinou group,[9] even though there still remains chemoselectivity issue. Encouraged by Sinou group's work, we decided to utilize their protocol for allyl aryl ether. To this end, ethyl cinnamyl carbonate **15** was prepared from commercially available 4-benzyloxy-3-methoxybenzaldehyde (**14**) in 92% overall yield by Horner–Wadsworth–Emmons olefination, DIBAL-H reduction, and ethoxycarbonylation. To our delight, the treatment of chrysin (**9**) with ethyl cinnamyl carbonate **15** in the presence of $(Ph_3P)_4Pd$ and K_2CO_3 in THF/DMF (2:1) at room temperature, smoothly provided the desired **7** in high yield (94%) and regio- and chemoselectivity selectivity (Scheme 3).[10]



Scheme 3. Completion of synthesis of flavone (±)-**2**.

With the aryl allyl ether **7** in hand, we turned our attention to aromatic [3,3]-sigmatropic rearrangement to introduce 1-prop-2-en-1-ylphenyl moiety in the natural products (Scheme 3). As expected, aryl allyl ether **7** in diethylaniline at 270 °C smoothly provided (±)-**16** in 81% yield in a highly regioselective manner (>20:1).[11–14] There is one report related on regioselective aromatic Claisen rearrangement of C(7) allyl ether in chrysin derivatives with C(5) acetyl protecting group.[10] Therefore our result consists of the first case on Claisen rearrangement of C(7) allyl ether with C(5) free hydroxyl in chrysin moiety and led to step-economy synthesis.[15]

The rationale on highly regioselectivity of aromatic Claisen rearrangement is not clear. However, assuming that the steric and electronic factors would be involved in the reaction, the transition state **7A** could be favored over **7B** due to steric hindrance between C(5) hydroxyl and Ar group in **7B** compared with O(1) oxygen and Ar group in **7A** and electronically more stable *endo*-conjugated pyrone system in **7A** than *exo*-system in **7B** described in Fig. 2.

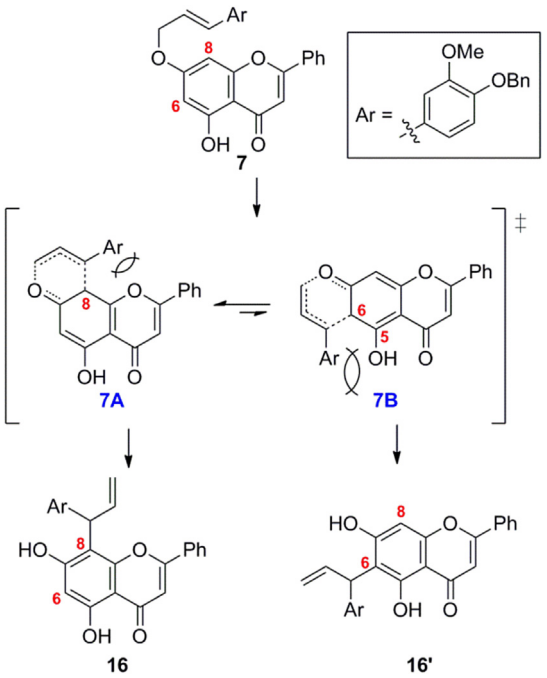
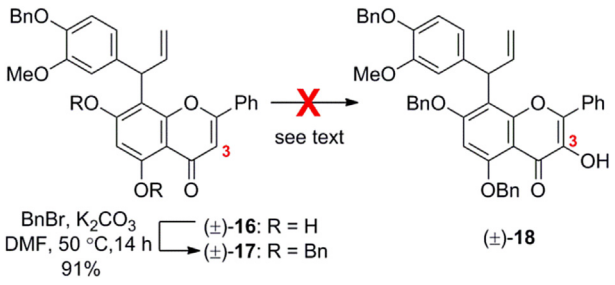


Fig. 2. The rationale on highly regioselectivity of aromatic Claisen rearrangement of aryl ally ether **7**.

Finally, deprotection of benzyl groups in the flavone (±)-**16** with BCl_3 in CH_2Cl_2 furnished (±)-**2** in 91% yield.[2] The spectral data for synthetic (±)-**2** were identical in every respect with those reported for the natural compound (^1H, ^{13}C, IR, and HRMS). It is worth to note that synthesis of (±)-**2** has been accomplished with 65% overall yield in six total steps from commercially available aldehyde **14** [three steps from commercially available chrysin (**9**)], and this short and efficient route to the synthesis enabled to prepare the multigram quantity of the (±)-**2**.

