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Synthesis and Characterization of Novel Unnatural Bichalcones

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Five bichalcones (**5-1** ~ **5-4**, **9**) were prepared by the reaction of biphenyl-4,4'-dicarbaldehyde (**4**) and 4,4'-dioxybenzaldehyde (**8**) with the respective acetophenone analogs via Claisen-Schmidt condensation and were then fully identified by ^{1}H-NMR, ^{13}C-NMR and mass analyses.

Key words: Bichalcones, Chalcone dimers, Claisen-Schmidt condensation, Suzuki-Miyaura reaction, Stille reaction, Ullmann diaryl ether synthesis

INTRODUCTION

Plant flavonoids are previously demonstrated to possess anti-inflammatory activity *in vitro* and *in vivo* (Amellal et al., 1985; Sun et al., 1997; Lin et al., 2001). Biflavonoids, one of the subclasses of flavonoids, are flavonoid dimers having a C-C or C-O-C linkage between monomers. Several biflavonoids such as amentoflavone, ochnaflavone and ginkgetin (Fig. 1) were for the first time found to be inhibitors of group II secretory phospholipase A_2 (sPLA$_2$ IIA) (Sawada et al., 1999). Morelloflavone (Fig. 1), a flavone-flavanone dimer, was also revealed as a sPLA$_2$ inhibitor (Shinohara et al., 1999). Moreover, it was found that certain biflavonoids such as ginkgetin exerted the inhibitory activity against COX-2-mediated PGE_2 production and iNOS-mediated NO production from macrophages mainly by an inhibition of COX-2 and iNOS expression (Murakami et al., 1998, 1999). Recently, some C-C biflavonoids were prepared and they were found to be PLA_2 inhibitors and inhibitors of PGE_2 production (Kim et al., 1999; Chen et al., 2006). Bichalcones are very interesting targets for synthesis since some chalcones were previously found to strongly inhibit iNOS-mediated NO production from macrophages (Kim et al., 2007) and several natural bichalcones (Fig. 1) isolated from the root bark of *Rhus pyroids*, have been reported to show activities on melanoma and colon cancer cell lines (Mdee et al., 2003). Therefore, efficient synthetic pathways for diverse bichalcones are required.

The total syntheses of C-C and C-O-C bichalcone were initiated by retrosynthetic analysis as shown in Scheme 1. On doing retrosynthetic analyses of designed C-C and C-O-C bichalcones, the C-C bichalcones could be synthesized by dimerization of chalcone units where direct C-C coupling of two monomeric chalcone units occurs under the Suzuki-Miyaura (Miyaura and Suzuki, 1995) and Stille coupling condition (Stille, 1995). Also C-O-C bichalcones could be synthesized by dimerization of chalcone units where direct C-O-C coupling of two monomeric chalcone units occurs under Ullmann type diaryl ether synthesis (Sawyer, 2000).

Our initial attempts at syntheses employed Suzuki-Miyaura and Stille coupling were not successful though the pathways were more straightforward and versatile procedures for synthesis of diverse symmetrical and unsymmetrical C-C bichalcones. Also reaction conditions of Ullmann type diaryl ether synthesis were tried for synthesis of C-O-C bichalcones but no good result was observed (Scheme 1). Therefore, other synthetic procedures for C-C and C-O-C bichalcones were explored. Herein, we report procedures for syntheses of novel unnatural C-C and C-O-C bichalcones via Claisen-Schmidt condensation of biphenyl-4,4'-dicarbaldehyde (**4**) and 4,4'-oxydibenzaldehyde (**8**) with the respective acetophenones.

