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A Versatile Synthesis of *O*-Desmethylangolensin Analogues from Methoxy-Substituted Benzoic Acids

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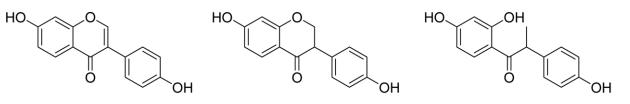
ABSTRACT. The synthesis of *O*-desmethylangolensin (*O*-DMA) analogues from methoxy-substituted benzoic acids was described. Treatment of methoxy-substituted benzoic acids with 2 equiv of ethyllithium afforded methoxypropiophenones, which were subsequently transformed to ethyl 2-(methoxyphenyl)propionates *via* 1,2-rearrangement of the methoxyphenyl group using $Pb(OAc)_4/HClO_4$ in triethyl orthoformate. After hydrolysis with KOH, the 2-(methoxyphenyl)propionic acids were reacted with di-2-pyridyl carbonate to afford 2-pyridyl 2-(methoxyphenyl)propionates, which were acylated with methoxy-substituted phenylmagnesium bromides to give methoxy-α-methyldesoxybenzoins. The methoxy groups of these compounds were selectively or fully demethylated using boron tribromide to give diverse *O*-DMA analogues in high yields.

Key words: *O*-Desmethylangolensin, Condensation, Substitution, Rearrangement, Demethylation

INTRODUCTION

O-Desmethylangolensin (*O*-DMA) is created in the ring cleavage of dihydrodiadzein, an intestinal bacteria metabolite of the diadzein that is found mainly in soybean (*Scheme* 1).[1] Approximately 80–90% of people produces *O*-DMA after consumption of diadzein, which is detected in human urine, plasma, serum, and breast milk.[2] The analysis of *O*-DMA has been performed with various instruments[3] including GC-MS/SPE-HPLC, and the (*R*)-enantiomer was identified as the main metabolite by circular dichroism.[4] *O*-DMA has attracted much attention for various biological activities that include estrogenic activity,[5] diminution of plasma lipids concentration,[6] radical scavenging effect,[7] and antimicrobial susceptibility.[8] Recently we reported that *O*-DMA inhibited cell proliferation of human breast cancer MCF-cells by inducing apoptosis.[9]

O-DMA analogues have generally been synthesized by Friedel-Crafts acylation of substituted phenols and 2-phenylpropionic acids using $BF_3 \cdot Et_2O$ at 120 °C, but yields were low to moderate.[7] A similar condensation of 1,3-dimethoxybenzene and 2-(4-methoxyphenyl)propionic acid in polyphosphoric acid at 75 °C afforded trimethoxy-α-methyldesoxybenzoin, which was demethylated with 4 equiv of boron tribromide to give *O*-DMA.[10] However, 2-phenylpropionic acids are typically synthesized from 1-phenylethanol[11] or phenylacetic acids[12] in three steps. The condensation of resorcinol and 4-hydroxyphenylacetic acid[13] or 4-benzyloxybenzyl cyanide[14] using $BF_3 \cdot Et_2O$ and zinc chloride, respectively, afforded the corresponding deoxybenzoin, which was *C*-methylated with methyl iodide to give *O*-DMA.[15] Another condensation of resorcinol and 2-(4-hydroxyphenyl)propionic acid using bis[(trifluoromethyl) sulfanyl]amine under microwave irradiation also afforded *O*-DMA.[16]



***Scheme* 1.** Chemical structures of diadzein, dihydrodiadzein, and *O*-DMA.

The reaction of 2'-hydroxypropiophenones and *o*-nitrofluorobenzenes using potassium carbonate in DMSO afforded the corresponding diaryl ethers, which were rearranged to form *O*-DMA derivatives.[17] However, this method was only effective for fluorobenzenes with an electron-withdrawing substituent such as a nitro group. The reduction of hydroxy and/or methoxy-substituted isoflavones with an excess of lithium aluminum hydride afforded *O*-DMA analogues, but yields were low to moderate.[18] The reduction of methoxy-substituted isoflavones with lithium tri(*t*-butoxy)aluminum hydride improved the yields of *O*-DMA derivatives, but the corresponding propenals were also obtained as minor products.[19]

Although several methods for the synthesis of *O*-DMA analogues have been reported, the scope of these proce-

dures has not been fully investigated. Furthermore, the synthesis by Friedel-Crafts acylation was effective for symmetrical phenols as starting materials and some methods suffered from the harsh reaction conditions and low yields. In this paper we describe a versatile synthesis of *O*-DMA analogues from commercially inexpensive methoxy-substituted benzoic acids under mild conditions.

