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Total Syntheses of 4′,6′-Dimethoxy-2'-Hydroxy-3′,5′-Dimethylchalcone Derivatives

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Chalcone derivatives afford several pharmacological activities. However, a general synthetic method for 2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone (DMC) derivatives has not been reported thus far. To address this, the preparation of 4',6'-dimethoxy-2'-hydroxy-3',5'-dimethylchalcone (MDMC) derivatives, modified compounds of DMC, in excellent overall yields is reported herein. These compounds have recently attracted growing attention due to their various pharmacological activities. Di-*O*-methyl-dimethylphloroacetophenone, the key intermediate containing the B-ring moiety, was fabricated by four efficient reaction steps from commercially available phloroglucinol in a 50.1% isolated yield overall. Our synthetic route, which constructs the chalcone skeleton in the final stage via a Claisen–Schmidt condensation of the key intermediate with the desired benzaldehyde derivative, can rapidly produce a vast library of DMC derivatives.

Keywords: Total synthesis, 4',6′-dimethoxy-2'-hydroxy-3',5'-dimethylchalcone, Phloroglucinol, Claisen–Schmidt condensation, Benzaldehyde

Introduction

Chalcone derivatives bearing a scaffold composed of two benzene moieties connected by an α,β-unsaturated carbonyl bridge are known to exhibit a wide range of pharmacological activities.[1–4] In addition, they have been used as important precursors for a variety of new drug candidates, including flavonoids and isoflavonoids.[5–7] It is well-known that the pharmacological activity of a compound is greatly influenced not only by the basic skeleton of the compound but also by the electronic property and size of functional groups attached to the skeleton. As we may expect, the pharmacological activities of chalcone compounds are dependent on the functionalities of the two phenyl rings.[8–15] Indeed, we recently disclosed that the antidiabetic activity of 2',4',6'-trihydroxychalcone derivatives was largely dependent on the substituents present on the phenyl rings.[16] Thus, the syntheses of systematically designed chalcone derivatives could be considered necessary to understand the structure–activity relationship of the chalcones and ultimately lead to promising new drug candidates.

2′,4′-Dihydroxy-6′-methoxy-3′,5′-dimethylchalcone (DMC, **1**), a highly substituted chalcone extracted from many natural plants[17–21] has recently attracted growing attention due to its various pharmacological activities, including anti-tumor,[22–25] antivirus,[26] anti-oxidative,[27,28] anti-inflammatory,[29,30] hepatoprotective,[31,32] and anti-diabetic effects.[33–35] During our studies into the optimization of the specific pharmacological activity of **1**, we planned to tune its structure by modifying the substituents on the B and A rings, while retaining the key five functionalities present on the B ring, namely the alternatively attached three hydroxy/alkoxy groups and the two methyl groups (Figure 1).

Considering that a large amount of bioactive compounds should be examined to characterize the various biological activities of such structures, an appropriate synthetic method capable of rapidly producing the desired compounds in large quantities is necessary. Although various methods have been developed for the preparation of chalcones,[36,37] a general synthetic method for DMC derivatives is yet to be reported, presumably because the regioselective arrangement of the three hydroxy/alkoxy groups and the two alkyl groups on the B-ring is challenging. Thus, we herein report an efficient total synthesis for 4′,6′-dimethoxy-2′-hydroxy-3′,5′-dimethylchalcone (MDMC, **2**) derivatives starting from affordable phloroglucinol.

Experimental

General Information. *N,N*-Dimethylformamide (DMF), phloroglucinol, boron trifluoride diethyl etherate, 4-fluorobenzaldehyde, 4-hydroxybenzaldehyde, and 4-methoxybenzaldehyde were purchased from Alfa Aesar (Ward Hill, MA). Mercury(II) chloride and zinc powder was purchased from Samchun Chemicals (Seoul, Republic of Korea). Dimethyl sulfate, benzaldehyde and *p*-toluenesulfonic acid were purchased from Sigma–Aldrich Co. (St. Louis, MO). 4-Methylbenzaldehyde and 4-isopropylbenzaldehyde were purchased from Acros Orgacins (Morris Plains, NJ).

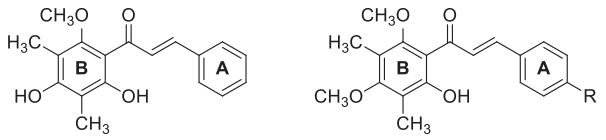


Figure 1. Structures of DMC (**1**) and the MDMC derivatives (**2**).