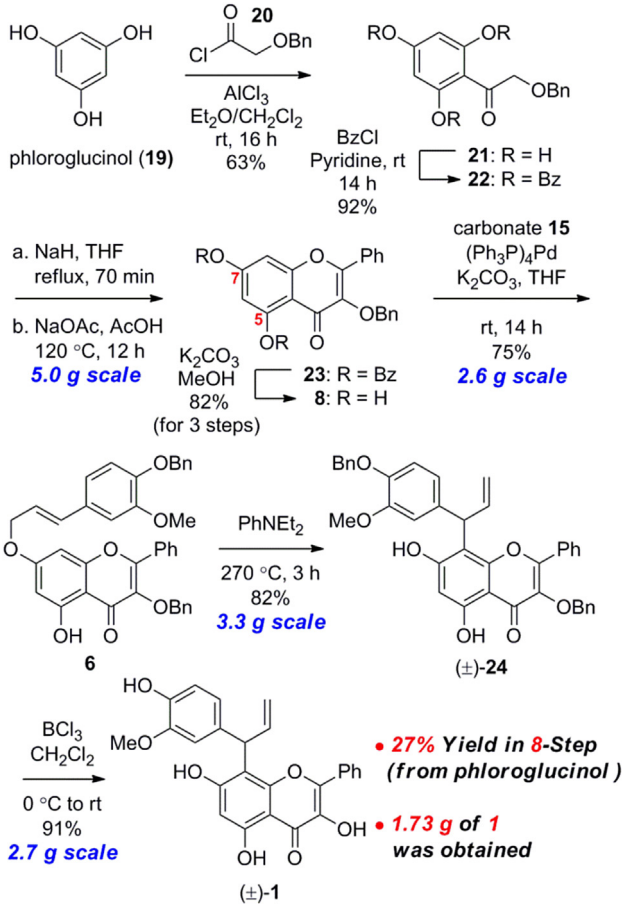
After completion of flavone (±)-**2**, we embarked on the synthesis of flavonol (±)-**1**. In the context of step-economy,[15] the direct synthesis of flavonol from flavone would be desirable. Encouraged by other group's results, we expected that the C(3) hydroxylation of flavone using oxidation condition, such as DIAB,[16] DMDO,[17] or LDA/$B(OMe)_3/H_2O_2$,[18] etc. would provide a direct route to flavonol (±)-**1**. To this end, hydroxyls in flavone (±)-**16** were protected as benzyl ether (±)-**17** (Scheme 4). Disappointingly our all attempts did not provide desired flavonol (±)-**18**, but recovery or decomposition of starting material (±)-**17**, which led us to utilize the same protocol used to synthesis of flavone (±)-**2**.



Scheme 4. Attempted C(3) hydroxylation for synthesis of flavonol (±)-**1**.

Since C(8) appendage was successfully installed in chemo- and regioselective manners in the flavone (±)-**2** synthesis, we focused on the efficient preparation of 5,7-dihydroxy flavonol **8** for synthesis of flavonol (**1**). Initially, we attempted to use Algar–Flynn–Oyamada (AFO) reaction[19] from chalcone, however, this methods gave rise to aurone derivative exclusively.[20]

Next, we decided to utilize Baker–Venkataraman rearrangement and dehydration protocol,[21] of which successfully led us to gain the key 5,7-dihydroxy flavonol **8** (vide infra). Known 2-(benzyloxy)-1-(2,4,6-trihydroxyphenyl)ethanone (**21**)[22] prepared by Friedel–Crafts acylation of commercially available materials phloroglucinol (**19**) and 2-(benzyloxy)acetyl chloride (**20**) in 63%, was converted to the tribenzoate **22** in 92% yield (Scheme 5). The treatment of tribenzoate **22** with NaH in THF and the exposure to NaOAc in AcOH provided flavonol **23**, followed by methanolysis led to the key 5,7-dihydroxy flavonol **8** in 82% overall yield for the three steps. For the completion of flavonol (±)-**1** synthesis, the installation sequence of C(8) (1-prop-2-en-1-yl)phenyl appendage was analogous to the 'sequence' earlier described in flavone (±)-**2**



Scheme 5. Completion of synthesis of flavonol (±)-**1**.

synthesis. The synthesis of flavonol (±)-**1** was completed in 56% overall yield for three steps from 5,7-dihydroxy flavonol **8** [27% from phloroglucinol (**19**)]. The spectral data for synthetic (±)-**1** were identical in every respect with those reported for the natural compound (^{1}H, ^{13}C, IR, and HRMS).

