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A concise synthetic approach to brazilin *via* Pd-catalyzed allylic arylation†

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A short synthetic route to the trimethyl ether of brazilin was developed in 6 steps from 7-methoxychromene with 78% overall yield. Regioselective installation of a formyl group onto 7-methoxychromene followed by reduction and acetylation afforded allylic acetate. Palladium-catalyzed allylic coupling of allylic acetate with arylboronic acid provided direct access to 3-benzylchromene which was converted to the target molecule upon ensuing dihydroxylation and acid-catalyzed cyclization in a highly concise manner.

Recently, we have communicated on the succinct total synthesis of a homoisoflavanoid natural product, brazilin, by relying on a highly efficient Mitsunobu coupling/alkyne-aldehyde metathesis sequence to facilitate construction of the core framework.[1] The key intermediate **2** was rapidly elaborated to the trimethyl ether analogue (**3**) of brazilin *via* a short sequence of high-yielding and simple synthetic manipulations (Scheme 1).

Although the efficiency of this route was demonstrated by its very high overall yield (~70%), deoxygenation of the ketone moiety of **2** using the Barton–McCombie procedure was required as a means to modulate the oxidation levels. To obviate these steps, compound **4** was deemed as a viable alternative precursor, which would be available *via* palladium-catalyzed allylic substitution[2] with allylic acetate **5** and arylboronic acid.[3] Compared with ample reports on Pd-catalyzed allylic substitution reactions with various *C*-, *N*-, or *O*-nucleophiles *via* the formation of π-allylpalladium complexes, the use of boronic acid as a coupling partner is rare. Moreover, to the best of our knowledge, Pd-catalyzed allylic arylation with arylboronic acid has not been applied to the total synthesis of natural products. Here we wish to report another succinct synthetic route to brazilin and its analogues.[4]

As shown in Scheme 2, we commenced our synthesis by preparation of **5**. We expected that Vilsmeier–Haack formylation[5] of chromene **6**[6] would allow for regioselective introduction of a formyl group at the C3 position to produce **7**[7] which would be transformed to allylic acetate **5** *via* subsequent reduction and acetylation. Indeed, we were able to obtain the requisite **5** from the known chromene **6** in gram quantities by this procedure.

When we reacted allylic acetate **5** with 3,4-dimethoxyphenylboronic acid in the presence of $Pd(PPh_3)_4$ and several bases at 100 °C, K_3PO_4 afforded the best isolated yield of **4** (Table 1, entries 1–3).[8] No regioisomer was observed. Lowering the reaction temperature to 80 °C resulted in incomplete conversion even at a prolonged reaction time (entry 4). The other solvents instead of THF gave inferior results (entries 5–7). Under these optimized conditions, several arylboronic acids were allowed to react with **5** to give the corresponding products **8–10** in good yields (entries 8–10). For comparison, allylic *t*-BOC carbonate instead of **5** was also subjected to the identical conditions but only 26% yield of **4** was isolated (not listed).

The resulting chromene **4** was then subjected to the Upjohn dihydroxylation process[9] to furnish the diol **11** in 100% yield (Scheme 3). Cyclization of **11** under acid catalysis gave **3** in 94% yield.[10] Spectral data of **3** matched the literature values in all respects. In the meantime, asymmetric dihydroxylation[11] was also conducted as it would engender this asymmetric route.[12] When **4** was treated with AD-mix-α at 0 °C for 48 h, 76 : 24 er was observed with 59% isolated yield (84% based on the recovered starting material).[13]

In summary, we have devised another succinct synthetic route to brazilin in connection with our previous synthetic efforts towards this tetracyclic natural product. Regioselective Vilsmeier–Haack formylation of chromene and Pd-catalyzed regioselective allylic substitution of allylic acetates with an arylboronic acid facilitated the construction of the full carbon skeleton of brazilin from which oxidation and cyclization enabled ready access to the trimethyl ether **3** of brazilin in high overall yield. Asymmetric access to **3** was also investigated by Sharpless asymmetric dihydroxylation of **4** although moderate er was observed. This flexible and practical approach should be particularly suitable for the synthesis of diverse