Phosphorus oxychloride was purchased from Daejung chemicals (Gyeonggi-do, Republic of Korea). Chloromethyl methyl ether was purchased from Kanto Chemical Co., Inc. (Tokyo, Japan). 4-Methoxymethoxybenzaldehyde was prepared as previously described.[38]

Acetone was dehydrated using 4 Å molecular sieves prior to use. Analytical thin-layer chromatography (TLC) was performed using Merck Kieselgel 60 F_{254} precoated plates (0.25 mm) with a fluorescent indicator and visualized either under UV light (254 and 365 nm) or by iodine staining. Column chromatography was performed on silica gel 60 (70–230 mesh; Merck, Darmstadt, Germany). Gas chromatography (GC) was performed on a bonded 5% phenyl polysiloxane BPX five-capillary column (SGE, 30 m, 0.32 mm i.d.) using a GC system (HP 6890 series; Hewlett-Packard, Palo Alto, CA). ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were acquired on a 600-MHz spectrometer (VNS, Varian, Palo Alto, CA) using DMSO-d_6 or $CDCl_3$ as the solvent. ^{1}H NMR (300 MHz) spectra were acquired on a 300-MHz spectrometer (Germini 2000, Varian, Palo Alto, CA) using DMSO-d_6 as a solvent. The chemical shifts were referenced to the residual solvent peaks (δ_H 2.50 and δ_C 39.5 for DMSO-d_6 in the ^{1}H NMR and ^{13}C NMR spectra, respectively). All coupling constants, *J*, are reported in hertz (Hz). Melting points were measured using a melting point apparatus (Barnstead Electrothermal 9100, Cole-Palmer Ltd., Stone, UK; 15 V, 45 W, 1 A).

Synthesis of 2,4-diformylphloroglucinol (5). Phosphorus oxychloride (59.3 mL, 0.636 mol) was added dropwise to DMF (49.1 mL, 0.636 mol) with stirring at 0 °C. After complete addition, the mixture was vigorously stirred for 30 min at 25°C. The resulting yellow viscous liquid (Vilsmeier reagent) was added dropwise to a solution of anhydrous phloroglucinol (40.0 g, 0.317 mol) in 1,4-dioxane (200 mL) with stirring at 0 °C. After vigorous stirring for 4 h at 25°C, the resulting yellow amorphous solid was transferred to a 2 L round-bottom flask using water (1.5 L), and vigorously stirred for 3 h at 25°C. The precipitated yellow solid was filtered, washed with water, and dried in a vacuum oven for 12 h at 30°C to afford **5** (56.8 g, 0.312 mol, 98.4%). The crude product was sufficiently pure for use in the next step without further purification: mp 221–224°C (lit.[39,40] mp >220°C); TLC R_f = 0.21 (*n*-hexane: acetone = 1:2); IR ν_{max} (cm^{-1}) 2888, 1599, 1503, 1439, 1393, 1254, 1187; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.52 (br s, 2H, —OH), 10.01 (s, 2H, —CHO), 5.90 (s, 1H, Ar—H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 191.4 (2C), 169.4 (2C), 169.0 (1C), 103.8 (2C), 94.1 (1C).

Synthesis of 2,4-dimethylphloroglucinol (4). Zinc powder (30.0 g) that had been activated by stirring in a 1% HCl aqueous solution (300 mL) was added to a 3% HCl aqueous solution (450 mL). Mercury(II) chloride (0.900 g) was then added, and the resulting mixture was stirred vigorously at 25°C for 4 h. The obtained fluffy solid was washed with water and 1,4-dioxane, filtered, and added to a solution of **5** (3.00 g, 16.5 mmol) in 1,4-dioxane (300 mL). The reaction mixture was stirred at 25°C for 20 min and then cooled to 0 °C. Subsequently, a 36% HCl aqueous solution (12 mL) was added slowly, and the mixture was stirred for 30 min. After this time, the reaction mixture was filtered, washed with water (200 mL), and extracted with ethyl acetate (EtOAc, 3 × 100 mL). The combined organic layer was washed with saturated NaCl aqueous solution and dried over anhydrous $MgSO_4$. The organic solvent was evaporated under reduced pressure, and the crude product was purified via column chromatography (*n*-hexane: acetone = 8:1) to afford **4** (1.72 g, 11.2 mmol, 67.9%) as a brown powder: mp 162–163°C (lit.[41] mp 158–16 °C); TLC R_f = 0.67 (*n*-hexane:acetone = 1:2); IR ν_{max} (cm^{-1}) 3527, 3465, 3425, 2921, 2852, 1609, 1457, 1433, 1247, 1150; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.62 (s, 2H, —OH), 7.76 (s, 1H, —OH), 5.92 (s, 1H, Ar—H), 1.86 (s, 6H, —CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 154.1 (2C), 153.2 (2C), 102.6 (1C), 94.6 (1C), 8.7 (2C).