EXPERIMENTAL

4'-Methoxypropiophenone (2b)

To a solution of 4-methoxybenzoic acid (**1b**, 1.22 g, 8.0 mmol) in THF (16 mL) was added ethyllithium (0.5 M, 32.0 mL, 16.0 mmol) at 0 °C, and the solution was stirred for 0.5 h. The mixture was quenched with 1 N HCl solution (5 mL) and THF was evaporated *in vacuo*. The mixture was poured into 0.5 N HCl solution (40 mL) and was extracted with methylene chloride (3×25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using 20% EtOAc/*n*-hexane as eluant to afford **2b** (1.26 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H), 2.95 (q, J = 7.3 Hz, 2H), 1.21 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3, 163.3, 130.2 (overlapped), 113.7, 55.4, 31.4, 8.4; FT-IR (film) 1675 (C=O) cm^{-1}; Ms *m/z* (%) 164 (M^+, 56), 135 (100), 107 (36), 92 (40), 77 (55).

Ethyl 2-(4-methoxyphenyl)propionate (3b)

To a solution of **2b** (1.15 g, 7.0 mmol) in triethyl orthoformate (35 mL) was added perchloric acid (70%, 1.2 mL, 14.0 mmol) and then lead(IV) acetate (3.10 g, 7.0 mmol) at room temperature. After stirring for 2 h, the excess triethyl orthoformate was evaporated *in vacuo*. The mixture was redissolved in methylene chloride (40 mL) and the resulting precipitate was removed by filtration. The organic phase was washed with saturated $NaHCO_3$ solution (40 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by vacuum distillation using a Kugelrohr apparatus to give **3b** (1.21 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.11 (q, J = 7.2 Hz, 2H), 3.78 (s, 3H), 3.65 (q, J = 7.2 Hz, 1H), 1.47 (d, J = 7.2 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 158.6, 132.8, 128.5, 113.9, 60.7, 55.2, 44.7, 18.7, 14.1; FT-IR (film) 1726 (C=O) cm^{-1}. Ms *m/z* (%) 208 (M^+, 93), 135 (100), 105 (72), 91 (63).

2-(4-Methoxyphenyl)propionic acid (4b)

To a solution of **3b** (1.04 g, 5.0 mmol) in H_2O (8 mL) was added 0.5 N KOH (0.5 N in CH_3OH, 12.0 mL, 6.0 mmol) at room temperature. After stirring overnight, CH_3OH was evaporated *in vacuo*. The mixture was acidified with 1 N HCl solution (6 mL) and extracted with methylene chloride (3×20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using 50% EtOAc/*n*-hexane as eluant to give **4b** (838 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (br s, 1H), 7.24 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H), 3.68 (q, J = 7.2 Hz, 1H), 1.48 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.2, 158.9, 131.8, 128.6, 114.1, 55.3, 44.5, 18.2; FT-IR (film) 3430 (broad, COOH), 1706 (C=O) cm^{-1}; Ms *m/z* (%) 180 (M^+, 49), 135 (100), 105 (19), 91 (15).

2-Pyridyl 2-(4-methoxyphenyl)propionate (5b)

To a solution of **4b** (721 mg, 4.0 mmol) in methylene chloride (20 mL) were added di-2-pyridyl carbonate (865 mg, 4.0 mmol) and 4-(dimethylamino)pyridine (49 mg, 0.4 mmol) at room temperature, and the solution was stirred for 2 h. The mixture was poured into saturated $NaHCO_3$ solution (30 mL) and was extracted with methylene chloride (3×20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by short pathway Davisil® (pH=7) column chromatography using 50% EtOAc/*n*-hexane as eluant to give **5b** (834 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 5.6 Hz, 1H), 7.69–7.75 (m, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.15–7.20 (m, 1H), 6.92–6.96 (m, 1H), 6.92 (d, J = 8.4 Hz, 2H), 3.96 (q, J = 7.2 Hz, 1H), 3.79 (s, 3H), 1.61 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 158.9, 158.0, 148.5, 139.4, 131.8, 128.7, 122.0, 116.3, 114.2, 55.3, 44.8, 18.5; FT-IR (film) 1758 (C=O) cm^{-1}; Ms *m/z* (%) 180 (98), 135 (100), 105 (71), 91 (55).