3. Conclusion

Gram-scale first total synthesis of (±)-8-[1-(4′-hydroxy-3′-methoxyphenyl)prop-2-en-1-yl]galangin (**1**) and (±)-8-[1-(4′-hydroxy-3′-methoxyphenyl)prop-2-en-1-yl]chrysin (**2**) has been accomplished in eight steps from commercially available phloroglucinol (**19**) and three steps from commercially available chrysin (**9**), respectively [or total 11 steps and 6 steps from commercially available 4-benzyloxy-3-methoxybenzaldehyde (**14**), respectively], featuring an efficient introduction of C(8) (1-prop-2-en-1-yl)phenyl moiety in the natural products through chemo- and regioselective cinnamylation and regioselective aromatic Claisen rearrangement. We strongly insist that our synthetic routes provide a gram-scale preparation of flavonoids (±)-**1** and (±)-**2**, and firmly believe that their gram-quantities enable to investigate extensive in vitro/in vivo biological studies to develop lead compounds for anti-pancreatic cancer drug. Asymmetric synthesis and the biological evaluation of (±)-**1** and (±)-**2** to the other pancreatic cancer cells are underway and will be reported in due course.

4. Experimental

4.1. General procedure

Proton (^{1}H) and carbon (^{13}C) NMR spectra were obtained on a Varian Mercury 400 (400/100 MHz), spectrometer. Chemical shifts are reported in parts per million units with Me_4Si or $CHCl_3$ as the internal standard. All reactions were routinely carried out under an inert atmosphere of dry nitrogen or argon. Reactions were checked by thin layer chromatography (Kieselgel 60 F_{254}, Merck). Spots were detected by viewing under a UV light, and by colorizing with charring after dipping in anisaldehyde solution in a mixture of acetic acid, sulfuric acid, and methanol. In aqueous work-up, all organic solutions were dried over anhydrous sodium sulfate and filtered prior to rotary evaporation. The crude compounds were purified by column chromatography on a silica gel (Kieselgel 60, 70–230 mesh, Merck). Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. All solvents were purified and dried by standard techniques just before use. THF and Et_2O were freshly distilled from sodium and benzophenone. Methylene chloride, toluene, and benzene were purified by refluxing with CaH_2. Hexanes and ethylacetate were purified by simple distillation.

4.2. Experimental procedure

*4.2.1. Allyl ether **10**.* To a solution of chrysin (**9**) (2.542 g, 10.0 mmol) in DMF (30 mL) were added K_2CO_3 (2.764 g, 20.0 mmol) and allyl chloride (1.63 g, 20.0 mmol) at room temperature. The reaction mixture was stirred for 12 h and quenched with saturated aqueous NH_4Cl. The resulting mixture was diluted with EtOAc, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford allyl ether **10** (2.714 g, 86%) as a white solid (mp; 145–146 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.68 (s, 1H), 7.82 (dd, J=8.0, 1.2 Hz, 2H), 7.51–7.45 (m, 3H), 6.59 (s, 1H), 6.45 (d, J=2.0 Hz, 1H), 6.33 (d, J=2.0 Hz, 1H), 6.03 (dddd, J=17.2, 10.8, 5.6, 5.6 Hz, 1H), 5.43 (dd, J=17.2, 1.2 Hz, 1H), 5.33 (dd, J=10.4, 1.2 Hz, 1H), 4.57 (d, J=5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.3, 164.5, 163.8, 162.1, 157.6, 132.3, 131.9, 131.2, 129.1, 126.3, 118.5, 105.8, 98.9, 93.4, 69.5; IR (neat) 3075, 1665, 1622 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $C_{18}H_{15}O_4$ 295.0970; Found 295.0972.

*4.2.2. Benzyl ether **11**.* To a solution of **10** (1.429 g, 4.856 mmol) in DMF (20 mL) were added K_2CO_3 (850.4 mg, 5.827 mmol) and benzyl bromide (0.578 mL, 4.856 mmol) at room temperature and the reaction mixture was stirred at 60 °C for 10 h. The reaction mixture was allowed to cool to room temperature and quenched with saturated aqueous NH_4Cl. The resulting mixture was diluted with EtOAc and H_2O, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford benzyl ether **11** (1.862 g, 100%) as a white solid (mp; 150–151 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.82 (m, 2H), 7.63 (d, J=7.6 Hz, 2H), 7.49–7.45 (m, 3H), 7.40 (dd, J=7.6, 7.2 Hz, 2H), 7.29 (dd, J=7.2, 7.2 Hz, 1H), 6.64 (s, 1H), 6.55 (d, J=2.8 Hz, 1H), 6.42 (d, J=2.4 Hz, 1H), 6.03 (dddd, J=17.2, 10.4, 5.2, 5.2 Hz, 1H), 5.43 (dd, J=17.2, 1.6 Hz, 1H), 5.33 (dd, J=10.8, 1.6 Hz, 1H), 5.22 (s, 2H), 4.57 (dd, J=5.2, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 162.8, 160.7, 159.80, 159.71, 136.6, 132.2, 131.7, 131.3, 129.1, 128.7, 127.8, 126.7, 126.1, 118.7, 109.3, 98.5, 94.3, 71.0, 69.5; IR (neat) 1646, 1607 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $C_{25}H_{21}O_4$ 385.1440; Found 385.1446.