Synthesis of 2,4,6-trimethoxy-3,5-dimethylbenzene (6). To a suspension of **4** (1.72 g, 11.2 mmol) and K_2CO_3 (6.16 g, 44.6 mmol) in dry acetone (30 mL), dimethyl sulfate (4.22 mL, 44.5 mmol) was added under a N_2 atmosphere. The reaction mixture was stirred at reflux overnight and then cooled to room temperature. The reaction mixture was diluted with EtOAc (300 mL) and acidified with a 1% HCl aqueous solution (300 mL). The organic layer was separated, washed with water (3 × 300 mL) and saturated NaCl aqueous solution (300 mL), and dried over anhydrous $MgSO_4$. The organic solvent was then evaporated under reduced pressure, and the crude product was purified via column chromatography (*n*-hexane:acetone = 300:1) to afford **6** (2.16 g, 11.0 mmol, 98.2%) as a white powder: mp 52–55°C (lit.[41] mp 46–48°C); TLC R_f = 0.69 (*n*-hexane:acetone = 3:2); IR ν_{max} (cm^{-1}) 2926, 1608, 1496, 1464, 1435, 1401, 1321, 1219, 1193, 1127; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.41 (s, 1H, Ar—H), 3.77 (s, 6H, —OCH_3), 3.57 (s, 3H, —OCH_3), 1.98 (s, 6H, —CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 157.2 (1C), 156.3 (2C), 109.9 (2C), 91.8 (1C), 59.7 (1C), 55.5 (2C), 8.5 (2C).

Synthesis of 2-hydroxy-4,6-dimethoxy-3,5-dimethylacetophenone (3). Acetic anhydride (2.07 mL, 22.0 mmol) was added to **6** (2.16 g, 11.0 mmol) under a N_2 atmosphere. The solution was cooled at 0 °C, and BF_3·Et_2O (2.76 mL, 22.4 mmol) was added to the solution by syringe. After stirring for 3 h at 90°C, the reaction mixture was diluted with EtOAc (300 mL), acidified with a

1% HCl aqueous solution (300 mL), washed with water (3 × 300 mL) and saturated NaCl aqueous solution (300 mL), and then dried over anhydrous $MgSO_4$. The organic solvent was evaporated under reduced pressure, and the crude product was purified via column chromatography using *n*-hexane as an eluent to afford **3** (1.88 g, 8.39 mmol, 76.3%) as a yellow powder: mp 48–50°C (lit.[41] mp 49–51°C); TLC R_f = 0.66 (*n*-hexane:acetone = 3:2); IR ν_{max} (cm^{-1}) 3440, 2941, 1621, 1454, 1417, 1364, 1318, 1283, 1198, 1171, 1120; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.80 (s, 1H, —OH), 3.71 (s, 3H, —OCH_3), 3.69 (s, 3H, —OCH_3), 2.65 (s, 3H, —$COCH_3$), 2.09 (s, 3H, —CH_3), 2.03 (s, 3H, —CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 204.3 (1C), 162.8 (1C), 159.4 (1C), 158.4 (1C), 115.1 (1C), 114.4 (1C), 112.3 (1C), 61.5 (1C), 59.8 (1C), 31.5 (1C), 9.0 (1C), 8.5 (1C).