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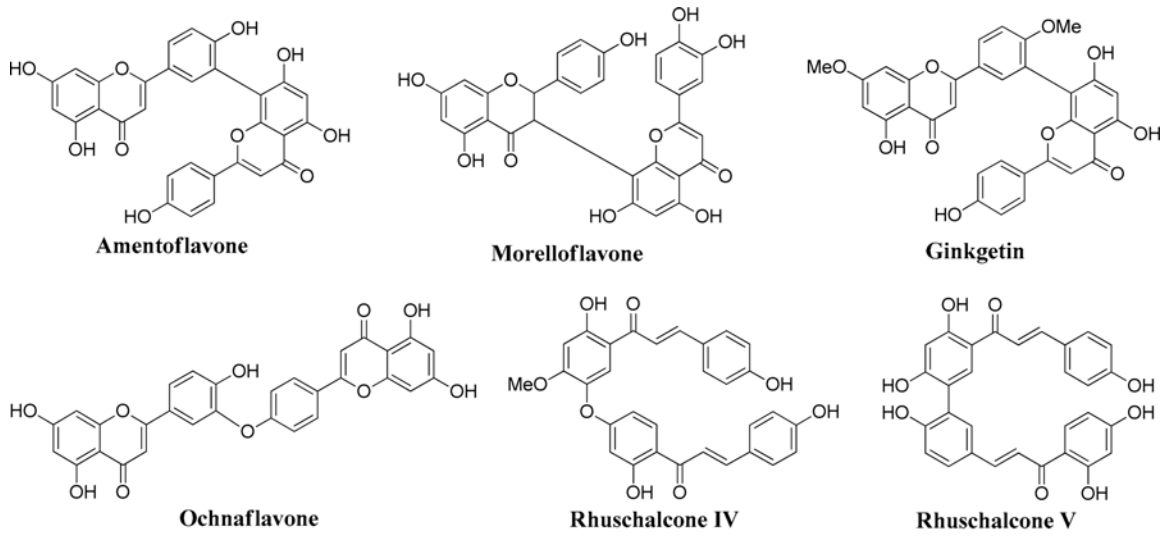
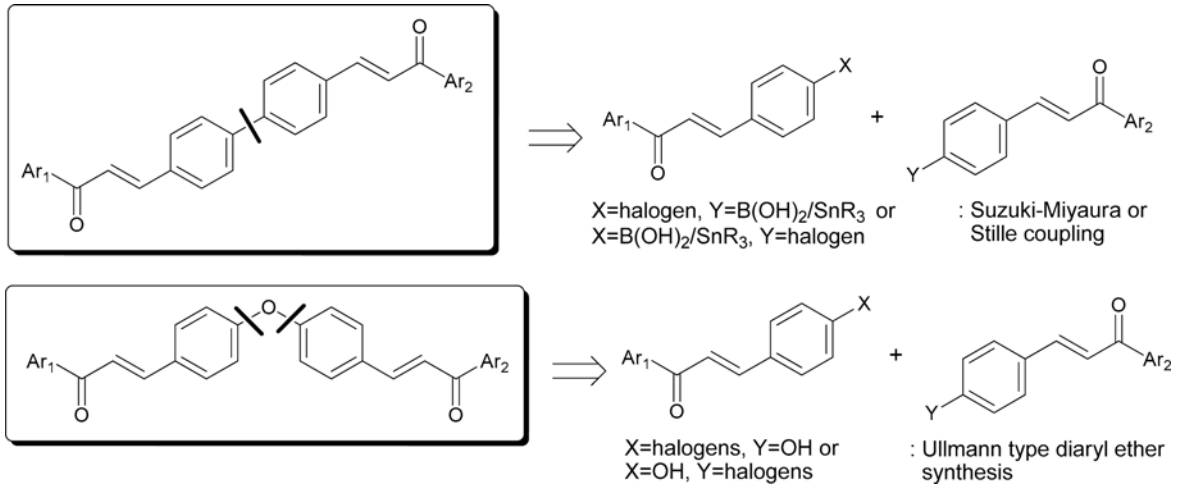


Fig. 1. Chemical structures of naturally occurring biflavonoids and bichalcones



Scheme 1. Retrosynthetic analyses for C-C and C-O-C bichalcones

MATERIALS AND METHODS

All chemicals were obtained from commercial suppliers, and used without further purification. All solvents used for reaction were freshly distilled from proper dehydrating agent under nitrogen gas. All solvents used for chromatography were purchased and directly applied without further purification. ^{1}H-NMR spectra were recorded on a Varian Gemini 2000 (200 MHz) and a Bruker DPX 400 (400 MHz) spectrometers. Chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane as an internal standard. Peak splitting patterns are abbreviated as m (multiplet), s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), t (triplet), dd (doublet of doublets) and ddd (doublet of double doublet). ^{13}C-NMR spectra were recorded on a Bruker DPX 400 (100 MHz) spectrometer, fully decoupled and chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane as an internal standard. Melting points were recorded on a Fisher-Johns microscopic scale melting point apparatus. EI mass spectra were recorded on a Autospec M363. Analytical thin-layer chromatography (TLC) was performed using commercial glass plate with silica gel 60F_{254} purchased from Merck. Chromatographic purification was carried out by flash chromatography using Kieselgel 60 (230~400 mesh, Merck).