1-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)propan-1-one (7bf)

To a solution of **5b** (772 mg, 3.0 mmol) in THF (9 mL) was added 2,4-dimethoxyphenylmagnesium bromide (**6f**, 0.5 M in THF, 6.0 mL, 3.0 mmol) at 0 °C. After stirring for 0.5 h, the mixture was quenched with saturated NH_4Cl solution (5 mL) and THF was evaporated *in vacuo*. The mixture was poured into saturated NH_4Cl solution (30 mL) and was extracted with methylene chloride (3×20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified

by silica gel column chromatography using 30% EtOAc/*n*-hexane as eluant to give **7bf** (802 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 8.7 Hz, 1H), 7.14 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.44 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 4.72 (q, J = 6.9 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 1.45 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 164.0, 159.9, 158.1, 134.2, 133.0, 129.1, 121.4, 113.8, 105.0, 98.3, 55.4, 55.3, 55.2, 50.3, 19.3; FT-IR (film) 1666 (C=O) cm^{-1}; Ms *m/z* (%) 300 (M^+, 81), 165 (100), 135 (94), 107 (40), 77 (43).

1-(2,4-Dihydroxyphenyl)-2-(4-hydroxyphenyl)propan-1-one (12)

To a solution of **7bf** (751 mg, 2.5 mmol) in methylene chloride (12 mL) was slowly added boron tribromide (1 M in CH_2Cl_2, 10.0 mL, 10.0 mmol) at 0 ºC. Stirring was continued for 24 h at room temperature, and then the reaction was quenched by the slow addition of H_2O. After evaporation of CH_2Cl_2, the mixture was poured into 5% $NaHCO_3$ solution (30 mL) and was extracted with ethyl acetate (3×20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was recrystallized twice from 20% EtOAc/*n*-hexane to give **12** (581 mg, 90%) as a pale yellow solid. mp 102–103 ºC (lit.[10] 103 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.77 (s, 1H), 10.64 (s, 1H), 9.33 (s, 1H), 7.88 (d, J = 9.0 Hz, 1H), 7.13 (d, J = 8.7 Hz, 2H), 6.69 (d, J = 8.7 Hz, 2H), 6.31 (dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1H), 6.22 (d, J = 2.4 Hz, 1H), 4.77 (q, J = 6.6 Hz, 1H), 1.34 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 204.9, 165.0, 164.7, 156.1, 133.3, 131.9, 128.4, 115.5, 111.4, 108.1, 102.5, 44.4, 18.9; FT-IR (KBr) 3399 (OH), 1629 (C=O) cm^{-1}; Ms *m/z* (%) 258 (M^+, 65), 137 (100), 121 (89), 91 (21), 77 (31).

1-(2-Hydroxy-4-methoxyphenyl)-2-(3-methoxyphenyl)propan-1-one (8): mp 70–71 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.90 (s, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.22 (t, J = 7.9 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 6.82–6.84 (m, 1H), 6.73–6.77 (m, 1H), 6.39 (d, J = 2.5 Hz, 1H), 6.34 (dd, J_1 = 8.9 Hz, J_2 = 2.5 Hz, 1H), 4.60 (q, J = 6.9 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 1.52 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 166.1, 165.9, 160.1, 143.1, 131.9, 129.9, 120.0, 113.5, 112.9, 112.2, 107.5, 101.2, 55.4, 55.2, 47.0, 19.0; FT-IR (KBr) 3646 (OH), 1626 (C=O) cm^{-1}; Ms *m/z* (%) 286 (M^+, 59), 151 (100), 135 (12), 108 (27), 95 (26).

1-(2,4-Dihydroxyphenyl)-2-(3-hydroxyphenyl)propan-1-one (9): viscous liquid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.72 (s, 1H), 10.67 (s, 1H), 9.37 (s, 1H), 7.86 (d, J = 9.0 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.77 (d, J = 7.7 Hz, 1H), 6.69–6.73 (m, 1H), 6.60 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 6.32 (dd, J_1 = 8.9 Hz, J_2 = 2.3 Hz, 1H), 6.24 (d, J = 2.3 Hz, 1H), 4.79 (q, J = 6.8 Hz, 1H), 1.36 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 205.0, 165.5, 165.3, 158.0, 143.7, 133.7, 130.2, 118.7, 114.6, 114.3, 112.2, 108.6, 103.0, 45.9, 19.3; FT-IR (film) 3436 (OH), 1626 (C=O) cm^{-1}; Ms *m/z* (%) 258 (M^+, 39), 137 (100), 81 (34), 77 (18).