General synthetic route to MDMC derivatives (2). To a solution of **3** (2.23 mmol) in MeOH (20 mL), the desired benzaldehyde (2.68 mmol) was added. KOH (6.69 mmol) predissolved in MeOH with the aid of sonication was then added, and the reaction mixture was stirred for 48 h at 25°C. After this time, the obtained mixture was diluted with EtOAc (150 mL), acidified with a 1 M NH_4Cl aqueous solution (100 mL), washed with water (3 × 200 mL) and saturated NaCl aqueous solution (200 mL), and then dried over anhydrous $MgSO_4$. The organic solvent was evaporated under reduced pressure, and the crude product was purified via column chromatography (*n*-hexane to remove any unreacted aldehyde, then *n*-hexane: acetone = 300:1).

1-(2′-Hydroxy-4′,6′-dimethoxy-3′,5′-dimethylphenyl)-3-(4-fluorophenyl)-2-propen-1-one (2a). To a solution of **3** (0.500 g, 2.23 mmol) and 4-fluorobenzaldehyde (0.283 mL, 2.64 mmol) in MeOH (20 mL), KOH (0.375 g, 6.68 mmol) in MeOH (10 mL) was added. The crude product was purified via column chromatography to afford **2a** (0.664 g, 2.01 mmol, 90.1%) as a pale orange solid: mp 89–91°C; TLC R_f = 0.71 (*n*-hexane:acetone = 3:2); IR ν_{max} (cm^{-1}) 3447, 2941, 1629, 1580, 1449, 1416, 1342, 1285, 1218, 1158, 1113; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.99 (s, 1H, −OH), 7.82(dd, J = 8.83 Hz, J = 5.57 Hz, 2H, Ar − H) 7.69 (d, J = 15.70 Hz, 1H, —C═C—H), 7.66 (d, J = 15.90 Hz, 1H, —C═C—H), 7.29 (dd, J = 8.83 Hz, J = 8.82 Hz, 2H, Ar—H), 3.70 (s, 3H, —OCH_3), 3.61 (s, 3H, —OCH_3), 2.11 (s, 3H, —CH_3), 2.06 (s, 3H, —CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 193.7 (1C), 163.4 (d, J = 249.09 Hz, 1C), 162.1 (1C), 158.3 (1C), 157.4 (1C), 142.3 (1C), 131.2 (d, J = 3.06 Hz, 1C), 130.9 (d, J = 8.67 Hz, 2C), 126.7 (1C), 116.1 (d, J = 21.81 Hz, 2C), 115.4 (1C), 114.7 (1C), 113.5 (1C), 62.0 (1C), 59.9 (1C), 8.8 (1C), 8.7 (1C).

1-(2′-Hydroxy-4′,6′-dimethoxy-3′,5′-dimethylphenyl)-3-phenyl-2-propen-1-one (2b). To a solution of **3** (0.500 g, 2.23 mmol) and benzaldehyde (0.273 mL, 2.68 mmol) in MeOH (20 mL), KOH (0.375 g, 6.68 mmol) in MeOH (10 mL) was added. The crude product was purified via column chromatography to afford **2b** (0.650 g, 2.08 mmol, 93.3%) as a pale orange solid: mp 138–140°C; TLC R_f = 0.58 (*n*-hexane:acetone = 3:2); IR ν_{max} (cm^{-1}) 3369, 2924, 1627, 1606, 1553, 1512, 1348, 1261, 1141, 1108, 1023; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.05 (s, 1H, —OH), 7.73 (m, 2H, Ar—H), 7.71 (t, J = 18.16 Hz, 2H, —C═C—H), 7.45 (m, 3H, Ar − H), 3.70 (s, 3H, —OCH_3), 3.62 (s, 3H, —OCH_3), 2.11 (s, 3H, —CH_3), 2.07 (s, 3H, —CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 193.8 (1C), 162.2 (1C), 158.4 (1C), 157.4 (1C), 143.6 (1C), 134.6 (1C), 130.7 (1C), 129.1 (2C), 128.5 (2C), 126.8 (1C), 115.5 (1C), 114.7 (1C), 113.4 (1C), 62.0 (1C), 59.9 (1C), 8.8 (1C), 8.7 (1C).