Reaction conditions for synthesis of C-C bichalcones intermediates (2, 3, & 4)

Diethyl biphenyl-4,4'-dicarboxylate (2)

Reactions of 4-bromobenzoic acid in ethanol with concentrated sulfuric acid provided ethyl 4-bromo-

benzoate (**1**) in 95% yield after purification. A flask charged with ethyl 4-bromobenzoate (1.3 mmol, 0.21 mL), bis(pinacolato)diboron (0.36 gm, 1.44 mmol), anhydrous KOAc (0.51 gm, 5.2 mmol) and $PdCl_2$(dppf) (0.05 gm, 0.065 mmol) were flushed with nitrogen. DMF (6.5 mL) was added to the reaction mixture and the reaction was stirred at 80°C for 2 h. After cooling the solution to room temperature, ethyl 4-bromobenzoate (0.6 gm, 2.6 mmol), $PdCl_2$(dppf) (0.053 gm, 0.065 mmol) and potassium phosphate (0.82 gm, 3.9 mmol) were added and the reaction mixture was stirred at 100°C under nitrogen overnight. The solution was cooled to room temperature and filtered through filtering agent. The filtrate was extracted with ethyl acetate and the excess DMF was destroyed with 3% aqueous HCl solution. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and filtered with a glass filter. The filtrate was concentrated under reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using hexane:ethyl acetate (20:1) as a mobile phase. The product was further purified by recrystallisation in hot MeOH to afford the target compound as white needle crystal in 62% yield; m.p. 108-111°C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.11~8.15 (d, 4H, J = 7.2 Hz, H3, H3', H5, H5'), 7.66~7.70 (d, 4H, J = 7.8 Hz, H2, H2', H6, H6'), 4.35~4.42 (q, 4H, J = 6.6 Hz, 7.00 Hz, 2 × CH_2), 1.38~1.44 (t, 6H, J = 6.6 Hz, 2 × CH_3).

Biphenyl-4,4'-diyldimethanol (3)

To an ice-cold solution of diethyl biphenyl-4,4'-dicarboxylate (0.30 gm, 1.0 mmol) in anhydrous THF (3.3 mL) was added $LiAlH_4$ (freshly ground powder form from lump, 0.11 gm, 3.0 mmol) was added slowly under nitrogen with slow stirring so that without forming any crust layer at the wall, bottom and upper layer of flask. The mixture was stirred for 30 min at ice-cold bath and continued to reflux for overnight. The reaction mixture was cooled to room temperature and the excess of $LiAlH_4$ was destroyed by slow addition of aqueous saturated solution of $Na_2SO_4 \cdot 10H_2O$ at ice-cold bath. The solution was refluxed for 30 min, brought to room temperature, filtered through filtering agent and washed with THF (10 mL). The THF from filtrate was evaporated under reduced pressure by rotary evaporator and the residue was extracted with ethyl acetate. The organic layer was washed with brine, dried over with anhydrous $MgSO_4$ and filtered by a glass filter. The filtrate was concentrated in reduced pressure. The crude residue was purified by column chromatography using hexane:acetone (5:2) as a mobile phase. The product was further purified by recrystallisation in hot MeOH to afford the target compound as white crystal in 54% yield; m.p. 188-191°C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.54~7.62 (t, 4H, J = 8.0 Hz, 7.6 Hz, H3, H3', H5, H5'), 7.37~7.44 (t, 4H, J = 7.8 Hz, 7.2 Hz, H2, H2', H6, H6'), 4.61~4.67 (t, 4H, J = 5.6 Hz, 7.6 Hz, 2 × CH_2).

Biphenyl-4,4'-dicarbaldehyde (4)

Biphenyl-4,4'-diyldimethanol (1.5 gm, 7.0 mmol) was dissolved in 30 mL of anhydrous methylene chloride. To a two necked round bottom flask containing pyridinium chlorochromate (PCC) (4.52 gm, 21.0 mmol) and 4 Å MS (0.5 gm) was added 30 mL of fresh dry methylene chloride. The alcohol suspension was dropped slowly through addition funnel to the PCC solution with gentle stirring using the magnetic stir bar at room temperature under nitrogen. Once the addition was complete, the reaction mixture was refluxed for 2 h. After the completion of the reaction, the reaction mixture was cooled to room temperature. The solvent layer was decanted from the tarry black residue, and the residue was rinsed twice with about 20 mL of methylene chloride. The combined methylene chloride solution was evaporated on a rotary evaporator. The residue was diluted with 50 mL of diethyl ether and filtered through cotton plug to remove the insoluble chromium salts. The ether layer was washed with 20 mL of aqueous 1 M NaOH solution, followed by 20 mL of brine solution, dried over anhydrous $MgSO_4$ and filtered with a glass filter. The filtrate was concentrated in reduced pressure and the crude residue was recrystallised in hot MeOH to afford the target compound as white solid in 65% yield; m.p. 188-191°C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.54~7.62 (t, 4H, J = 8.0 Hz, 7.6 Hz, H3, H3', H5, H5'), 7.36~7.44 (t, 4H, J = 7.8 Hz, 7.2 Hz, H2, H2', H6, H6'), 4.61~4.67 (t, 4H, J = 5.6 Hz, 7.6 Hz, 2 × CH_2).

