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ARTICLE

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Total synthesis of 2′,4′,6′-trimethoxy-3′,5′-dimethylchalcone derivatives

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Abstract

2′,4′-Dihydroxy-6′-methoxy-3′,5′-dimethylchalcone (DMC), which is isolated from plants, has recently attracted much attention due to its beneficial pharmacological effects. The preparation of twelve 2′,4′,6′-trimethoxy-3′,5′-dimethylchalcone (DMDMC) derivatives, which are dimethylated-derivatives of DMC, is reported herein for the first time. Our synthetic method allowed the efficient construction of the DMDMC derivatives from phloroglucinol in 37.8%–46.5% overall yields. This promising approach would be advantageous for the production of many different DMDMC derivatives in a short period of time.

KEYWORDS
2′,4′,6′-trimethoxy-3′,5′-dimethylchalcone, antidiabetic compounds, chalcone derivatives, dimethyl cardamonin, total synthesis

INTRODUCTION

A variety of chalcone compounds, bicyclic flavonoids constructed of two substituted benzene rings connected by an α,β-unsaturated carbonyl bridge have been extracted from natural plants. They are known for their bioactivities such as anticancer, anti-inflammatory, antibacterial, antiviral, and antidiabetic and have many medicinal uses.[1–10] In particular, 2′,4′-dihydroxy-6′-methoxy-3′,5′-dimethylchalcone (DMC, **1**), a naturally occurring chalcone compound with a B-ring structure in which five substituents are complexly bonded (Figure 1),[11–13] has been reported to exhibit various effects such as anticancer, antioxidative, and anti-inflammatory effects.[14–21] Recently, it was reported to have antidiabetic effects by increasing the fatty acid oxidation ratio in C2C12 myotubes and skeletal muscle, along with significantly lowering blood sugar levels.[22]

Since the pharmacological activity of DMC has garnered considerable interest, research to develop new drug candidates based on this compound is underway. To develop promising new drugs, it is necessary to derive a molecular structure optimized for the desired drug efficacy. To this end, the correlation between the molecular structure and effectiveness must be investigated via studies to synthesize and evaluate a series of derivatives in which the substituents are systematically modified.

Although structurally simple chalcones and trihydroxychalcone compounds have been synthesized by many researchers,[23–26] very few methods have been reported to date for the general syntheses of DMC derivatives.[27–29] This is because it is difficult to regioselectively introduce three hydroxy or methoxy groups and two methyl groups into the B-ring of the DMC derivative. However, since the two methyl groups bonded to the B-ring was discovered to play an important role for their antidiabetic activity in our previous study with cardamonin derivatives,[30] the synthesis of DMC derivatives became essential.

As part of our ongoing effort to discover novel antidiabetic compounds, we sought to investigate the effect of changes in the electronic and steric properties of substituents attached to the A-ring as well as the B-ring on efficacy. Therefore, we have prepared new DMC derivatives with two methyl groups and three methoxy groups that are alternately attached on the B-ring, starting from affordable phloroglucinol. Herein, we report the first total synthesis for 2′,4′,6′-trimethoxy-3′,5′-dimethylchalcone (DMDMC) derivatives (**2**).

EXPERIMENT

General information

2-Fluorobenzaldehye, 2-chlorobenzaldehyde, and 4-chloroben zaldehyde were purchased from Tokyo Chemical Industry (Tokyo, Japan). 4-Hydroxybenzaldehyde, 4-fluorobenzaldehyde,

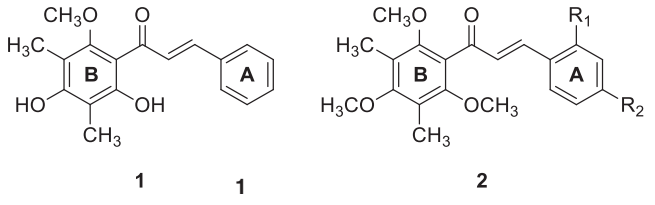


FIGURE 1 Structure of 2′,4′-dihydroxy-6′-methoxy-3′,5′-dimethylchalcone (DMC) (**1**) and 2′,4′,6′-trimethoxy-3′,5′-dimethylchalcone (DMDMC) derivatives (**2**)

and 4-methoxybenzaldehyde were purchased from Alfa Aesar (Ward Hill, MA, USA). Dimethyl sulfate (DMS), benzaldehyde, and *p*-toluenesulfonic acid (*p*-TsOH) were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). 4-Isopropylbenzaldehyde and 4-methylbenzaldehyde were purchased from Acros Organics (Morris Plains, NJ, USA). Chloromethyl methyl ether (MOMCl) was purchased from Kanto Chemical Co., Inc. (Tokyo, Japan). 4-Methoxymethoxybenzaldehyde was prepared as previously described.[31]

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 under UV light (254 and 365 nm). 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 id) using a GC system (HP 6890 series; Hewlett-Packard, Palo Alto, CA, USA). Proton nuclear magnetic resonance (^{1}H NMR, 600 MHz) and carbon nuclear magnetic resonance (^{13}C NMR, 150 MHz) spectra were acquired on a 600-MHz spectrometer (VNS, Varian, Palo Alto, CA, USA) with dimethyl sulfoxide-d_6 (DMSO-d_6) as the solvent. The chemical shifts were referenced to the residual solvent peaks (δ_H 2.50 and δ_C 39.52 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). Fourier transform infrared spectroscopy (FT-IR) spectra were acquired using a FT-IR Spectrometer (Nicolet 6700; Thermo Scientific, Waltham, MA, USA).