1-(2,5-Dihydroxyphenyl)-2-(3-hydroxyphenyl)propan-1-one (10): viscous liquid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.39 (s, 1H), 9.41 (s, 1H), 9.17 (s, 1H), 7.20 (d, J = 2.9 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 6.94 (dd, J_1 = 8.9 Hz, J_2 = 2.9 Hz, 1H), 6.78 (d, J = 8.9 Hz, 1H), 6.72 (d, J = 7.7 Hz, 1H), 6.59–6.66 (m, 2H), 4.80 (q, J = 6.7 Hz, 1H), 1.36 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 206.3, 158.1, 154.6, 149.7, 143.3, 130.3, 124.7, 120.0, 118.9, 118.7, 115.7, 114.7, 114.4, 47.3, 19.4; FT-IR (film) 3441 (OH), 1666 (C=O) cm^{-1}; Ms *m/z* (%) 258 (M^+, 98), 137 (100), 109 (31), 81 (33).

1-(2-Hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)propan-1-one (11): viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.92 (s, 1H), 7.69 (d, J = 8.9 Hz, 1H), 7.21 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.39 (d, J = 2.1 Hz, 1H), 6.35 (dd, J_1 = 8.9 Hz, J_2 = 2.5 Hz, 1H), 4.59 (q, J = 6.8 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 1.50 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.9, 166.2, 165.9, 158.7, 133.7, 131.9, 128.5, 114.5, 112.9, 107.4, 101.2, 55.4, 55.2, 46.0, 19.1; FT-IR (film) 3436 (OH), 1628 (C=O) cm^{-1}; Ms *m/z* (%) 286 (M^+, 79), 151 (100), 135 (95), 108 (21), 91 (25).

1-(2-Hydroxyphenyl)-2-(3,4-dihydroxyphenyl)propan-1-one (13): viscous liquid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.06 (s, 1H), 8.88 (s, 1H), 8.82 (s, 1H), 7.92 (dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz, 1H), 7.43–7.48 (m, 1H), 6.84–6.94 (m, 2H), 6.67 (d, J = 2.1 Hz, 1H), 6.65 (d, J = 8.7 Hz, 1H), 6.59 (dd, J_1 = 8.1 Hz, J_2 = 2.0 Hz, 1H), 4.83 (q, J = 6.7 Hz, 1H), 1.35 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 207.3, 161.7, 145.9, 144.8, 136.3, 132.6, 131.5, 120.0, 119.4, 119.0, 118.2, 116.4, 115.2, 46.4, 19.3; FT-IR (film) 3437 (OH), 1666 (C=O) cm^{-1}; Ms *m/z* (%) 258 (M^+, 79), 241 (46), 137 (100), 121 (98), 91 (35).

1-(2-Hydroxyphenyl)-2-(3,5-dihydroxyphenyl)propan-1-one (14): viscous liquid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.02 (s, 1H), 9.22 (s, 2H), 7.90 (dd, J_1 = 8.0 Hz, J_2 =