Reaction conditions for C-C bichalcones (5-1, 5-2, 5-3 and 5-4) by Claisen-Schmidt condensation

To a suspension of the respective acetophenone analogs (1.9 mmol) and biphenyl-4,4'-dicarbaldehyde (**4**, 0.2 gm, 0.95 mmol) in 2 mL of anhydrous methyl alcohol was added finely divided KOH (0.16 g, 2.85 mmol). The resultant mixture was stirred for 2 day at room temperature. An excess volume of aqueous HCl (3%) solution was added while stirring. The precipitate was filtered and the crude solid residue was washed with MeOH several times using vortex till the single spot was observed by TLC.

(2*E*,2'*E*)-3,3'-(Biphenyl-4,4'-diyl)-bis(1-phenylprop-2-ene) (5-1)

Pale yellow solid, 62%; m.p. 228-231°C; ^{1}H-NMR (400

MHz, $CDCl_3$): δ 8.04~8.06 (d, 4H, *J* = 8.5 Hz, H2', H2'', H6', H6''), 7.84~7.88 (d, 2H, *J* = 15.7 Hz, Hα, Hα'), 7.74~7.76 (d, 2H, *J* = 8.3 Hz, H3', H3''), 7.69~7.71 (d, 2H, *J* = 8.4 Hz, H5', H5''), 7.57~7.61 (m, 8H, Hβ, Hβ' H4, H4''', H3, H3''', H5, H5'''), 7.51~7.55 (t, 4H, *J* = 7.7 Hz, 7.2 Hz, H2, H2''', H6, H6'''); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 190.861 (2×C=O), 144.54 (C-α, C-α'), 142.51 (C-4, C-4'''), 138.6 (C-1', C-1''), 134.87 (C-4', C-4''), 133.29 (C-1, C-1'''), 129.51 (C-3', C-3'', C-5', C-5''), 129.09 (C-2', C-2'', C-6', C-6''), 128.94 (C-3, C-3''', C-5, C-5'''), 127.94 (C-2, C-2''', C-6, C-6'''), 122.63 (C-β, C-β'); *m/z* 416 (M^+, 11), 414 (100), 312 (9), 207 (43), 178 (16), 145 (16).

(2*E*,2'*E*)-3,3'-(Biphenyl-4,4'-diyl)-bis(1-(2-hydroxyphenyl)prop-2-ene) (5-2)

Yellow solid, 50%; m.p. 257-259ºC; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 12.83 (s, 2H, OH), 7.96~8.00 (m, 4H, Hα, Hα', H6', H6''), 7.71~7.80 (m, 8H, Hβ, Hβ' H4, H4''', H3, H3''', H5, H5'''), 7.51~7.55 (t, 2H, *J* = 1.2 Hz, 8.4 Hz, H2, H2'''), 7.04~7.07 (d, 2H, *J* = 8.5 Hz, H3', H3''), 6.96~7.00 (t, 2H, *J* = 0.9 Hz, 8.3 Hz, H6, H6'''); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 193.99 (2×C=O), 164.05 (C-2', C-2''), 145.12 (C-α, C-α'), 142.78 (C-4, C-4'''), 136.92 (C-4', C-4''), 134.66 (C-1, C-1'''), 130.05 (C-6', C-6''), 129.75 (C-3, C-3''', C-5, C-5'''), 128.04 (C-2, C-2''', C-6, C-6'''), 120.73 (C-5', C-5''), 120.44 (C-1', C-1''), 119.31 (C-β, C-β'), 119.12 (C-3', C-3''); *m/z* 446 (M^+, 74), 191 (28), 178 (40), 147 (87), 121 (100), 92 (28).

(2*E*,2'*E*)-3,3'-(Biphenyl-4,4'-diyl)-bis(1-(2-hydroxy-6-methoxyphenyl)prop-2-ene) (5-3)

Yellow solid, 60%; m.p. 236-239ºC; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 13.14 (s, 2H, OH), 7.91~7.95 (d, 2H, *J* = 15.6 Hz, Hα, Hα'), 7.84~7.88 (d, 2H, *J* = 15.6 Hz, Hβ, Hβ'), 7.68~7.74 (dd, 8H, *J* = 8.5 Hz, 4.4 Hz, H2, H2''', H6, H6''', H3, H3''', H5, H5'''), 7.36~7.41 (t, 2H, *J* = 8.3 Hz, H4', H4''), 6.63~6.65 (d, 2H, *J* = 8.4 Hz, H5', H5''), 6.45~6.47 (d, 2H, *J* = 8.3 Hz, H3', H3''); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 194.74 (2×C=O), 165.30 (C-6', C-6''), 161.39 (C-2', C-2''), 142.66 (C-α, C-α'), 142.34 (C-4, C-4'''), 136.42 (C-4', C-4''), 135.30 (C-1, C-1'''), 129.51 (C-3, C-3''', C-5, C-5'''), 128.19 (C-β, C-β'), 127.88 (C-2, C-2''', C-6, C-6'''), 112.43 (C-1', C-1''), 111.43 (C-3', C-3''), 101.98 (C-5', C-5''), 56.42 (2X OMe); *m/z* 506 (M^+,100), 505 (84), 355 (48), 206 (56), 193 (43), 177 (98), 151 (92).