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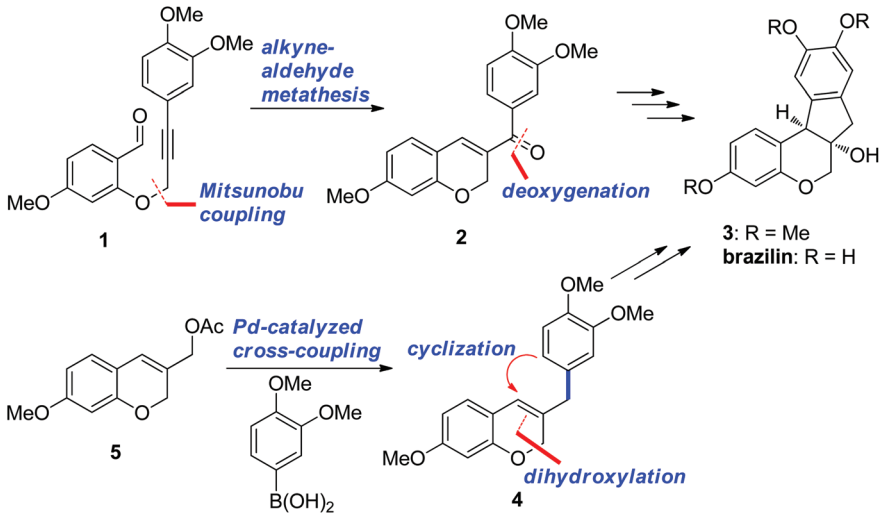
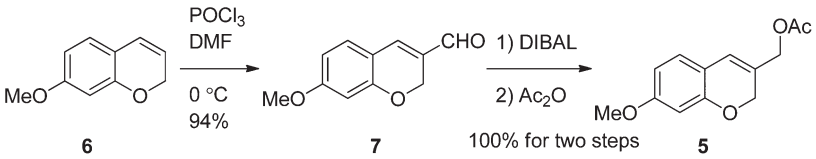
† Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra of **3–5**, **7–11**. See DOI: 10.1039/c5ob00216h

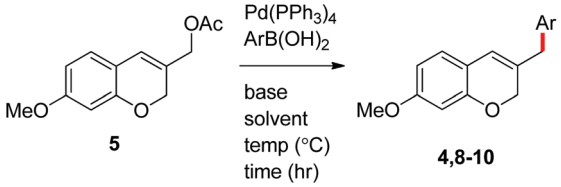


Scheme 1 Synthetic approaches to brazilin.



Scheme 2 Synthesis of **5**.

Table 1 Pd-catalyzed allylic substitution[a]



Entry	Base	Solvent	Temp (°C)	Time (h)	Product	Yield[b] (%)
1	K_2CO_3	THF	100	20	**4**	22 (41)
2	Et_3N	THF	100	20	**4**	57 (60)
3	K_3PO_4	THF	100	2	**4**	88
4	K_3PO_4	THF	80	26	**4**	28 (57)
5	K_3PO_4	DMF	100	26	**4**	60 (100)
6	K_3PO_4	CH_3CN	100	26	**4**	37 (51)
7	K_3PO_4	Toluene	100	26	**4**	13 (26)
8[c]	K_3PO_4	THF	100	1	**8**	78
9[d]	K_3PO_4	THF	100	1	**9**	60
10[e]	K_3PO_4	THF	100	3	**10**	93

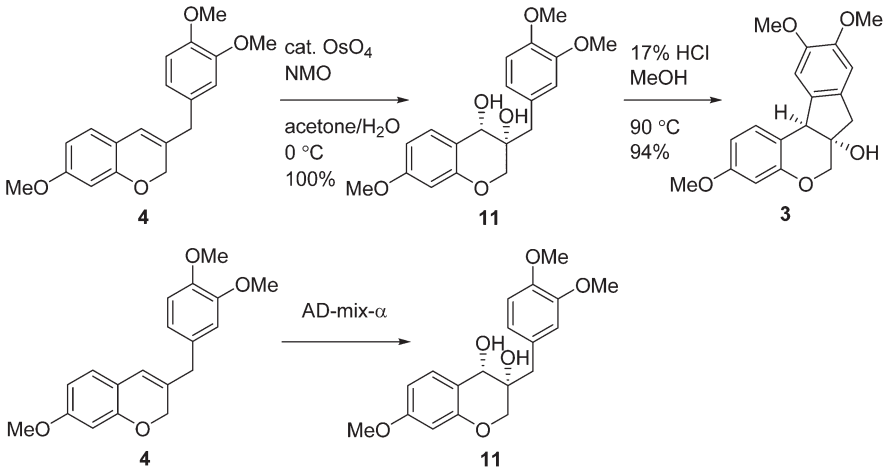
[a] A mixture of **5** (0.17 mmol), 3,4-dimethoxyphenylboronic acid (3 equiv.), base (2 equiv.), and $Pd(PPh_3)_4$ (0.05 equiv.) in solvent (2 mL) was heated unless otherwise stated. [b] Isolated yield (%). Yields in parentheses are based on recovered starting materials. [c] 4-$MeOC_6H_4$-$B(OH)_2$ was used as boronic acid. [d] 4-$ClC_6H_4B(OH)_2$ was used as boronic acid. [e] 3,4,5-$(MeO)_3C_6H_2B(OH)_2$ was used as boronic acid.

brazilin analogues as a number of (hetero)arylboronic acids could be employed in Pd-catalyzed cross-coupling reactions.