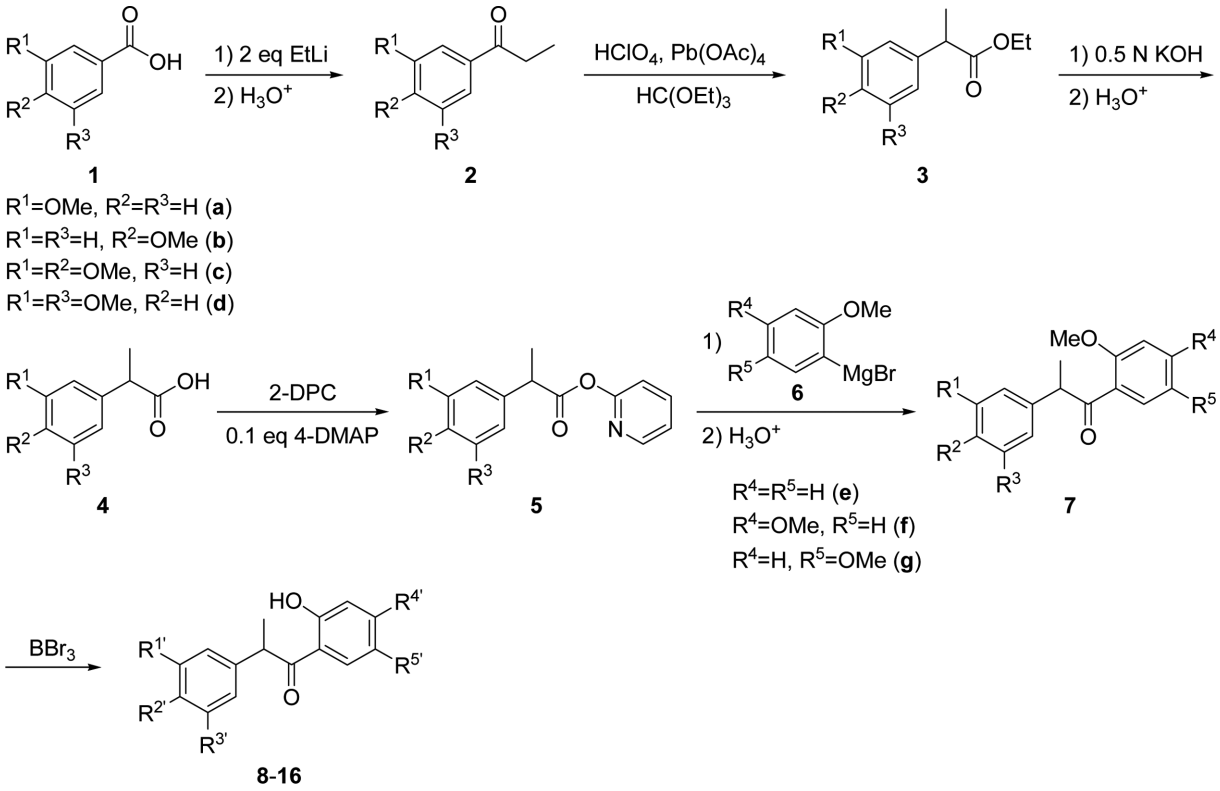
1.3 Hz, 1H), 7.44–7.50 (m, 1H), 6.93 (d, J = 8.3 Hz, 1H), 6.85–6.91 (m, 1H), 6.16 (d, J = 2.0 Hz, 2H), 6.05 (t, J = 2.1 Hz, 1H), 4.80 (q, J = 6.7 Hz, 1H), 1.35 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 206.9, 161.7, 159.1, 143.8, 136.4, 131.4, 120.1, 119.5, 118.2, 106.1, 101.7, 47.1, 19.1; FT-IR (film) 3437 (OH), 1667 (C=O) cm^{-1}; Ms *m/z* (%) 258 (M^+, 97), 137 (17), 121 (100), 93 (45), 65 (53).

1-(2-Hydroxy-5-methoxyphenyl)-2-(3,5-dimethoxyphenyl)propan-1-one (15): viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.97 (s, 1H), 7.25 (d, J = 3.0 Hz, 1H), 7.03 (dd, J_1 = 9.1 Hz, J_2 = 3.0 Hz, 1H), 6.88 (d, J = 9.1 Hz, 1H), 6.43 (d, J = 2.2 Hz, 1H), 6.32 (t, J = 2.2 Hz, 1H), 4.57 (q, J = 6.8 Hz, 1H), 3.75 (s, 6H), 3.69 (s, 3H), 1.52 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 161.4, 157.6, 151.6, 143.6, 124.3, 119.4, 118.3, 113.1, 105.9, 98.9, 55.8, 55.3, 48.0, 18.9; FT-IR (film) 3646 (OH), 1643 (C=O) cm^{-1}; Ms *m/z* (%) 316 (M^+, 94), 165 (23), 151 (100), 123 (24), 108 (20).