Synthesis of 2,4,6-trimethoxy-3,5-dimethylacetophenone (3)

To a solution of **7**[27] (1.88 g, 8.39 mmol) and potassium carbonate (K_2CO_3) (1.39 g, 10.06 mmol) in dry acetone (30 ml), DMS (0.95 ml, 10.06 mmol) was added in a two-necked round-bottomed flask under N_2 atmosphere and refluxed overnight. After the complete consumption of compound **7**, the reaction mixture was cooled to 25°C, extracted with ethyl acetate (EtOAc, 300 ml), and then washed with 1% hydrochloric acid (HCl) aqueous solution (200 ml), water (3 × 100 ml), and a saturated sodium chloride (NaCl) aqueous solution (200 ml). The resulting solution was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified using column chromatography (*n*-hexane/acetone = 300:1) to afford **3** (1.93 g, 96.7%) as a white solid: mp. 53–55°C; TLC R_f = 0.59 (*n*-hexane/acetone = 3:2); IR ν_{max} (cm^{-1}): 2940, 1648, 1454, 1170; ^{1}H NMR (300 MHz, DMSO-d_6, δ): 3.66 (s, 3H, $-OCH_3$), 3.62 (s, 6H, $-OCH_3$), 2.43 (s, 3H, $-COCH_3$), 2.10 (s, 6H, $-CH_3$); and ^{13}C NMR (150 MHz, DMSO-d_6, δ): 201.5 (1C), 158.5 (1C), 153.0 (2C), 126.5 (1C), 120.1 (2C), 61.7 (2C), 59.7 (1C), 32.3 (1C), 9.0 (2C).

General synthetic route to DMDMC derivatives (2)

To a solution of **3** (2.10 mmol) and potassium hydroxide (KOH) (6.30 mmol) in methanol (MeOH) (20 ml), the corresponding benzaldehyde (2.52 mmol) was added. The reaction mixture was stirred for 48 h at 25°C. After the complete consumption of compound **3**, the reaction mixture was diluted with EtOAc (200 ml), acidified with 1-M NH_4Cl aqueous solution (200 ml), and washed with distilled water (3 × 100 ml) and saturated NaCl aqueous solution (200 ml). The resulting solution was dried over anhydrous $MgSO_4$. The solution was concentrated under reduced pressure. The crude product was purified by column chromatography to afford **2** (see NMR Spectrum in Supporting Information for detail).

Synthesis of 1-(2′,4′,6′-trimethoxy-3′,5′-dimethylphenyl)-3-(4-fluorophenyl)-2-propen-1-one (2a)

To a solution of **3** (0.25 g, 1.05 mmol) and KOH (0.18 g, 3.15 mmol) in MeOH (20 ml), 4-fluorobenzaldehyde (0.13 ml, 1.26 mmol) was added. The crude product was purified by column chromatography (*n*-hexane: acetone = 300:1) to afford **2a** (0.36 g, 93.1%) as a white solid: mp. 71°C; TLC R_f = 0.55 (*n*-hexane/acetone = 3:2); IR ν_{max} (cm^{-1}): 2938, 1648, 1107; ^{1}H NMR (600 MHz, DMSO-d_6, δ): 7.80 (dd, *J* = 8.69 Hz, *J* = 5.65 Hz, 2H, Ar H), 7.30 (d, *J* = 16.15 Hz, 1H, –C=C–H), 7.24 (t, *J* = 8.86 Hz, 2H, Ar H), 7.09 (d, *J* = 16.15 Hz, 1H, –C=C–H), 3.70 (s, 3H, $-OCH_3$), 3.59 (s, 6H, $-OCH_3$), 2.13 (s, 6H, $-CH_3$); and ^{13}C NMR (150 MHz, DMSO-d_6, δ): 193.9 (1C), 163.4 (d, *J* = 249.23 Hz, 1C), 158.6 (1C), 153.8 (1C), 143.7 (1C), 131.0 (d, *J* = 8.67 Hz, 1C), 130.7 (d, *J* = 3.10 Hz, 1C), 128.3 (1C), 124.5 (1C), 120.0 (1C), 115.9 (d, *J* = 21.74 Hz, 1C), 61.5 (2C), 59.7 (1C), 9.1 (2C).