Experimental section

General methods

Unless specified, all reagents and starting materials were purchased from commercial sources and used as received without purification. "Concentrated" refers to the removal of volatile solvents *via* distillation using a rotary evaporator. "Dried" refers to pouring onto, or passing through, anhydrous magnesium sulfate followed by filtration. Flash chromatography was performed using silica gel (230–400 mesh) with hexanes, ethyl acetate, and dichloromethane as eluents. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) visualizing with UV light. ^1H and ^{13}C NMR spectra were recorded using a 400 MHz NMR spectrometer and were described as chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz (Hz), and number of protons. IR spectra were recorded by FT-IR using the diamond ATR technique and were described as wavenumbers (cm^{-1}). HRMS were measured by electrospray ionization (ESI) and a Q-TOF mass analyzer.



Scheme 3 Synthesis of **3**.

7-Methoxy-2*H*-chromene-3-carbaldehyde (7). To a stirred solution of **6** (700 mg, 4.3 mmol in DMF (1 mL), a pre-mixed solution of $POCl_3$ (4 mL, 43 mmol, 10 equiv.) and DMF (3.5 mL, 43 mmol, 10 equiv.) was added dropwise at 0 °C. After being stirred at 0 °C for 17 h, the reaction mixture was quenched with H_2O (3 mL) at 0 °C. The reaction mixture was basified with an aq. NaOH solution (pH ~ 8) and extracted with ethyl acetate (10 mL). The water layer was extracted with ethyl acetate (10 mL × 2) two more times. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate–dichloromethane = 10 : 1 : 2) to give **7** (768 mg, 94%). Yellow solid, mp: 81.6–82.9 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.22 (s, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.53 (dd, J = 2.4, 8.4 Hz, 1H), 6.42 (d, J = 2.4 Hz, 1H), 5.03 (s, 2H), 3.82 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.6, 164.3, 158.1, 141.7, 130.7, 129.0, 114.0, 109.0, 101.7, 63.7, 55.7; **IR** (ATR) 3069, 2815, 1656, 1269, 1557, 1167 cm^{-1}; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{11}H_{11}O_3$ 191.0703, found 191.0702.

(7-Methoxy-2*H*-chromen-3-yl)methyl acetate (5). To a stirred solution of **7** (300 mg, 1.58 mmol) in THF (5 mL) DIBAL (1.0 M solution in THF, 4.73 mL, 3 equiv.) was added dropwise at −78 °C. After being stirred at −78 °C for 1 h, the reaction mixture was quenched with MeOH at −78 °C and stirred at rt for 1 h. The mixture was suction-filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give allylic alcohol (303 mg, 100%). Colorless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.89 (d, J = 8.0 Hz, 1H), 6.43 (dd, J = 2.4, 8.0 Hz, 1H), 6.39 (d, J = 2.0 Hz, 1H), 6.34 (s, 1H), 4.79 (s, 2H), 4.19 (d, J = 5.6 Hz, 2H), 3.77 (s, 3H), 1.60 (t, J = 6.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.7, 154.8, 130.5, 127.5, 120.2, 115.5, 107.3, 101.7, 66.6, 63.7, 55.5; **IR** (ATR) 3350, 2908, 2834, 1458, 1271, 1026 cm^{-1}; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{11}H_{13}O_3$ 193.0859, found 193.0854.

To a solution of allylic alcohol (644 mg, 3.35 mmol) in CH_2Cl_2 (4 mL), Et_3N (0.7 mL, 1.5 equiv.), DMAP (41 mg, 0.1 equiv.) and Ac_2O (0.38 mL, 1.2 equiv.) were added at 0 °C. After being stirred at rt for 1 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 10% aq. HCl and aq. $NaHCO_3$, successively. The water layer was extracted with CH_2Cl_2 (10 mL × 2) two more times. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford **5** (785 mg, 100%). White solid, mp: 75.8–77.6 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.90 (d, J = 8.4 Hz, 1H), 6.44 (dd, J = 2.4, 8.4 Hz, 1H), 6.41 (s, 1H), 6.39 (d, J = 2.4 Hz, 1H), 4.75 (s, 2H), 4.62 (s, 2H), 3.77 (s, 3H), 2.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.0, 161.1, 154.8, 127.7, 125.3, 123.5, 115.1, 107.4, 101.7, 66.6, 65.0, 55.5, 21.0; **IR** (ATR) 3443, 2936, 1721, 1615, 1460, 1260, 1018 cm^{-1}; **HRMS** (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{13}H_{15}O_4$ 257.0784, found 257.0785.