(2*E*,2'*E*)-3,3'-(Biphenyl-4,4'-diyl)-bis(1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-ene) (5-4)

Yellow solid, 57%; m.p. 261-264ºC; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 14.32 (s, 2H, OH), 7.94~7.98 (d, 2H, *J* = 15.5 Hz, Hβ, Hβ'), 7.81~7.85 (d, 2H, *J* = 15.5 Hz, Hα, Hα'), 7.67~7.72 (m, 8H, H2, H2''', H3, H3''', H6, H6''', H5, H5'''), 6.10~6.13 (d, 2H, *J* = 2.2 Hz, H5', H5''), 5.98~5.99 (d, 2H, *J* = 2.1 Hz, H3', H3''), 3.95 (s, 6H, 4'OMe, 4''OMe), 3.85 (s, 6H, 6'OMe, 6''OMe); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 192.88 (2×C=O), 168.87 (C-4', C-4''), 166.70 (C-6', C-6''), 162.90 (C-2', C-2''), 142.15 (C-α, C-α'), 142.09 (C-4, C-4'''), 135.49 (C-1, C-1'''), 129.39 (C-3, C-3''', C-5, C-5'''), 128.11 (C-β, C-β'), 127.82 (C-1, C-1'''), 106.78 (C-1', C-1''), 94.21 (C-3', C-3''), 91.74 (C-5', C-5''), 56.32 (4'OMe, 4''OMe), 56.05 (6'OMe, 6''OMe) *m/z* 566 (M^+, 56), 414 (34), 368 (27), 207 (100), 181 (78), 129 (38).

Reaction conditions for synthesis of C-O-C bichalcone intermediates (6, 7 & 8)

Diethyl 4,4'-dioxybenzoate (6)

4-Hydroxybenzoic acid (2.0 gm, 14.5 mmol) was dissolved in ethyl alcohol (15 mL). To the solution, concentrated sulfuric acid (1 mL) was added and refluxed for 5 h. After the completion of reaction, the reaction mixture was cooled to room temperature. The saturated solution of aqueous $NaHCO_3$ was added till pH 7. The precipitated out solid was filtered and washed with excess water. The white solid was air dried and used for the next reaction without further purification. To a flask containing ethyl 4-hydroxybenzoate (0.2 gm, 1.2 mmol), copper (I) iodide (0.012 gm, 0.06 mmol), cesium carbonate (0.08 gm, 0.024 mmol), *N,N*-dimethylglycine (0.002 gm, 0.024 mmol) was added freshly dried 1,4-dioxane (2.4 mL) through syringe. To the reaction mixture, ethyl-4-bromobenzoate (0.2 mL, 1.2 mmol) was added and degassed by nitrogen for 10 min. The reaction mixture was refluxed for 1 day. The reaction mixture was cooled to room temperature and evaporated under reduced pressure to remove 1,4-dioxane. The residue was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and filtered with a glass filter. The filtrate was concentrated in reduced pressure. The crude residue was purified by column chromatography using hexane:ethyl acetate (10:1) as a mobile phase to afford product as colorless oil in 35% yield. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.98~8.02 (d, 4H, *J* = 7.8 Hz, H3, H3', H5, H5'), 6.98~7.02 (d, 4H, *J* = 7.4 Hz, H2, H2', H6, H6'), 4.35~4.41 (q, 4H, *J* = 6.5 Hz, 7.00 Hz, 2 × CH_2), 1.32~1.40 (t, 6H, *J* = 6.6 Hz, 7.1 Hz, 2 × CH_3).