Synthesis of 1-(2′,4′,6′-trimethoxy-3′,5′-dimethylphenyl)-3-phenyl-2-propen-1-one (2b)

To a solution of **3** (0.50 g, 2.10 mmol) and KOH (0.35 g, 6.30 mmol) in MeOH (20 ml), benzaldehyde (0.26 ml, 2.52 mmol) was added. The crude product was purified by column chromatography (*n*-hexane/acetone = 300:1) to afford **2b** (0.66 g, 96.3%) as a white solid: mp. 70°C; TLC $R_f = 0.54$ (*n*-hexane/acetone = 3:2); IR ν_{max} (cm^{-1}): 2938, 1648; ^{1}H NMR (600 MHz, DMSO-d_6, δ): 7.71 (dd, $J = 7.84$ Hz, $J = 1.80$ Hz, 2H, Ar H), 7.43–7.39 (m, 3H, Ar H), 7.30 (d, $J = 16.17$ Hz, 1H, –C=C–H), 7.11 (d, $J = 16.17$ Hz, 1H, –C=C–H), 3.70 (s, 3H, $-OCH_3$), 3.59 (s, 6H, $-OCH_3$), 2.13 (s, 6H, $-CH_3$); and ^{13}C NMR (150 MHz, DMSO-d_6, δ): 194.4 (1C), 159.0 (1C), 154.2 (1C), 145.4 (1C), 134.5 (1C), 131.2 (1C), 129.4 (2C), 129.1 (2C), 128.8 (1C), 125.0 (1C), 120.5 (2C), 70.2 (1C), 62.0 (2C), 60.2 (1C), 9.61 (2C).

Synthesis of 1-(2′,4′,6′-trimethoxy-3′,5′-dimethylphenyl)-3-(*p*-tolyl)-2-propen-1-one (2c)

To a solution of **3** (0.25 g, 1.05 mmol) and KOH (0.18 g, 3.15 mmol) in MeOH (20 ml), *p*-tolubenzaldehyde (0.15 ml, 1.26 mmol) was added. The crude product was purified using column chromatography (*n*-hexane/acetone = 300:1) to afford **2c** (0.33 g, 92.1%) as a yellow oil: TLC $R_f = 0.57$ (*n*-hexane/acetone = 3:2); IR ν_{max} (cm^{-1}): 2938, 2867, 1649; 1404; ^{1}H NMR (600 MHz, DMSO-d_6, δ): 7.60 (d, $J = 8.08$ Hz, 2H, Ar H), 7.25 (d, $J = 16.12$ Hz, 1H, –C=C–H), 7.22 (d, $J = 8.08$ Hz, 1H, Ar H), 7.05 (d, $J = 16.12$ Hz, 1H, 1H, –C=C–H), 3.70 (s, 3H, $-OCH_3$), 3.58 (s, 6H, $-OCH_3$), 2.32 (s, 3H, $-CH_{3)}$, 2.13 (s, 6H, $-CH_3$); and ^{13}C NMR (150 MHz, DMSO-d_6, δ): 194.0 (1C), 158.5 (1C), 153.7 (2C), 145.1 (1C), 140.86 (1C), 131.31 (1C), 129.5 (2C), 128.6 (2C), 127.5 (1C), 124.6 (1C), 120.0 (2C), 61.5 (2C), 59.7 (1C), 21.0 (1C), 9.1 (2C).

Synthesis of 1-(2′,4′,6′-trimethoxy-3′,5′-dimethylphenyl)-3-(4-isopropylphenyl)-2-propen-1-one (2d)

To a solution of **3** (0.50 g, 2.10 mmol) and KOH (0.35 g, 6.30 mmol) in MeOH (20 ml), 4-isopropylbenzaldehyde (0.38 ml, 2.52 mmol) was added. The crude product was purified using column chromatography (*n*-hexane/acetone = 300:1) to afford **2d** (0.73 g, 94.3%) as a white solid: mp. 132–133°C; TLC $R_f = 0.59$ (*n*-hexane/acetone = 3:2); IR ν_{max} (cm^{-1}): 2938, 1649, 1333; ^{1}H NMR (600 MHz, DMSO-d_6, δ): 7.63 (d, $J = 8.28$ Hz, 2H, Ar H), 7.29–7.25 (m, 3H, Ar H, –C=C–H), 7.05 (d, $J = 16.1$ Hz, 1H, –C=C–H), 3.70 (s, 3H, $-OCH_3$), 3.58 (s, 6H, $-OCH_3$), 2.90 (septet, $J = 6.92$ Hz, 1H, –CH–), 2.13 (s, 6H, $-CH_3$), 1.19 (d, $J = 6.91$ Hz, 6H, $-CH_3$); and ^{13}C NMR (150 MHz, DMSO-d_6, δ): 193.9 (1C), 158.5 (1C), 153.7 (2C), 151.5 (1C),145.0 (1C), 131.7 (1C), 128.8 (2C), 127.5 (1C), 126.9 (2C), 124.6 (1C), 120.0 (2C), 61.5 (2C), 59.7 (1C), 33.3 (1C), 23.5 (2C), 9.1 (2C).