*4.2.3. Aryl allyl ether **7**.* To a solution of olefin **10** (485.3 mg, 1.649 mmol) and styrene 12 (1.024 g, 3.298 mmol) in toluene under sealed tube (10 mL, 0.165 M) was added Grubbs' second-generation catalyst (140.0 mg, 0.165 mmol) at 25 °C and the reaction mixture was stirred for 10 h at 150 °C. The reaction mixture was allowed to cool to room temperature, concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 4/1 to 2/1) to afford aryl allyl ether **7** (69.3 mg, 8%) a white solid (mp; 140–141 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J=6.4 Hz, 2H), 7.57–7.50 (m, 3H), 7.42 (d, J=7.6 Hz, 2H), 7.34 (dd, J=6.8, 7.6 Hz, 2H), 7.30 (d, J=7.6 Hz, 1H), 6.99 (d, J=1.6 Hz, 1H), 6.89 (dd, J=8.4, 1.6 Hz, 1H), 6.83 (d, J=8.4 Hz, 1H), 6.67 (d, J=16.0 Hz, 1H), 6.67 (s, 1H), 6.55 (d, J=2.0 Hz, 1H), 6.43 (d, J=2.0 Hz, 1H), 6.27 (ddd, J=16.0, 6.0, 6.0 Hz, 2H), 5.16 (s, 2H), 4.75 (d, J=5.2 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.3, 164.5, 163.9, 162.1, 157.7, 149.7, 148.4, 136.9, 133.8, 131.8, 131.3, 129.6, 129.1, 128.6, 127.9, 127.2, 126.3, 122.1, 119.9, 113.8, 109.6, 105.9, 98.9, 93.5, 71.1, 69.4, 56.2; IR (neat) 2919, 2350, 1658, 1615 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $C_{32}H_{27}O_6$ 507.1808; Found 507.1801.

*4.2.4. Aryl allyl ether **13**.* Compound **13** (166 mg, 20%) was obtained from **11** (530 mg, 1.379 mmol) a white solid (mp; 141–142 °C): by same method used to synthesis of compound 7: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J=8.0, 2.4 Hz, 2H), 7.61 (d, J=7.6 Hz, 2H), 7.41–7.21 (m, 11H), 6.93 (d, J=0.8 Hz, 1H), 6.82 (d, J=8.4 Hz, 1H), 6.78 (d, J=8.4 Hz, 1H), 6.574 (s, 1H), 6.571 (d, J=15.6 Hz, 1H), 6.47 (d, J=2.0 Hz, 1H), 6.35 (d, J=1.6 Hz, 1H), 6.15 (ddd, J=15.6, 6.0, 5.6 Hz, 1H), 5.11 (s, 2H), 5.08 (s, 2H), 4.58 (d, J=5.6 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.0, 162.7, 160.3, 159.55, 159.42, 149.6, 148.3, 136.9, 136.5, 133.7, 131.38, 131.09, 129.6, 128.85, 128.55, 127.9, 127.6, 127.3, 126.5, 125.8, 121.1, 119.9, 113.8, 109.7, 109.0, 98.2, 94.0, 71.0, 70.6, 69.3, 56.1; IR (neat) 1646, 1607 cm^{-1}; HRMS (EI) m/z: $[M+H]^+$ Calcd for $C_{39}H_{33}O_6$ 597.2277; Found 597.2274.