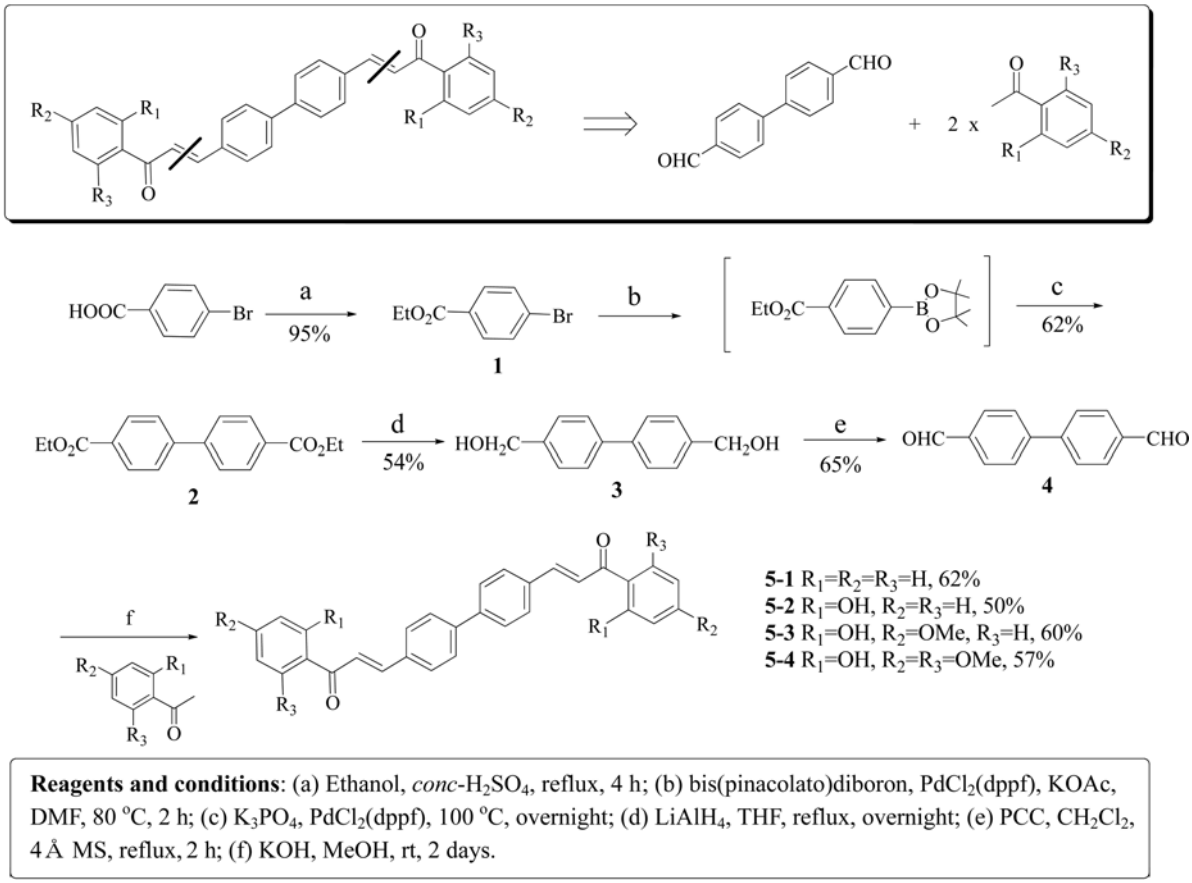
4,4'-Oxy-bis(4,1-phenylene) dimethanol (7)

To an ice-cold solution of diethyl 4,4'-dioxybenzoate (**6**, 0.17gm , 0.55 mmol) in anhydrous THF (3.0 mL) was added $LiAlH_4$ (freshly ground powder form from lump, 0.062 gm, 1.65 mmol) was added portionwise under nitrogen with slow stirring so that without forming any crust layer in the wall, bottom and upper layer

flask. The mixture was stirred for 30 min at ice-cold bath and continued to reflux for overnight. After the reaction mixture was cooled to room temperature, excess $LiAlH_4$ was destroyed by slowly adding saturated aqueous of $Na_2SO_4.10H_2O$ in ice-cold bath. The reaction mixture was refluxed for 30 min, cooled to room temperature and filtered through filtering reagent. Filter cake was washed with THF (10 mL) and filtrate THF solution was evaporated under reduced pressure and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and filtered with a glass filter. The filtrate was concentrated in reduced pressure using rotary evaporator. The crude residue was purified by column chromatography using hexane:acetone (5:2) as a mobile phase. The product was further recrystallised in hot MeOH to afford product as white solid in 50% yield; m.p. 127-133°C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.26~7.30 (d, 4H, J = 8.4 Hz, H3, H3', H5, H5'), 6.85~6.89 (d, 4H, J = 8.8 Hz, H2, H2', H6, H6'), 4.52 (s, 4H, 2 × CH_2).

4,4'-Oxydibenzaldehyde (8)

4,4'-Oxybis(4,1-phenylene)dimethanol (**7**, 1.5 gm, 6.5 mmol) was dissolved in 25 mL of anhydrous methylene chloride. To a two necked round bottom flask containing pyridinium chlorochromate (PCC) (4.21 gm, 19.5 mmol) and 4 Å MS (0.5 gm) was added fresh dry methylene chloride (25 mL). The alcohol suspension was dropped slowly through addition funnel to the PCC solution with gentle stirring at room temperature under nitrogen. Once the addition was complete, the reaction mixture was refluxed for 2 h. After the completion of the reaction, the reaction mixture was cooled to room temperature. The solvent layer was decanted from the tarry black residue, and the residue was rinsed twice with about 20 mL of methylene chloride. The combined methylene chloride solution was evaporated on a rotary evaporator. The residue was diluted with 50 mL of diethyl ether and filtered through cotton plug to remove the insoluble chromium salts. The ether layer was washed with 20 mL of 1 M NaOH aqueous solution, followed by 20 mL of brine solution, dried over anhydrous $MgSO_4$ and filtered with a glass filter. The filtrate was concentrated in reduced pressure using rotary evaporator. The crude residue was recrystallised in hot MeOH to afford the target com-