1-(2,5-Dihydroxyphenyl)-2-(3,5-dihydroxyphenyl)propan-1-one (16): viscous liquid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.44 (s, 1H), 9.23 (s, 2H), 9.18 (s, 1H), 7.19 (d, J = 2.9 Hz, 1H), 6.95 (dd, J_1 = 8.9 Hz, J_2 = 2.9 Hz, 1H), 6.78 (d, J = 8.9 Hz, 1H), 6.12 (d, J = 2.1 Hz, 2H), 6.06 (t, J = 2.1 Hz, 1H), 4.66 (q, J = 6.7 Hz, 1H), 1.32 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 206.4, 159.1, 154.7, 149.6, 143.8, 124.8, 120.0, 118.8, 115.8, 106.1, 101.7, 47.3, 19.2; FT-IR (film) 3442 (OH), 1666 (C=O) cm^{-1}; Ms *m/z* (%) 274 (M^+, 98), 137 (100), 109 (28), 81 (28).

RESULTS AND DISCUSSION

Methoxypropiophenones (**2**) were efficiently prepared by treatment of methoxybenzoic acids (**1**) with 2 equiv of ethyllithium in THF for 0.5 h at 0 °C. After an acidic workup, the residue was purified by silica gel column chromatography to give **2** (**2a**: 91%, **2b**: 96%, **2c**: 92%, **2d**: 88%) (*Scheme* 2). The conversion of **2** to ethyl 2-(methoxyphenyl)propionates (**3**) was carried out using 70% perchloric acid and lead (IV) acetate in triethyl orthoformate for 2–4 h at room temperature in a similar method of the previous report.[10,20] It appears that the enolized methoxypropiophenone by perchloric acid substitute an acetate group of lead (IV) acetate accompanying ketalization to form the corresponding hemiketal lead intermediate. This intermediate underwent 1,2-rearrangement of the methoxyphenyl group by electron participation of the hydroxy group, fol-



***Scheme* 2.** Synthesis of *O*-DMA analogues from methoxy-substituted benzoic acids.

lowed by elimination of lead (II) acetate, to form **3**. After evaporation of triethyl orthoformate and filtration of the precipitate, the extracted residue was purified by vacuum distillation using a Kugelrohr apparatus to give **3** (**3a**: 80%, **3b**: 83%, **3c**: 86%, **3d**: 78%). The products **3** were further hydrolyzed by treatment with 0.5 N KOH in *aq* CH_3OH overnight. The mixture was acidified with 1 N HCl solution and was separated by the usual workup after evaporation of CH_3OH. The condensed residue was purified by silica gel column chromatography to give **4** (**4a**: 91%, **4b**: 93%, **4c**: 92%, **4d**: 92%).

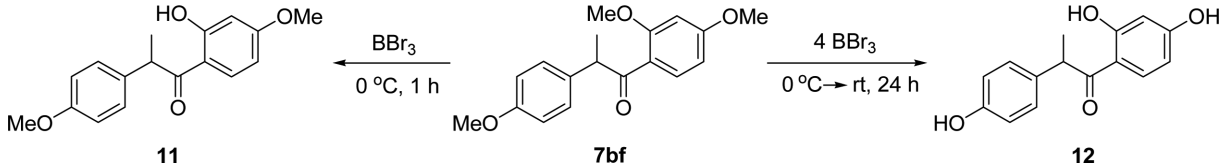
2-Pyridyl 2-(methoxyphenyl)propionates (**5**) were prepared by the addition of di-2-pyridyl carbonate (2-DPC)[21] to a solution of **4** in methylene chloride in the presence of 0.1 equiv of 4-(dimethylamino)pyridine (4-DMAP) for 2 h at room temperature. The reaction proceeded *via N*-acylpyridinium salts, with the evolution of carbon dioxide, which were then converted to the corresponding **5** by nucleophilic acyl substitution of 2-pyridyl oxide. After a typical basic workup, the residue was purified by short pathway Davisil® column chromatography to give **5** (**5a**: 82%, **5b**: 81%, **5c**: 84%, **5d**: 78%). The synthesis of methoxy-α-methyldesoxybenzoins (**7**) was successfully accomplished by acylation of **5** with methoxy-substituted phenylmagnesium bromides (**6**) in THF for 0.5 h at 0 °C. The addition of **6** to a solution of **5** in THF led to a precipitate, which was hydrolyzed with saturated NH_4Cl solution. The mixture was subjected to an acidic workup and the residue was purified by silica gel column chromatography to give **7** in 78–94% yields (*Table* 1).