*4.2.5. Ethylcarbonate **15**.* [**Olefination**] To a solution of triethylphosphonoacetate (33.49 mL, 168.8 mmol) in THF (500 mL) were added LiCl (14.31 g, 337.6 mmol) and DBU (12.62 mL, 168.8 mmol) at room temperature and the resulting mixture was stirred at 60 °C for 30 min. To this mixture commercially available aldehyde **14**

(20.45 g, 84.4 mmol) was added and the reaction mixture was stirred for 5 h at the same temperature. The reaction mixture was allowed to cool to room temperature and quenched with saturated aqueous NH_4Cl. The resulting mixture was diluted with EtOAc and H_2O, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford crude α,β-unsaturated ester (~27 g). The crude ester was employed in next step without purification. [**Reduction**] To a cooled solution (−78 °C) of crude α,β-unsaturated ester (~27 g) in toluene (600 mL) was added DIBAL-H (253.2 mL, 1.0 M solution, 253.2 mmol) and the resulting mixture was stirred for 16 h at the same temperature. The reaction mixture was quenched with MeOH (3 mL), diluted with saturated aqueous K,Na-tartrate (*Rochelle salt*), and stirred vigorously for 5 h at room temperature. The resulting mixture was diluted with Et_2O, the layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford crude allylic alcohol (~25 g). The crude alcohol was employed in next step without purification. [**Ethoxycarbonylation**] To a cooled solution (0 °C) of crude allylic alcohol (~25 g) in CH_2Cl_2 (500 mL) were added pyridine (20.48 mL, 253.2 mmol) and ethylchloroformate (9.684 mL, 101.3 mmol) and the resulting mixture was stirred for 10 h at room temperature. The reaction mixture was cooled to 0 °C and quenched carefully with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 2/1 to 1/1) to afford ethylcarbonate **15** a white solid (mp; 65–66 °C): (26.54 g, 92% for three steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J=7.2 Hz, 2H), 7.33 (dd, J=7.6, 7.6 Hz, 2H), 7.27 (d, J=7.6 Hz, 1H), 6.94 (d, J=1.6 Hz, 1H), 6.85 (dd, J=8.4, 2.0 Hz, 1H), 6.80 (d, J=8.4 Hz, 1H), 6.59 (d, J=15.6 Hz, 1H), 6.15 (ddd, J=16.0, 6.4, 6.4 Hz, 1H), 5.12 (s, 2H), 4.73 (dd, J=6.8, 0.8 Hz, 2H), 4.19 (ddd, J=7.6, 7.6, 6.8 Hz, 1H), 3.86 (s, 3H), 1.29 (dd, J=7.2, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 149.5, 148.2, 136.8, 134.5, 129.5, 128.4, 127.7, 127.1, 120.6, 119.9, 113.7, 109.5, 70.9, 68.3, 64.0, 56.0, 14.4; IR (neat) 1743, 1255 cm^{-1}; HRMS (EI) m/z: $(M)^+$ Calcd for $C_{20}H_{22}O_5$ 342.1467; Found 342.1466.

4.2.6. Aryl allyl ether **7** *by Pd^0-catalyzed coupling reaction.* To a solution of chrysin (**9**) (8.89 g, 34.97 mmol) and carbonate **15** (11.97 g, 34.97 mmol) in THF/DMF (2:1, total 60 mL) were added K_2CO_3 (9.67 g, 69.9 mmol) and $(Ph_3P)_4Pd$, (404.4 mg, 0.350 mmol) at room temperature and the resulting mixture was stirred for 14 h. The reaction mixture was acidified with 1 N HCl, and diluted with Et_2O to form yellow precipitate. The yellow precipitate was collected by filtration, and washed sequentially with cold (0 °C) H_2O and Et_2O to afford aryl allyl ether **7** (16.63 g, 94%).

*4.2.7. Compound (±)-**16** by aromatic Claisen rearrangement.* A solution of aryl allyl ether **7** (4.521 g, 8.923 mmol) in diethylaniline (100 mL) was stirred for 3 h at 270 °C. The reaction mixture was allowed to cool to room temperature, concentrated in vacuo, and purified by column chromatography (silica gel; hexanes/EtOAc, 4/1 to 2/1) to afford (±)-**16** (3.672 g, 81%) a yellow solid (mp; 77–78 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.71 (s, 1H), 7.84 (br s, 1H), 7.55 (d, J=8.4 Hz, 1H), 7.547 (s, 1H), 7.45 (dddd, J=8.4, 8.4, 1.2, 1.2 Hz, 1H), 7.22–7.41 (m, 7H), 6.89 (d, J=1.2 Hz, 1H), 6.83 (d, J=8.0 Hz, 1H), 6.79 (dd, J=7.6, 0.8 Hz, 1H), 6.67 (dd, J=8.4, 8.8 Hz, 1H), 6.63 (s, 1H), 6.47 (ddd, J=17.2, 10.0, 7.6 Hz, 1H), 6.41 (s, 1H), 5.49 (d, J=7.2 Hz, 1H), 5.30 (ddd, J=10.4, 1.6, 1.6 Hz, 1H), 5.24 (d, J=17.2, 1.6, 1.6 Hz, 1H), 5.09 (s, 2H), 3.76(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 164.2, 161.5, 160.5, 155.0, 149.6, 146.8, 138.1, 136.9, 134.4, 131.8, 131.3, 129.0, 128.5, 127.8, 127.3, 126.4, 119.5, 117.7, 114.0, 111.5, 107.8, 105.6, 100.4, 71.2, 56.1, 43.5; IR (neat) 3027, 2937, 2350, 1655, 1611 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $C_{32}H_{27}O_6$ 507.1808; Found 507.1805.