3-(3,4-Dimethoxybenzyl)-7-methoxy-2*H*-chromene (4). To a stirred solution of **5** (40 mg, 0.17 mmol) in THF (2 mL), 3,4-dimethoxyphenylboronic acid (93 mg, 3 equiv.), K_3PO_4 (73 mg, 2 equiv.), and $Pd(PPh_3)_4$ (9.9 mg, 0.05 equiv.) were added at rt. After being stirred at 100 °C for 2 h, the reaction mixture was suction-filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give the residue which was purified by silica gel column chromatography (hexanes–ethyl acetate–dichloromethane = 30 : 1 : 2 to 20 : 1 : 2) to give **4** (47 mg, 88%). Yellow gum; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.84 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.76 (dd, J = 1.2, 8.4 Hz, 1H), 6.73 (d, J = 1.2 Hz, 1H), 6.41 (dd, J = 2.4, 8.4 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 6.11 (s, 1H), 4.62 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.75 (s, 3H), 3.35 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.2, 154.2, 149.1, 147.8, 131.2, 130.3, 126.8, 121.1, 119.8, 116.1, 112.1, 111.3, 106.9 101.6, 68.2, 56.01, 55.97, 55.4, 39.5; **IR** (ATR) 2933, 2831, 1612, 1459, 1258, 1024 cm^{-1}; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{19}H_{21}O_4$ 313.1434, found 313.1441.

7-Methoxy-3-(4-methoxybenzyl)-2*H*-chromene (8). Prepared with **5** (40 mg, 0.17 mmol) and 4-methoxyphenylboronic acid by following the same procedure as that of **4**. Yellow gum; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 (d, J = 8.4 Hz, 2H), 6.84

(d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.0 Hz, 1H), 6.41 (dd, J = 2.0, 8.0 Hz, 1H), 6.35 (d, J = 2.0 Hz, 1H), 6.08 (s, 1H), 4.60 (s, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.33 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.2, 158.4, 154.1, 131.3, 130.0, 129.8, 126.8, 119.8, 116.1, 114.1, 106.9 101.5, 68.3, 55.43, 55.37, 39.0; **IR** (ATR) 2929, 2830, 1608, 1239, 1030, 1154 cm^{-1}; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd $C_{18}H_{19}O_3$ 283.1329, found 283.1322.

3-(4-Chlorobenzyl)-7-methoxy-2*H*-chromene (9). Prepared with **5** (25 mg, 0.11 mmol) and 4-chlorophenylboronic acid by following the same procedure as that of **4**. Yellow gum; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 8.4 Hz, 1H), 6.41 (dd, J = 2.4, 8.4 Hz, 1H), 6.36 (d, J = 2.0 Hz, 1H), 6.09 (s, 1H), 4.59 (s, 2H), 3.75 (s, 3H), 3.36 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.4, 154.1, 136.3, 132.5, 130.4, 130.3, 128.8, 126.9, 120.5, 115.9, 107.1, 101.6, 68.1, 55.5, 39.2; **IR** (ATR) 2931, 2832, 1737, 1610, 1487, 1270, 1154, 1030, 804 cm^{-1}; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd $C_{17}H_{16}ClO_2$ 287.0833, found 287.0833.

7-Methoxy-3-(3,4,5-trimethoxybenzyl)-2*H*-chromene (10). Prepared with **5** (40 mg, 0.17 mmol) and 3,4,5-trimethoxyphenylboronic acid by following the same procedure as that of **4**. Pale orange solid, mp: 112.8–114.3 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87 (d, J = 8.4 Hz, 1H), 6.43 (s, 2H), 6.42 (dd, J = 2.4, 8.4 Hz, 1H), 6.37 (d, J = 2.0 Hz, 1H), 6.14 (s, 1H), 4.63 (s, 2H), 3.84 (s, 9H), 3.76 (s, 3H), 3.35 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.3, 154.2, 153.4, 136.7, 133.6, 130.7, 126.9, 120.2, 116.0, 107.0, 105.9, 101.6, 68.2, 61.0, 56.2, 55.5, 40.3; **IR** (ATR) 2934, 2833, 1588, 1456, 1235, 1120, 1019 cm^{-1}; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd $C_{20}H_{23}O_5$ 343.1540, found 343.1546.