Synthesis of 1-(2′,4′,6′-trimethoxy-3′,5′-dimethylphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (2e)

To a solution of **3** (0.50 g, 2.10 mmol) and KOH (0.35 g, 6.30 mmol) in MeOH (20 ml), 4-methoxybenzaldehyde (0.31 ml, 2.52 mmol) was added. The crude product was purified using column chromatography (*n*-hexane/acetone = 300:1) to afford **2e** (0.69 g, 92.9%) as a white solid: mp. 84–85°C; TLC $R_f = 0.56$ (*n*-hexane/acetone = 3:2); IR ν_{max} (cm^{-1}): 2962, 1630, 1412; ^{1}H NMR (600 MHz, DMSO-d_6, δ): 7.67 (d, $J = 8.8$ Hz, 2H, Ar H), 7.23 (d, $J = 16.04$ Hz, 1H, –C=C–H), 6.98–6.96 (m, 3H, –C=C–H, Ar H), 3.70 (s, 3H, $-OCH_3$), 3.58 (s, 6H, $-OCH_3$), 2.13 (s, 6H, $-CH_3$); and ^{13}C NMR (150 MHz, DMSO-d_6, δ): 193.8 (1C), 161.4 (1C), 158.4 (1C), 153.6 (2C), 145.1 (1C), 130.5 (2C), 126.5 (1C), 126.2 (1C), 124.8 (1C), 119.9 (2C), 114.4 (2C), 61.5 (2C), 59.7 (1C), 55.3 (1C), 9.1 (2C).

Synthesis of 1-(2′,4′,6′-trimethoxy-3′,5′-dimethylphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one (2f)

To a solution of **3** (0.5 g, 2.10 mmol) and KOH (0.35 g, 6.30 mmol) in MeOH (20 ml), 4-dimethylaminobenzaldehyde (0.38 g, 2.52 mmol) was added. The crude product was purified using column chromatography (*n*-hexane/acetone = 300:1) to afford **2f** (0.61 g, 78.3%) as a white solid: mp. 84°C; TLC $R_f = 0.62$ (*n*-hexane/acetone = 3:2); IR ν_{max} (cm^{-1}): 2962, 2754, 1627; ^{1}H NMR (600 MHz, DMSO-d_6, δ): 7.50 (d, $J = 8.98$ Hz, 2H, Ar H), 7.14 (d, $J = 15.91$ Hz, 1H, –C=C–H), 6.81 (d, $J = 15.91$ Hz, 1H, –C=C–H), 6.69 (d, $J = 8.98$ Hz, Ar H), 3.69 (s, 3H, $-OCH_3$), 3.57 (s, 6H, $-OCH_3$), 2.98 (s, 6H, $-CH_3$), 2.12 (s, 6H, $-CH_3$); and ^{13}C NMR (150 MHz, DMSO-d_6, δ): 193.4 (1C), 158.1 (1C), 153.5 (2C), 151.9 (1C), 146.3 (1C), 130.4 (2C), 125.2 (1C), 123.1 (1C), 121.1 (1C), 119.8 (2C), 111.7 (2C), 61.4 (2C), 59.7 (1C), 39.63 (2C), 9.1 (2C).

Synthesis of 1-(2′,4′,6′-trimethoxy-3′,5′-dimethylphenyl)-3-(2-fluorophenyl)-2-propen-1-one (2g)

To a solution of **3** (0.5 g, 2.10 mmol) and KOH (0.35 g, 6.30 mmol) in MeOH (20 ml), 2-fluorobenzaldehyde (0.27 ml, 2.52 mmol) was added. The crude product was purified using column chromatography (*n*-hexane/acetone = 300:1) and recrystallization in MeOH to afford **2g** (0.67 g, 92.9%) as a white solid: mp. 54–56°C; TLC $R_f = 0.52$ (*n*-hexane/acetone = 3:2); IR ν_{max} (cm^{-1}): 2962, 1650, 1104; ^{1}H NMR (600 MHz, DMSO-d_6, δ): 7.88 (dt, $J = 7.91$ Hz, $J = 7.62$ Hz, 1H, Ar H), 7.48 (dq, $J = 8.01$ Hz, $J = 7.62$ Hz, $J = 5.33$ Hz, $J = 1.79$ Hz, 1H, Ar H), 7.38 (d, $J = 16.25$ Hz, 1H, –C=C–H), 7.16 (d, $J = 16.25$ Hz, 1H, –C=C–H), 7.26 (t, $J = 7.91$ Hz, 1H, Ar H), 7.24 (t, $J = 8.01$ Hz, 1H, Ar H), 3.68 (s, 3H, $-OCH_3$), 3.57 (s, 6H, $-OCH_3$), 2.11 (s, 6H, $-CH_3$); and