Scheme 2. Retrosynthetic analysis and synthetic pathway of C-C bichalcones

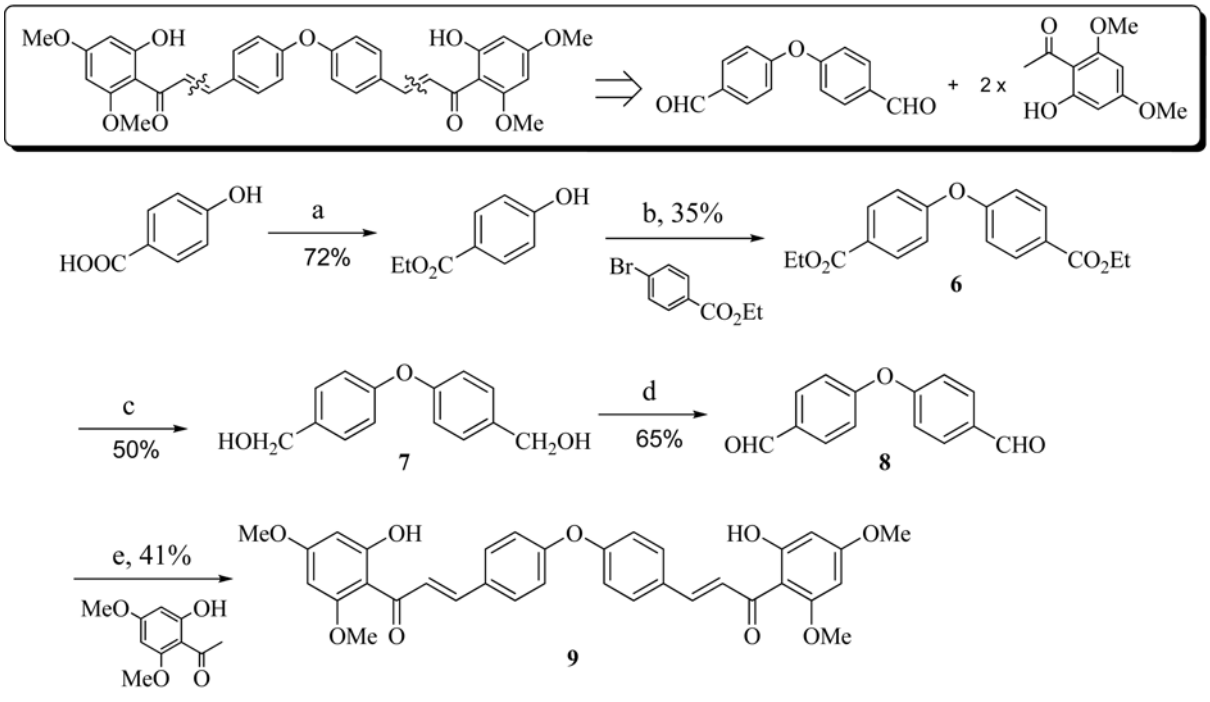
pound as white solid in 65% yield; m.p. 56-58°C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 9.99 (s, 2H, 2 × CHO), 7.91 ~7.95 (d, 4H, *J* = 8.2 Hz, H3, H3', H5, H5'), 7.16~7.20 (d, 4H, *J* = 8.0 Hz, H2, H2', H6, H6').

(2*E*,2'*E*)-3,3'-(4,4'-Oxybis(4,1-phenylene))-bis(1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one) (9)