(3*R,4*S**)-3-(3,4-Dimethoxybenzyl)-7-methoxychroman-3,4-diol (11).** To a stirred solution of **4** (93 mg, 0.298 mmol) in acetone–H_2O (3 : 1, 8 mL), NMO (105 mg, 3 equiv.) and OsO_4 (2.5 wt% in *t*-BuOH, 0.15 mL, 0.04 equiv.) were added at 0 °C. After being stirred at 0 °C for 3 h, the reaction mixture was concentrated under reduced pressure and extracted with CH_2Cl_2 (5 mL). The water layer was extracted with CH_2Cl_2 (5 mL × 2) two more times. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate–dichloromethane = 3 : 1 : 2) to give **11** (103 mg, 100%). White solid, mp: 116.9–118.0 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 1.6 Hz, 1H), 6.75 (dd, J = 8.0, 1.6 Hz, 1H), 6.58 (dd, J = 8.4, 2.4 Hz, 1H), 6.43 (d, J = 2.4 Hz, 1H), 4.37 (d, J = 6.0 Hz, 1H), 3.95 (d, J = 10.8 Hz, 1H), 3.87 (s, 6H), 3.80 (d, J = 10.8 Hz, 1H), 3.79 (s, 3H), 2.82 (d, J = 14.0 Hz, 1H), 2.77 (d, J = 14.0 Hz, 1H), 2.60 (s, 1H), 2.24 (d, J = 6.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.2, 154.6, 148.8, 148.1, 131.5, 128.1, 122.7, 115.3, 113.9, 111.1, 108.7, 101.3, 69.7, 69.1, 67.7, 56.0, 55.5, 39.9; **IR** (ATR) 3294, 2912, 2833, 1618, 1503, 1260, 1023 cm^{-1}; **HRMS** (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{22}NaO_6$ 369.1309, found 369.1302.

Asymmetric dihydroxylation of 4

To a stirred solution of **4** (23 mg, 0.074 mmol) in CH_3CN–H_2O (1 : 1, 3 mL), methanesulfonamide (8.4 mg, 1.2 equiv.) and AD-mix-α (185 mg) were added at 0 °C. After being stirred at 0 °C for 42 h, the reaction mixture was quenched with aq. Na_2SO_3 at 0 °C. The mixture was concentrated under reduced pressure and extracted with ethyl acetate (3 mL). The water layer was extracted with ethyl acetate (3 mL × 2) two more times. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate–dichloromethane = 10 : 1 : 2 to 1 : 1 : 1) to give **11** (15.1 mg, 59%, 84% based on the recovered starting material).

(6a*S,11b*R**)-3,9,10-Trimethoxy-6,6a,7,11b-tetrahydroindeno-[2,1-*c*]chromen-6a-ol (3).** A solution of **11** (58 mg, 0.167 mmol) in 17% HCl–MeOH (1 : 1, 3 mL) was heated at 90 °C for 1 h. After being cooled to rt, the reaction mixture was concentrated under reduced pressure to give the crude residue, diluted with CH_2Cl_2 (3 mL) and H_2O (5 mL), and the layers were separated. The water layer was extracted with CH_2Cl_2 (3 mL × 2) two more times. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the residue which was purified by silica gel column chromatography (hexanes–ethyl acetate–dichloromethane = 5 : 1 : 2) to give **3** (52.2 mg, 94%). White solid, mp: 131.8–133.4 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.8 Hz, 1H), 6.79 (s, 1H), 6.74 (s, 1H), 6.66 (dd, J = 2.4, 8.4 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 4.13 (s, 1H), 4.04 (d, J = 11.2 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.82 (d, J = 11.2 Hz, 1H), 3.78 (s, 3H), 3.26 (d, J = 16.0 Hz, 1H), 2.88 (d, J = 15.6 Hz, 1H), 2.46 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.6, 154.5, 148.8, 148.6, 136.2, 131.2, 130.7, 114.5, 109.0, 108.6, 107.8, 102.1, 77.7, 70.4, 56.24, 56.21, 55.5, 50.7, 41.5; **IR** (ATR) 3449, 2998, 2920, 2833, 1617, 1500, 1280, 1157 cm^{-1}; **HRMS** (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{21}O_5$ 329.1384, found 329.1382.

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