1-(2′-Hydroxy-4′,6′-dimethoxy-3′,5′-dimethylphenyl)-3-*p*-tolyl-2-propen-1-one (2c). To a solution of **3** (0.500 g, 2.23 mmol) and *p*-tolualdehyde (0.316 mL, 2.68 mmol) in MeOH (20 mL), KOH (0.375 g, 6.68 mmol) in MeOH (10 mL) was added. The crude product was purified via column chromatography to afford **2c** (0.651 g, 2.00 mmol, 89.7%) as a pale orange solid: mp 83–85°C; TLC R_f = 0.74 (*n*-hexane:acetone = 3:2); IR ν_{max} (cm^{-1}) 3513, 2962, 1630, 1560, 1412, 1344, 1261, 1141, 1109, 1019; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.12 (s, 1H, —OH), 7.67 (t, J = 16.97 Hz, J = 17.06 Hz, 2H, —C═C—H), 7.63 (d, J = 7.85 Hz, 2H, Ar—H), 7.27 (d, J = 7.85 Hz, 2H, Ar—H), 3.70 (s, 3H, —OCH_3), 3.61 (s, 3H, —OCH_3), 2.35 (s, 3H, —CH_3), 2.11 (s, 3H, —CH_3), 2.06 (s, 3H, —CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 193.7 (1C), 162.1 (1C), 158.5 (1C), 157.4 (1C), 143.7 (1C), 140.8 (1C), 131.9 (1C), 129.7 (2C), 128.6 (2C), 125.8 (1C), 115.2 (1C), 114.7 (1C), 113.4 (1C), 61.9 (1C), 59.9 (1C), 21.1 (1C), 8.8 (1C), 8.7 (1C).

1-(2′-Hydroxy-4′,6′-dimethoxy-3′,5′-dimethylphenyl)-3-(4-isopropylphenyl)-2-propen-1-one (2d). To a solution of **3** (0.500 g, 2.23 mmol) and 4-isopropylbenzaldehyde (0.405 mL, 2.67 mmol) in MeOH (20 mL), KOH (0.375 g, 6.68 mmol) in MeOH (10 mL) was added. The crude product was purified via column chromatography to afford **2d** (0.730 g, 2.06 mmol, 92.4%) as a pale orange solid: mp 76–78°C; TLC R_f = 0.74 (*n*-hexane:acetone = 3:2); IR ν_{max} (cm^{-1}) 3535, 2960, 1630, 1560, 1458, 1416, 1344, 1280, 1194, 1142, 1111; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.14 (s, 1H, —OH), 7.69 (t, J = 18.42 Hz, 2H, —C═C—H), 7.66 (d, J = 8.19 Hz, 2H, Ar—H), 7.33 (d, J = 8.19 Hz, 2H, Ar—H), 3.70 (s, 3H, —OCH_3), 3.61 (s, 3H, —OCH_3), 2.93 (septet, J = 6.90 Hz, 1H, —CH), 2.11 (s, 3H, —CH_3), 2.06 (s, 3H, —CH_3), 1.23 (s, 3H, —CH_3), 1.21 (s, 3H, —CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 193.7 (1C), 162.2 (1C), 158.5 (1C), 157.4 (1C), 151.6 (1C), 143.7 (1C), 132.3 (1C), 128.7 (2C), 127.1 (2C), 126.5 (1C), 125.8 (1C), 114.6 (1C), 113.3 (1C), 61.9 (1C), 59.9 (1C), 33.4 (1C), 23.6 (2C), 8.8 (1C), 8.7 (1C).

1-(2′-Hydroxy-4′,6′-dimethoxy-3′,5′-dimethylphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (2e). To a solution of **3** (0.500 g, 2.23 mmol) and 4-methoxybenzaldehyde (0.324 mL, 2.68 mmol) in MeOH (20 mL), KOH (0.375 g,

6.68 mmol) in MeOH (10 mL) was added. The crude product was purified via column chromatography to afford **2e** (0.694 g, 2.03 mmol, 91.0%) as a pale orange solid: mp 86–88°C; TLC R_f = 0.68 (*n*-hexane:acetone = 3:2); IR ν_{max} (cm^{-1}) 3430, 2936, 1628, 1605, 1556, 1510, 1421, 1348, 1256, 1172, 1141, 1110; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.19 (s, 1H, —OH), 7.71 (d, J = 8.78 Hz, 2H, Ar—H), 7.70 (d, J = 15.63 Hz, 1H, —C═C—H), 7.60 (d, J = 15.63 Hz, 1H, —C═C—H), 7.02 (d, J = 8.78 Hz, 2H, Ar—H), 3.82 (s, 3H, —OCH_3), 3.69 (s, 3H, —OCH_3), 3.61 (s, 3H, —OCH_3), 2.11 (s, 3H, —CH_3), 2.06 (s, 3H, —CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 193.6 (1C), 162.0 (1C), 161.5 (1C), 158.5 (1C), 157.3 (1C), 143.9 (1C), 130.5 (2C), 127.8 (1C), 127.1 (1C), 124.2 (1C), 114.6 (2C), 114. 6 (1C), 113.3 (1C), 61.9 (1C), 59.9 (1C), 55.4 (1C), 8.8 (1C), 8.7 (1C).