^{13}C NMR (150 MHz, DMSO-d_6, δ): 193.7 (d, J = 251.58 Hz, 1C), 158.8 (1C), 153.9 (2C), 136.2 (d, J = 3.6 Hz, 1C), 132.8 (d, J = 8.9 Hz, 1C), 130.4 (d, J = 4.91 Hz, 1C), 129.3 (d, J = 2.37 Hz, 1C), 125.1 (d, J = 3.35 Hz, 1C), 124.2 (1C), 121.7 (d, J = 11.09 Hz, 1C), 120.1 (2C), 116.1 (d, J = 21.73 Hz, 1C), 61.6 (2C), 59.7 (2C), 9.1 (2C).

Synthesis of 1-(2′,4′,6′-trimethoxy-3′,5′-dimethylphenyl)-3-(2-chlorophenyl)-2-propen-1-one (2h)

To a solution of **3** (0.5 g, 2.10 mmol) and KOH (0.35 g, 6.30 mmol) in MeOH (20 ml), 2-chlorobenzaldehyde (0.28 ml, 2.52 mmol) was added. The crude product was purified using column chromatography (*n*-hexane/acetone = 300:1) and recrystallized in MeOH to afford **2h** (0.68 g, 89.5%) as a white solid: mp. 74–75°C; TLC R_f = 0.54 (*n*-hexane/acetone = 3:2); IR ν_{max} (cm^{-1}): 2939, 1650, 1107; ^{1}H NMR (600 MHz, DMSO-d_6, δ): 8.00 (d, J = 7.70 Hz, 1H, Ar H), 7.63 (d, J = 16.03 Hz, 1H, –C=C–H), 7.54 (d, J = 7.97 Hz, 1H, Ar H), 7.46 (t, J = 7.97 Hz, 1H, Ar H), 7.40 (t, J = 7.70 Hz, 1H, Ar H), 7.19 (d, J = 16.03 Hz, 1H, –C=C–H), 3.70 (s, 3H, –OCH_3), 3.30 (s, 6H, –OCH_3), 2.13 (s, 6H, –CH_3); and ^{13}C NMR (150 MHz, DMSO-d_6, δ): 193.5 (1C), 158.8 (1C), 153.9 (2C), 139.3 (1C), 133.9 (1C), 132.1 (1C), 131.6 (1C), 130.6 (1C), 130.0 (1C), 128.4 (1C), 127.8 (1C), 124.2 (1C), 120.1 (2C), 61.6 (2C), 59.7 (1C), 9.1 (2C).

Synthesis of 1-(2′,4′,6′-trimethoxy-3′,5′-dimethylphenyl)-3-(4-chlorophenyl)-2-propen-1-one (2i)

To a solution **3** (0.5 g, 2.10 mmol) and KOH (0.35 g, 6.30 mmol) in MeOH (20 ml), 4-chlorobenzaldehyde (0.35 g, 2.52 mmol) was added. The crude product was purified using column chromatography (*n*-hexane/acetone = 300:1) to afford **2i** (0.65 g, 86.4%) as a clear oil: TLC R_f = 0.56 (*n*-hexane/acetone = 3:2); IR ν_{max} (cm^{-1}): 2939, 1650, 1107; ^{1}H NMR (600 MHz, DMSO-d_6, δ): 7.76 (d, J = 8.58 Hz, 2H, Ar H), 7.45 (d, J = 8.58 Hz, 2H, Ar H), 7.30 (d, J = 16.15 Hz, 1H, –C=C–H), 7.13 (d, J = 16.15 Hz, 1H, –C=C–H), 3.70 (s, 3H, –OCH_3), 3.58 (s, 6H, –OCH_3), 2.13 (s, 6H, –CH_3); and ^{13}C NMR (150 MHz, DMSO-d_6, δ): 193.8 (1C), 158.6 (1C), 153.8 (2C), 143.4 (1C), 135.2 (1C), 133.0 (1C), 130.4 (2C), 129.0 (2C), 128.9 (1C), 124.4 (1C), 120.0 (2C), 61.5 (2C), 59.7 (1C), 9.1 (2C).