*4.2.8. (±)-8-[1-(4′-Hydroxy-3′-methoxyphenyl)prop-2-en-1-yl] chrysin (**2**).* To a cooled solution (0 °C) of (±)-**16** (3.672 g, 7.249 mmol) in CH_2Cl_2 (100 mL) was added BCl_3 (21.8 mL, 1.0 M solution in heptane, 21.8 mmol) and the reaction mixture was stirred for 2 h at the room temperature. The reaction mixture was quenched with H_2O and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 3/1 to 1/1) to afford (±)-**2** (2.752 g, 91%) a yellow solid (mp; 87–88 °C): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (s, 1H), 11.05 (br s, 1H), 8.77 (s, 1H), 7.66 (d, J=7.6 Hz, 2H), 7.53 (dd, J=7.6, 7.6 Hz, 1H), 7.44 (dd, J=7.6, 7.6 Hz, 2H), 6.92 (s, 1H), 6.80 (d, J=2.0 Hz, 1H), 6.69 (d, J=8.0 Hz, 1H), 6.61 (dd, J=8.0, 1.2 Hz, 1H), 6.46 (ddd, J=17.6, 10.0, 8.0 Hz, 1H), 6.40 (s, 1H), 5.31 (d, J=8.0 Hz, 1H), 5.20 (d, J=17.2, Hz, 1H), 5.18 (d, J=9.6 Hz, 1H), 3.59 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.9, 163.0, 161.8, 159.4, 154.4, 147.2, 144.6, 138.5, 132.9, 131.7, 130.6, 128.8, 126.2, 119.2, 116.2, 115.2, 111.1, 108.2, 105.0, 104.2, 98.8, 55.5, 42.8; IR (neat) 3068, 2935, 2350, 1654, 1613, 1511 cm^{-1}; HRMS (EI) m/z: $[M]^+$ Calcd for $C_{25}H_{20}O_6$ 416.1260; Found 416.1257.

*4.2.9. Tribenzyl ether (±)-**17**.* To a solution of (±)-**16** (678.3 mg, 1.339 mmol) in DMF (20 mL) were added K_2CO_3 (740.3 mg, 5.356 mmol) and BnBr (0.478 mL, 4.017 mmol), and the reaction mixture was stirred for 14 h at 50 °C. The reaction mixture was quenched with NH_4Cl and diluted with EtOAc and H_2O. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 5/1 to 3/1) to afford (±)-**17** (834.8 mg, 91%) a white solid (mp; 150–151 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J=7.2, 2H), 7.45–7.19 (m, 18H), 6.79 (d, J=2.0 Hz, 1H), 6.77 (d, J=8.4 Hz, 1H), 6.67 (dddd, J=8.4, 1.6, 1.2, 0.4 Hz, 1H), 6.61 (s, 1H), 6.54 (s, 1H), 6.46 (ddd, J=16.8, 10.0, 8.4, Hz, 1H), 5.55 (d, J=8.4 Hz, 1H), 5.241(d, J=17.2 Hz, 1H), 5.240 (s, 2H), 5.18 (dd, J=10.0, 2.0 Hz, 1H), 5.10 (d, J=2.8 Hz, 2H), 5.05 (d, J=9.2 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 160.8, 159.9, 158.5, 156.3, 149.4, 146.3, 138.2, 137.2, 136.4, 135.83, 135.68, 131.6, 131.0, 128.8, 128.57, 128.43, 128.19, 127.70, 127.65, 127.3, 127.1, 126.7, 126.1, 119.1, 117.1, 114.0, 112.4, 111.1, 110.0, 108.7, 96.3, 71.25, 71.20, 70.8, 56.0, 43.9; IR (neat) 1646, 1595 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $C_{46}H_{39}O_6$ 687.2747; Found 687.2745.