1-(2′-Hydroxy-4′,6′-dimethoxy-3′,5′-dimethylphenyl)-3-(4-(methoxymethoxy)phenyl)-2-propen-1-one (2f)**.** To a solution of **3** (0.500 g, 2.23 mmol) and 4-methoxymethoxybenzaldehyde (0.445 g, 2.68 mmol) in MeOH (20 mL), KOH (0.375 g, 6.68 mmol) in MeOH (10 mL) was added. The crude product was purified via column chromatography to afford **2 f** (0.771 g, 2.07 mmol, 92.8%) as a pale orange solid: mp 77–79°C; TLC R_f = 0.69 (*n*-hexane:acetone = 3:2); IR ν_{max} (cm^{-1}) 3430, 2959, 1630, 1604, 1560, 1509, 1421, 1346, 1241, 1142, 1110; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.17 (s, 1H, —OH), 7.71 (d, J = 8.76 Hz, 2H, Ar—H), 7.63 (t, J = 15.77 Hz, 2H, —C═C—H), 7.09 (d, J = 8.76 Hz, 2H, Ar—H), 5.26 (s, 2H, —CH_2—O—), 3.69 (s, 3H, —OCH_3), 3.61 (s, 3H, —OCH_3), 3.38 (s, 3H, —OCH_3), 2.11 (s, 3H, —CH_3), 2.06 (s, 3H, —CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 193.6 (1C), 162.0 (1C), 158.9 (1C), 158.5 (1C), 157.4 (1C), 143.6 (1C), 130.4 (2C), 128.1 (1C), 127.7 (1C), 124.7 (1C), 116.5 (2C), 115.3 (1C), 114.6 (1C), 113.3 (1C), 93.7 (1C), 61.9 (1C), 59.9 (1C), 55.7 (1C), 8.8 (1C), 8.7 (1C).

Synthesis of 1-(2′-hydroxy-4′,6′-dimethoxy-3′,5′-dimethylphenyl)-3-(4-hydroxyphenyl)-2-propen-1-one (2g)**.** To a solution of **2f** (1.00 g, 2.69 mmol) in MeOH (300 mL), *p*-toluenesulfonic acid monohydrate (0.562 g, 2.95 mmol) was added, and the resulting solution stirred for 36 h at 25°C. Thereafter, the resulting mixture was diluted with EtOAc (150 mL), washed with water (3 × 200 mL) and saturated NaCl aqueous solution (200 mL), and then dried over anhydrous $MgSO_4$. The organic solvent was evaporated under reduced pressure to afford the crude product, which was subsequently purified via column chromatography (*n*-hexane:acetone = 30:1) to afford **2g** (0.836 g, 2.55 mmol, 94.8%) as a pale orange solid: mp 138–140°C; TLC R_f = 0.58 (*n*-hexane:acetone = 3:2); IR ν_{max} (cm^{-1}) 3367, 2962, 1627, 1606, 1551, 1512, 1439, 1348, 1261, 1141, 1108, 1022; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.31 (s, 1H, —OH), 10.14 (s, 1H, —OH), 7.68 (d, J = 15.49 Hz, 1H, —C═C—H), 7.59 (d, J = 8.58 Hz, 1H, Ar − H), 7.56 (d, J = 15.49 Hz, 2H, —C═C—H), 6.83 (d, J = 8.58 Hz, 2H, Ar—H), 3.69 (s, 3H, —OCH_3), 3.61 (s, 3H, —OCH_3), 2.10 (s, 3H, —CH_3), 2.06 (s, 3H, —CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 193.5 (1C), 161.9 (1C), 160.3 (1C), 158.6 (1C), 157.4 (1C), 144.6 (1C), 130.8 (2C), 125.6 (1C), 123.0 (1C), 116.0 (2C), 115.3 (1C), 114.6 (1C), 113.2 (1C), 61.9 (1C), 59.9 (1C), 8.8 (1C), 8.7 (1C).