Synthesis of 1-(2′,4′,6′-trimethoxy-3′,5′-dimethylphenyl)-3-(2,4-dimethylphenyl)-2-propen-1-one (2j)

To a solution **3** (0.1 g, 0.42 mmol) and KOH (0.07 g, 1.26 mmol) in MeOH (10 ml), 2,4-dimethylbenzaldehyde (0.07 ml, 0.50 mmol) was added. The crude product was purified using column chromatography (*n*-hexane/acetone = 300:1) and recrystallization in MeOH to afford **2j** (0.12 g, 83.0%) as a white solid: mp. 100°C; TLC R_f = 0.61 (*n*-hexane/acetone = 3:2); IR ν_{max} (cm^{-1}): 2962, 1648, 1457, 1403, 1108; ^{1}H NMR (600 MHz, DMSO-d_6, δ): 7.67 (d, J = 8.05 Hz, 1H, Ar H), 7.52 (d, J = 15.94 Hz, 1H, –C=C–H), 7.07 (s, 1H, Ar H), 7.06 (d, J = 15.94 Hz, 1H, –C=C–H), 6.95 (d, J = 8.05 Hz, 1H, Ar H), 3.69 (s, 3H, –OCH_3), 3.59 (s, 6H, –OCH_3), 2.28 (s, 3H, –CH_3), 2.23 (s, 3H, –CH_3), 2.13 (s, 6H, –CH_3); and ^{13}C NMR (150 MHz, DMSO-d_6, δ): 193.6 (1C), 158.6 (1C), 153.8 (2C), 141.9 (1C), 140.4 (1C), 137.6 (1C), 131.4 (2C), 129.8 (1C), 128.0 (1C), 127.2 (1C), 126.7 (1C), 124.7 (2C), 120. (1C), 61.6 (2C), 59.7 (1C), 20.8 (1C), 18.9 (1C), 9.0 (2C).

Synthesis of 1-(2′,4′,6′-trimethoxy-3′,5′-dimethylphenyl)-3-(4-[methoxymethoxy]phenyl)-2-propen-1-one (2k)

To a solution of **3** (0.50 g, 2.10 mmol) and KOH (0.35 g, 6.30 mmol) in MeOH (20 ml), 4-methoxymethoxybenzaldehyde (0.37 ml, 2.52 mmol) was added. The crude product was purified using column chromatography (*n*-hexane/acetone = 300:1) to afford **2k** (0.74 g, 91.8%) as a white solid: mp. 52°C; TLC R_f = 0.51 (*n*-hexane/acetone = 3:2); IR ν_{max} (cm^{-1}): 2938, 2835, 1641, 1253; ^{1}H NMR (600 MHz, DMSO-d_6, δ): 7.67 (d, J = 8.79 Hz, 2H, Ar H), 7.24 (d, J = 16.10 Hz, 1H, –C=C–H), 7.04 (d, J = 8.79 Hz, Ar H), 6.98 (d, J = 16.10 Hz, 1H, –C=C–H), 5.24 (s, 2H, –CH_2–O–), 3.70 (s, 3H, –OCH_3), 3.58 (s, 6H, –OCH_3), 3.37 (s, 3H, –OCH_3), 2.13 (s, 6H, –CH_3); and ^{13}C NMR (150 MHz, DMSO-d_6, δ): 193.8 (1C), 158.8 (1C), 158.4 (1C), 153.7 (2C), 144.8 (1C), 130.4 (2C), 127.5 (1C), 126.6 (1C), 124.7 (1C), 120.0 (2C), 116.3 (2C), 93.6 (1C), 61.5 (2C), 59.7 (1C), 55.7 (1C), 9.1 (2C).

Synthesis of 1-(2′,4′,6′-trimethoxy-3′,5′-dimethylphenyl)-3-(4-hydroxyphenyl)-2-propen-1-one (2l)

Compound **2k** (1 g, 2.59 mmol) and *p*-toluensulfonic acid (0.49 g, 2.85 mmol) dissolved with MeOH (30 ml) in a round-bottomed flask and stirred for 36 h at 25°C. The reaction mixture was extracted with EtOAc (200 ml) and washed with 1-M NH_4Cl aqueous solution (200 ml), water (3 × 100 ml), and saturated NaCl aqueous solution (200 ml). The resulting solution was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified using column chromatography (*n*-hexane/acetone = 30:1) to afford **2l** (0.83 g, 93.6%) as an orange oil: TLC R_f = 0.39 (*n*-hexane/acetone = 3:2); IR ν_{max} (cm^{-1}): 3340, 2939, 1625; ^{1}H NMR (600 MHz, DMSO-d_6, δ): 10.08 (s, 1H, OH), 7.54 (d, J = 8.68 Hz, 2H, Ar H), 7.17 (d, J = 16.05 Hz, 1H, –C=C–H), 6.68 (d, J = 16.05 Hz, 1H, –C=C–H), 6.78 (d,

J = 8.68 Hz, Ar H), 3.69 (s, 3H, –OCH_3), 3.57 (s, 6H, –OCH_3), 2.12 (s, 6H, –CH_3); and ^{13}C NMR (150 MHz, DMSO-d_6, δ): 193.8 (1C), 161.4 (1C), 158.4 (1C), 153.6 (1C), 145.1 (1C), 130.5 (2C), 126.5 (1C), 126.2 (1C), 124.8 (1C), 119.9 (2C), 114.4 (2C), 61.5 (2C), 59.7 (1C), 55.3 (1C), 9.1 (2C).