*4.2.10. Tribenzoate **22**.* To a cooled solution (0 °C) of trihydroxyphenol **21** (5.0 g, 18.23 mmol) in pyridine (40 mL) were added BzCl (8.46 mL, 72.92 mmol) and catalytic amount of DMAP (20 mg), and the reaction mixture was stirred for 14 h at room temperature. The reaction mixture was cooled to 0 °C, and quenched carefully with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 10/1) to afford tribenzoate **22** (9.8 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J=8.0 Hz, 2H), 8.11 (d, J=8.0 Hz, 4H), 7.64 (dd, J=7.6, 7.2 Hz, 3H), 7.50 (ddd, J=7.2, 7.2, 7.2 Hz, 6H), 7.27 (s, 2H), 7.20 (dd, J=3.6, 2.8 Hz, 3H), 7.14 (dd, J=3.8, 2.4 Hz, 2H), 4.47 (s, 2H), 4.44 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 163.9, 152.3, 148.9, 136.9, 134.13, 134.02, 133.6, 130.25, 130.19, 130.06, 128.73, 128.65, 128.50, 128.37, 128.25, 127.8,

122.7, 114.6, 75.4, 73.4; IR (neat) 1746, 1242 cm^{-1}; HRMS (FAB) *m/z*: $[M-H]^+$ Calcd for $C_{36}H_{25}O_8$ 585.1549; Found 585.1556.

*4.2.11. Bis-phenol **8**.* [**Benzoyl migration**] To a solution of tribenzoate **22** (5.0 g, 8.52 mmol) in THF (200 mL) was added NaH (1.96 g, 60% dispersion in mineral oil, ca. 41.1 mmol) at room temperature, and the reaction mixture was refluxed for 70 min. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl solution. The resulting mixture was acidified with 3 N HCl, and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford crude benzoyl migrated compound, which was employed in next step without purification. [**Cyclization**] To a solution of the above crude compound in acetic acid (40 mL) was added NaOAc (1.04 g, 12.78 mmol) at room temperature, and the resulting mixture was stirred at 120 °C for 12 h. The reaction mixture was cooled to 0 °C, diluted with H_2O and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford crude **23**. The crude **23** was employed in next step without purification. [**Debenzoylation**] To a solution of the crude **23** in MeOH (100 mL) was added K_2CO_3 (7.3 g, 52.75 mmol) at room temperature. After being stirred for 16 h at the same temperature, MeOH was evaporated in vacuo. The resulting residue was diluted H_2O and EtOAc, and acidified with 3 N HCl. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 2/1 to 1/1) to afford 1,3-diphenol **8** (2.52 g, 82% for three steps) a white solid (mp; 183–184 °C): ^1H NMR (400 MHz, DMSO-d_6) δ 12.59 (s, 1H), 7.93 (dd, *J*=8.0, 1.6 Hz, 2H), 7.56–7.49 (m, 3H), 7.33–7.27 (m, 5H), 6.45 (d, *J*=2.0 Hz, 1H), 6.23 (d, *J*=2.0 Hz, 1H), 5.05 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.9, 164.2, 161.1, 156.4, 155.6, 137.1, 136.2, 130.8, 129.9, 128.31, 128.24, 128.18, 128.04, 127.94, 104.3, 98.7, 93.8, 73.6; IR (neat) 3183, 2321, 1650, 1164 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{17}O_5$ 361.1076; Found 361.1072.

*4.2.12. Aryl allyl ether **6**.* To a solution of **8** (2.582 g, 7.165 mmol) and carbonate **15** (4.906 g, 14.33 mmol) in THF (80 mL) were added K_2CO_3 (1.981 g, 14.33 mmol) and $(Ph_3P)_4Pd$ (166 mg, 0.144 mmol) at room temperature and the resulting mixture was stirred for **14** h. The reaction mixture was acidified with 1 N HCl, and diluted Et_2O to form yellow precipitate. The yellow precipitate was collected by filtration, washed sequentially with H_2O and Et_2O, and dried in vacuo to afford aryl allyl ether **6** (3.295 g, 75%) a yellow solid (mp; 133–134 °C): ^1H NMR (400 MHz, $CDCl_3$) δ 12.65 (s, 1H), 7.95 (dd, *J*=8.0, 1.2 Hz, 2H), 7.48–7.41 (m, 5H), 7.35 (dd, *J*=7.2, 7.2 Hz, 2H), 7.31–7.23 (m, 5H), 6.98 (d, *J*=1.6 Hz, 1H), 6.89 (dd, *J*=8.4, 2.0 Hz, 1H), 6.83 (d, *J*=8.8 Hz, 1H), 6.66 (d, *J*=15.6 Hz, 1H), 6.48 (d, *J*=2.0 Hz, 1H), 6.42 (d, *J*=2.0 Hz, 1H), 6.25 (ddd, *J*=15.6, 5.6, 5.6 Hz, 1H), 5.16 (s, 2H), 5.07 (s, 2H), 4.74 (d, *J*=6.0 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 164.4, 161.9, 156.77, 156.67, 149.5, 148.3, 137.9, 136.8, 136.2, 133.8, 130.8, 130.4, 129.5, 128.74, 128.69, 128.53, 128.31, 128.23, 128.19, 127.9, 127.2, 121.0, 119.9, 113.6, 109.4, 106.2, 98.6, 93.0, 74.5, 71.0, 69.4, 56.1; IR (neat) 3033, 2321, 1655, 1603, 1510, 1169 cm^{-1}; HRMS (FAB) *m/z*: $[M+1H]^+$ Calcd for $C_{39}H_{33}O_7$ 613.2226; Found 613.2222.