To a suspension of 2'-hydroxy-4', 6'-dimethoxyacetophenone (0.21gm, 2.65 mmol) and 4, 4'-oxydibenzaldehyde (0.3 gm, 1.32 mmol) in 2 mL of anhydrous methyl alcohol and 1 mL of anhydrous THF was added finely divided KOH (0.44 gm, 3.96 mmol). The resultant mixture was stirred for 2 day at room temperature. An excess volume of aqueous HCl (3%) solution was added while stirring. The precipitate was filtered and the crude solid residue was washed with MeOH several times using vortex till the single spot was observed by TLC. Yellow solid, 41%; m.p. 157-159°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 14.34 (s, 2H, OH), 7.83~7.87 (d, 2H, *J* = 15.6 Hz, Hβ, Hβ'), 7.75~7.79 (d, 2H, *J* = 15.6 Hz, Hα, Hα'), 7.59~7.61 (d, 4H, *J* = 8.5 Hz, H2, H2''', H6, H6'''), 7.05~7.07 (d, 4H, *J* = 8.0 Hz, H3, H3''', H5, H5'''), 6.10~6.11 (d, 2H, *J* = 2.0 Hz, H3', H3''), 5.96~5.97 (d, 2H, *J* = 1.8 Hz, H5', H5''), 3.91 (s, 6H, 4'OMe, 4''OMe), 3.84 (s, 6H, 6'OMe, 6''OMe); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 192.43 (2×C=O), 168.43 (C-4', C-4''), 166.22 (C-6', C-6''), 162.46 (C-2', C-2''), 158.25 (C-4, C-4'''), 141.51 (C-α, C-α'), 132.00 (C-2, C-2''', C-6, C-6'''), 130.24 (C-β, C-β'), 126.69 (C-1', C-1''), 119.29 (C-3, C-3''', C-5, C-5'''), 106.30 (C-1, C-1'''), 93.82 (C-3', C-3''), 91.28 (C-5', C-5''), 55.86 (4'OMe, 4''OMe), 55.60 (6'OMe, 6''OMe); *m/z* 582 (M^+, 100), 389 (36), 207 (54), 181 (99), 154 (23), 69 (20).

RESULTS AND DISCUSSION

In this study, five C-C and C-O-C bichalcones were prepared via the reaction of biphenyl-4,4'-dicarbaldehyde (**4**) and 4,4'-dioxybenzaldehyde (**8**) with the respective acetophenone analogs via Claisen-Schmidt condensation (Dao et al., 2004). The general synthetic strategy employed to synthesize the C-C bichalcone analogs (**5-1**, **5-2**, **5-3** and **5-4**) based on Claisen-Schmidt condensation as the key reaction. 4,4'-Dicarbaldehyde (**4**), the key intermediate for Claisen-Schmidt condensation, was prepared from commercially available 4-bromobenzoic acid in good yields. Preparation of the key intermediate **4** from 4-bromobenzalde-



Scheme 3. Retrosynthetic analysis and synthetic pathway of C-O-C bichalcones

hyde following the precedent literatures (Moutloali et al., 2002; Kuhnert et al., 2005) yielded extremely low yields of the product. Reaction of ethyl 4-bromobenzoate and bis(pinacolato) diboron with catalytic amount of Pd-catalyst provided 4-(4,4,5,5-tetramethyl-[1,3,2] dioxaborolan-2-yl)-benzoic acid ethyl ester *in situ* (Giroux et al., 1997). Suzuki-Miyaura C-C cross coupling reaction of the intermediate and ethyl 4-bromobenzoate produced 4,4'-dicarbaldehyde (**4**) as shown in Scheme 1. Novel synthetic C-C bichalcone analogs (**5-1**, **5-2**, **5-3 and 5-4**) were synthesized by base-catalyzed condensation of biphenyl-4,4'-dicarbaldehyde (**4**) and the respective acetophenone analogs via Claisen-Schmidt condensation in 62%, 50%, 60% and 57% yields, respectively.

The C-O-C bichalcone analog (**9**) was prepared from commercially available ethyl 4-hydroxybenzoate in good yields. Copper-catalyzed Ullmann diaryl ether synthesis of the 4-bromo and 4-hydroxybenzoate analogs provided diaryl ether (**6**). Reduction of ester to alcohol with $LiAlH_4$ followed by PCC oxidation yielded 4,4'-dioxybenzaldehyde (**8**) as shown in Scheme 2. Preparation of the key intermediate **8** from 4-bromobenzaldehyde following the precedent literatures (Yang et al., 1999; Gawroński et al., 2005) yielded extremely low yields of the product. A novel synthetic C-O-C bichalcone analog (**9**) was synthesized by base-catalyzed condensation of 4,4'-dioxybenzaldehyde (**8**) and the respective acetophenone analog via Claisen-Schmidt condensation in 41% yield. Structures of all the intermediates and bichalcones were fully identified by ^{1}H-NMR, ^{13}C-NMR and mass analyses.

In conclusion, four novel C-C bichalcones and a C-O-C bichalcone were synthesized in this study. The key intermediate for C-C bichalcones, biphenyl-4,4'-dicarbaldehyde (**4**), was prepared by one pot biaryl synthesis via Suzuki-Miyaura C-C cross coupling reaction of ethyl 4-bromobenzoate and the boronate formed *in situ*. This procedure could be expanded to prepare various biphenyl dicarbaldehyde derivatives by using substituted bromobenzoates and the respective boronated benzoates, which lead to diverse C-C bichalcones generation. Also various 4,4'-dioxybenzaldehyde derivatives can be easily prepared via Ullmann type ether synthesis by using substituted bromobenzoates and hydroxybenzoates, which are key intermediates for synthesis of C-O-C bichalcones. Therefore, these synthetic procedures can be used for syntheses of novel unnatural C-C and C-O-C bichalcones.

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