RESULTS AND DISCUSSION

In this study, we propose a synthetic route for DMDMC derivatives (**2**) via Claisen–Schmidt condensation of 2,4,6-trimethoxy-3,5-dimethylacetophenone (**3**), the B-ring moiety where two methyl groups and three methoxy groups are alternatively attached, and benzaldehydes (Figure 2).

Trimethoxyxylene **6** was prepared from commercially available phloroglucinol by consecutive diformylation using *N*,*N*-dimethylformamide and phosphoryl chloride ($POCl_3$), Clemmensen reduction using zinc amalgam and concentrated HCl, and triple methylation using DMS and K_2CO_3 in 65.4% overall isolated yield (Scheme 1).[27] Various Friedel-Craft-type conditions using a combination of Lewis acid catalysts, aluminum chloride and bismuth(III) trifluoromethanesulfonate, and acetylating agents, acetyl chloride and acetic anhydride, in several solvents have been investigated to directly introduce a *C*-acetyl group to the intermediate **6** to construct the key intermediate **3**. However, none of these reaction conditions gave satisfactory results in our trials. Although the reaction of **6** using acetic anhydride in the presence of boron trifluoride

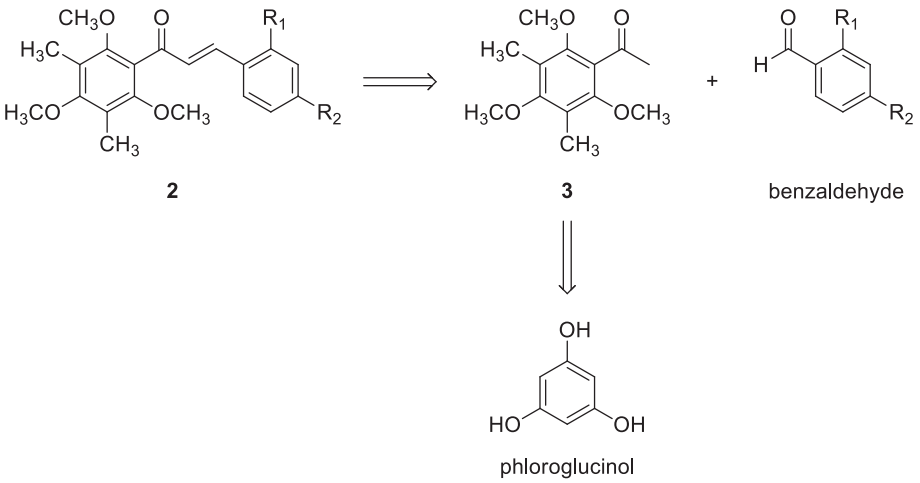
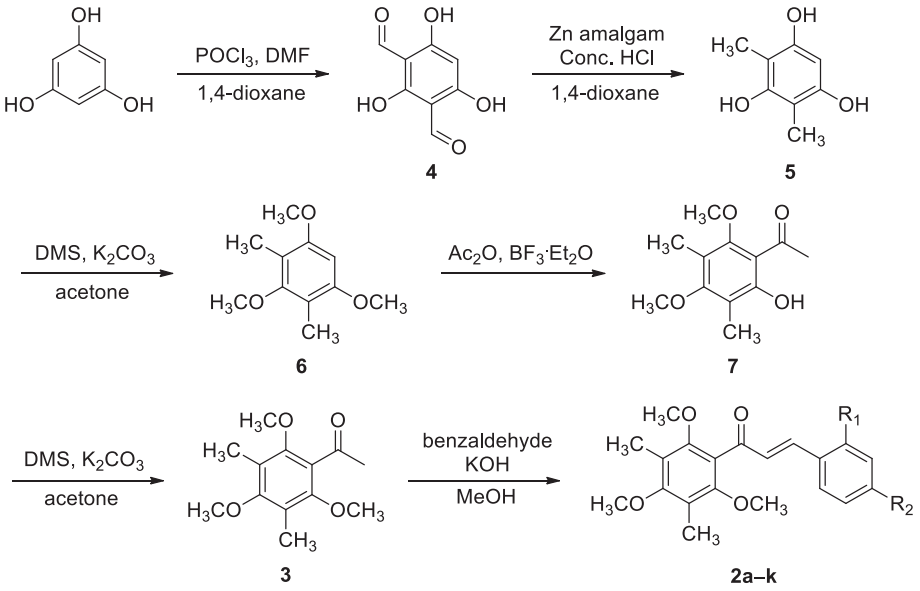
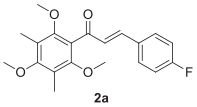
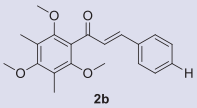
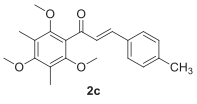
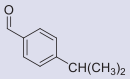
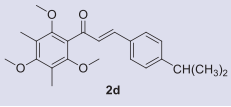
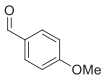
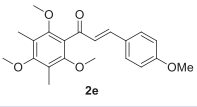
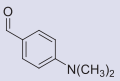
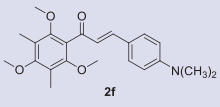
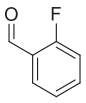
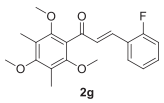
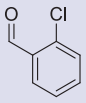
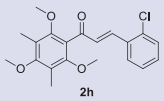
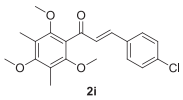
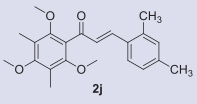
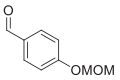
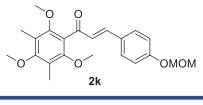