Results and Discussion

We proposed that the chalcone skeleton of MDMC could be con-structed via the Claisen–Schmidt condensation of di-*O*-methyl-dimethylphloroacetophenone (**3**) with the corresponding benzaldehyde (Figure 2). The key intermediate **3**, *i.e.*, the B-ring moiety in which two methyl groups are alternatively attached between three hydroxy or methoxy groups, could be obtained by the double *O*-methylation and single *C*-acetylation of dimethylphloroglucinol (**4**). Intermediate **4** could be prepared from commercially available phloroglucinol.

To develop a more straightforward synthetic route toward the key intermediate **3** and its substitute, a variety of synthetic routes starting from phloroacetophenone were initially investigated. However, all attempts to simultaneously introduce two *C*-methyl groups into phloroacetophenone without affecting the three hydroxyl groups yielded poor results, as in previous reports.[42,43] The attempted introduction of two *C*-methyl groups between the three hydroxyl groups of phloroglucinol to generate **4** were also unsuccessful primarily due to the competitive *O*-methylation of hydroxyl groups. Thus, two methyl groups had to be introduced to phloroglucinol through a relatively bypassing synthetic route.[41] As shown in Scheme 1, the Vilsmeier–Haack reaction of phloroglucinol using DMF and $POCl_3$ produced 2,4-diformylphloroglucinol (**5**) in an excellent yield. Product **5** was obtained as a yellow powder after a simple precipitation with water, and this product was sufficiently pure to be used in the subsequent step without any further purification.

Although typical metal hydride reagents, such as $NaBH_4$, $LiAlH_4$, and $NaBH_3CN$, were not successful in reducing both formyl groups of **5**, a Clemmensen reduction using

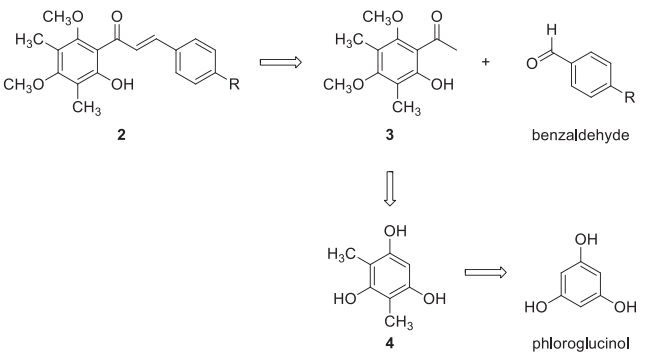
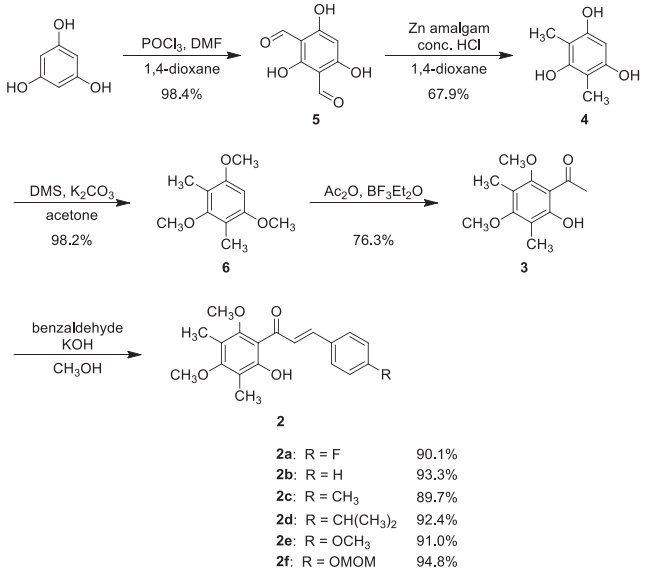
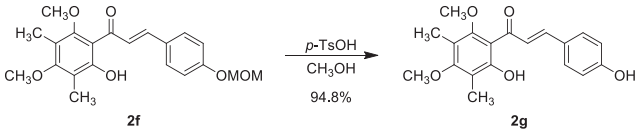


Figure 2. Retrosynthetic analysis for preparation of MDMC derivatives.



Scheme 1. Synthetic route toward the MDMC derivatives (**2**).