*4.2.13. (±)-**24** by aromatic Claisen rearrangement.* A solution of aryl allyl ether **6** (3.295 g, 5.378 mmol) in diethylaniline (100 mL) was stirred for 3 h at 270 °C. The reaction mixture was allowed to cool to room temperature, concentrated in vacuo, and purified by column chromatography (silica gel; hexanes/EtOAc, 4/1 to 2/1) to afford (±)-**24** (2.689 g, 82%): ^1H NMR (400 MHz, $CDCl_3$) δ 12.72 (s, 1H), 7.6 (d, *J*=7.2 Hz, 2H), 7.45–7.23 (m, 13H), 6.82 (d, *J*=8.0 Hz, 2H), 6.75 (d, *J*=8.0 Hz, 1H), 6.41 (ddd, *J*=17.2, 10.0, 6.8 Hz, 1H), 6.35 (br s, 1H), 5.41 (d, *J*=6.8 Hz, 1H), 5.33 (d, *J*=10.4 Hz, 1H), 5.16 (d, *J*=17.2 Hz, 1H), 5.12 (s, 2H), 5.03 (AB, J_{AB}=11.2 Hz, $\Delta\nu_{AB}$=16.4 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 161.1, 160.3, 156.9, 154.1, 149.4, 146.7, 138.1, 137.6, 136.9, 136.0, 134.7, 130.7, 130.3, 128.73, 128.67, 128.44, 128.21, 128.12, 127.8, 127.2, 119.6, 117.5, 114.0, 111.7, 107.5, 106.2, 100.0, 74.7, 71.2, 56.0, 43.3; IR (neat) 3063, 2321, 1651, 1510, 1215, 1159 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{39}H_{33}O_7$ 613.2226; Found 613.2224.

*4.2.14. (±)-8-[1-(4′-Hydroxy-3′-methoxyphenyl)prop-2-en-1-yl]galangin (**1**).* To a cooled solution (0 °C) of (±)-**24** (2.689 g, 4.389 mmol) in CH_2Cl_2 (50 mL) was added BCl_3 (17.6 mL, 1.0 M solution in heptane, 17.6 mmol) and the reaction mixture was stirred for 2 h at the room temperature. The reaction mixture was quenched with H_2O and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 4/1 to 2/1) to afford (±)-**1** (1.727 g, 91%) a yellow solid (mp; 112–113 °C): ^1H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 10.97 (s, 1H), 9.66 (s, 1H), 8.75 (s, 1H), 7.74 (d, *J*=4.0 Hz, 2H), 7.43–7.38 (m, 3H), 6.76 (d, *J*=1.2 Hz, 1H), 6.68 (d, *J*=8.0 Hz, 1H), 6.58 (dd, *J*=7.6, 1.2 Hz, 1H), 6.45 (ddd, *J*=16.8, 10.0, 8.0 Hz, 1H), 6.39 (s, 1H), 5.29 (d, *J*=7.6 Hz, 1H), 5.17 (d, *J*=17.6 Hz, 1H), 5.10 (d, *J*=8.8 Hz, 1H), 3.55 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.2, 161.4, 158.7, 153.4, 147.1, 145.7, 144.6, 138.6, 136.7, 133.0, 130.8, 129.7, 128.2, 127.4, 119.3, 116.0, 115.2, 111.2, 107.7, 103.5, 98.1, 55.4, 42.8; IR (neat) 3403, 2350, 2321, 1652, 1560, 1510 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{21}O_7$ 433.1287; Found 433.1281.

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Supplementary data

Copies of ^1H and ^{13}C NMR spectra (±)-**1**, (±)-**2**, **6**–**8**, **10**, **11**, **13**, **15**–**17**, **22**, and (±)-**24**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.05.057.

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