FIGURE 2 Retrosynthesis for 2′,4′,6′-trimethoxy-3′,5′-dimethylchalcone (DMDMC) derivatives (**2**)

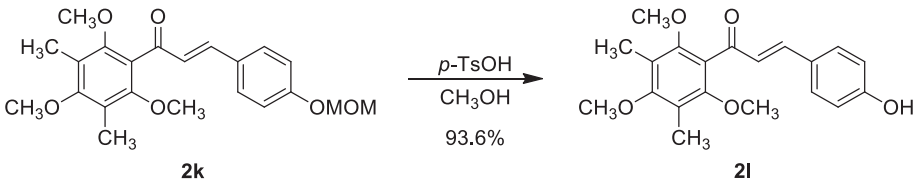


SCHEME 1 Synthetic route for the preparation of 2′,4′,6′-trimethoxy-3′,5′-dimethylchalcone (DMDMC) derivatives (**2**)

TABLE 1 Preparation of DMDMC derivatives (**2**) from various aldehydes[a]

Entry	Aldehyde	Product	Yield (%)[b]
1		 **2a**	93.1
2		 **2b**	96.3
3		 **2c**	92.1
4		 **2d**	94.3
5		 **2e**	92.9
6		 **2f**	78.3
7		 **2g**	92.9
8		 **2h**	89.5
9		 **2i**	86.4
10		 **2j**	83.0
11		 **2k**	91.8

Abbreviations: DMDMC, 2′,4′,6′-trimethoxy-3′,5′-dimethylchalcone; MeOH, methanol.
[a]Reactions of **3** (2.10 mmol) with the corresponding benzaldehyde (2.52 mmol) were carried out in MeOH (20 ml) by using KOH (6.30 mmol) at 25 °C.
[b]The yields refer to chromatographically isolated pure materials and are based on compound **3**.



SCHEME 2 Preparation of **2l** from **2k**

diethyl etherate ($BF_3{\cdot}Et_2O$) successfully introduced the *C*-acetyl group to the desired phenyl carbon atom, one *ortho*-*O*-methyl group was simultaneously removed to generate the dimethoxyacetophenone **7**. Therefore, an additional reaction was required to reintroduce the detached *O*-methyl group. The methylation was carried out using DMS and K_2CO_3 to generate **3** in excellent yield of 96.7%.

Claisen–Schmidt condensations of **3** with a variety of benzaldehydes proceeded well to construct the chalcone skeleton of the desired DMDMC derivatives (**2**). Following brief optimization studies, all reactions were carried out using three equivalents of KOH in MeOH. The optimized reaction conditions generated the chalcone compounds **2a**–**2k** in good isolated yields ranging from 78.3% to 96.3% (Table 1). It was found that the more electrophilic 2- or 4-halobenzaldehydes reacted faster than the less electrophilic aldehydes. No proportional correlation between reaction rate and yield was observed.

The efficiency of the reaction to prepare **2l** by cleaving the MOM group of **2k** was highly dependent on the type of acid catalyst and the reaction temperature (Scheme 2). In particular, a retro-aldol reaction rapidly occurred in the presence of strong acids to lower the yield of **2l**. The optimized reaction condition using 1.1 equivalent of *p*-TsOH in MeOH for 36 h at 25°C produced **2l** in 93.6% isolated yield.

CONCLUSION

We synthesized 12 novel 2′,4′,6′-trimethoxy-3′,5′-dimethylchalcone (DMDMC) derivatives (**2**). The synthetic method allowed the construction of various derivatives **2** from phloroglucinol in 37.8%–46.5% overall yields. To the best of our knowledge, a general method for the synthesis of these compounds has not yet been reported. The synthetic strategy of constructing the chalcone skeleton in the last step will allow the rapid preparation of many derivatives and, consequently, the fast discovery of promising lead compounds. The pharmacological effects of these compounds are currently being evaluated and the evaluation results will be reported in due course.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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