Selective demethylation of the *ortho*-methoxy group in **7** was successfully accomplished using 1 equiv of boron tribromide. Mechanistically, treatment of 1-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)propan-1-one (**7bf**) with 1 equiv of boron tribromide for 1 h at 0 °C afforded a six-membered chelate between the 2-methoxy/carbonyl oxygen and boron atoms. Subsequent substitution of the methyl group by bromide anion afforded the corresponding borate intermediate, which was hydrolyzed with H_2O to give 1-(2-hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)propan-1-one (**11**) in 75% yield (*Scheme* 3). This method has an advantage over the previous method,[22] where **11** was prepared by substitution of the dianion of *O*-desmethylangolensin using 2.6 equiv of methyl iodide for 48 h at 40 °C in 70% yield. Similarly, *ortho*-methoxy groups in **7af** and **7dg** were selectively demethylated with 1 equiv of boron tribromide to afford **8** and **15** in 83% and 89% yield, respectively. The characteristic ^{1}H NMR signal of the hydroxyl proton in **11** was appeared at δ 12.92 ppm, which is indicative of an intramolecular hydrogen bond between the 2-hydroxyl proton and carbonyl oxygen atom.

Treatment of **7** with 4–5 equiv of boron tribromide afforded the corresponding alkoxyborate intermediates, with the evolution of methyl bromide, which were hydrolyzed with H_2O to give the *O*-desmethylangolensin analogues. For example, the treatment of **7bf** with 4 equiv of boron tribromide for 24 h between 0 °C and room temperature afforded the borate complex. This intermediate was quenched by the slow addition of H_2O, extracted with ethyl acetate, and washed with 5% $NaHCO_3$ solution. The condensed residue was recrystallized twice from 20% EtOAc/*n*-hexane to give 1-(2,4-dihydroxyphenyl)-2-(4-hydroxyphenyl) propan-1-one (**12**) in 90% yield (*Scheme* 3). Characteristic ^{1}H NMR signals of the 2-hydroxyl protons in **9**, **10**, **12**–**14**, and **16** were appeared at δ 11.39–12.77 ppm due to intramolecular hydrogen bonding, while other hydroxyl pro-

***Table* 1.** Preparation of methoxy-α-methyldesoxybenzoins **7** from 2-pyridyl 2-(methoxyphenyl)propionates **5** and Grignard reagents **6**

Entry 7	R^1	R^2	R^3	R^4	R^5	Isolated yields, %
af	OMe	H	H	OMe	H	83
ag	OMe	H	H	H	OMe	94
bf	H	OMe	H	OMe	H	89
ce	OMe	OMe	H	H	H	78
de	OMe	H	OMe	H	H	88
dg	OMe	H	OMe	H	OMe	85



11 **7bf** **12**

***Scheme* 3.** Demethylation of **7bf** using boron tribromide.

***Table* 2.** Preparation of *O*-desmethylangolensin analogues **8**–**16** from methoxy-α-methyldesoxybenzoins **7** using boron tribromide

Entry	$R^{1'}$	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$	Isolated yields, %[a]
8	OMe	H	H	OMe	H	83 (37)
9	OH	H	H	OH	H	86 (39)
10	OH	H	H	H	OH	92 (47)
11	H	OMe	H	OMe	H	75 (40)
12	H	OH	H	OH	H	90 (48)
13	OH	OH	H	H	H	89 (42)
14	OH	H	OH	H	H	85 (37)
15	OMe	H	OMe	H	OMe	89 (37)
16	OH	H	OH	H	OH	91 (38)

[a]The numbers in parentheses indicate the overall yields from methoxybenzoic acids **1**.

tons appeared at δ 8.82–10.67 ppm.

As shown in *Tables* 1 and 2, various methoxy-α-methyldesoxybenzoins **7** and *O*-DMA analogues **8**–**16** were synthesized in 78–94% and 75–92% yields, respectively. The nucleophilic acyl substitution of **5** with **6** proceeded regardless of 3, 4, or 5-methoxy group substitution of **5** and 2, 4, or 5-methoxy substitution of **6**. Selective demethylation of the *ortho*-methoxy group of **7af**, **7bf**, **7dg** was accomplished with 1 equiv of boron tribromide to give the corrresponding **8**, **11**, **15** in 83%, 75%, 89% yields, respectively. In addition, all of the methoxy groups of **7** could be fully demethylated with a slight excess of boron tribromide to give the corresponding **9**, **10**, **12**–**14**, and **16** in 85–92% yields.

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