Scheme 2. Preparation of **2g** from **2f.**

Table 1. Optimization for the deprotection of **2f** to prepare **2g**.[a]

Entry	Acid (equiv.)	Temp. (°C)	Time	Yield (%)[b]
1	36% HCl (4.9)	reflux	20 min	50.8
2	36% HCl (4.9)	50	2 h	51.2
3	36% HCl (4.9)	25	3 h	52.6
4	1% HCl (1.0)	50	20 h	53.4
5	1% HCl (1.0)	25	20 h	55.9
6	*p*-TsOH (2.0)	reflux	20 h	78.6
7	*p*-TsOH (2.0)	50	20 h	80.4
8	*p*-TsOH (2.0)	25	36 h	92.6
9	*p*-TsOH (1.1)	25	36 h	94.8

[a] All reactions were performed using **2f** (1.00 g) in MeOH (300 mL). [b] Isolated yields based on **2f**.

zinc amalgam efficiently reduced these moieties to give 2,4-dimethylphloroglucinol (**4**) in a good yield.

Attempts to directly introduce two *O*-methyl groups and one acetyl group (independent of the order) at the desired positions of **4** to construct **3** were not successful. This was attributed to the fact that the regioselective bis-*O*-methylation of only two hydroxyl groups was challenging. In addition, the selective *C*-acetylation gave poor results in the presence of a phenolic hydroxyl group. Therefore, an alternative pathway based on trimethoxyxylene **6**, an intermediate bearing no hydroxyl groups and prepared by the *O*-methylation of all hydroxyl groups present in **4**, was investigated. The hydroxyl groups of **4** were, therefore, methylated by reaction with dimethylsulfate (DMS) and K_2CO_3 in acetone to generate **6** in a good yield. The Friedel-Crafts-type acetylation of **6** using acetic anhydride in the presence of $BF_3{\cdot}Et_2O$ not only successfully introduced a single *C*-acetyl group to the phenyl carbon atom but also simultaneously removed one *ortho*-*O*-methyl group to directly generate **3**.[41]

Construction of the chalcone skeleton of the desired MDMC derivatives (**2**) proceeded well via a Claisen–Schmidt condensation of **3** with the appropriate benzaldehyde. Following brief optimization studies, it was found that the use of three equivalents of KOH in MeOH was favored. The optimized reaction conditions generated the corresponding compounds **2a**–**2f** in good isolated yields ranging from 89.7 to 94.8%. It was found that additional electrophilic aldehydes, and in particular 4-fluorobenzaldehyde, reacted faster than less electrophilic aldehydes.

The efficiency of the acid-catalyzed cleavage of the MOM group of **2f** to prepare **2g** (Scheme 2) was found to be dependent on the reaction conditions. In particular, cleavage of the *O*-methyl groups and a retro-aldol condensation lowered the yield of **2g**.

Reactions carried out using an excess of aqueous HCl did not generate good results, regardless of the reaction temperature employed (Table 1, entries 1–3). Treatment with an exact equivalent of HCl was also not sufficient (entries 4–5). On the other hand, *p*-toluenesulfonic acid (*p*-TsOH) significantly reduced the degree of side reactions occurring to increase the reaction efficiency, in addition to giving a higher yield at lower temperatures (entries 6–8). The usage of a slight excess of *p*-TsOH resulted in the best reaction efficiency (entry 9). Overall, the optimized reaction conditions involved the reaction of 1.1 equiv. of *p*-TsOH in MeOH for 36 h at 25°C, to give **2g** in a 94.8% isolated yield.

Conclusion

In summary, we accomplished the total syntheses of seven 4′,6′-dimethoxy-2′-hydroxy-3′,5′-dimethylchalcone (MDMC) derivatives (**2**). To the best of our knowledge, a general method for the syntheses of these compounds has not been reported thus far. The key intermediate **3**, which contained the B-ring moiety of the skeleton, was prepared via four efficient reaction steps from commercially available phloroglucinol in a 50.1% overall isolated yield. This synthetic method allowed the construction of various derivatives **2** in 44.9–47.5% overall yields from phloroglucinol. Moreover, the synthetic strategy involving construction of the chalcone skeleton via a Claisen–Schmidt condensation of the B-ring moiety (**3**) with various benzaldehydes will be expected to facilitate pharmacological studies into DMC derivatives by allowing their rapid and large-scale production. The anti-diabetic effects of these compounds are currently under investigation and the results will be reported in due course.

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