# Synthesis of 5′-[1-(Methoxycarbonyl)-2-(*p*-methoxyphenyl)ethyl]- and 5′-[2-(Methoxycarbonyl)-1-(*p*-methoxyphenyl)ethyl]-2′,3′,4,4′,6′-pentamethoxychalcone

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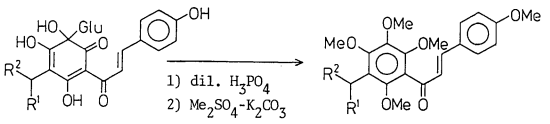
**Synopsis.** 5′-[1-(Methoxycarbonyl)-2-(*p*-methoxyphenyl)-ethyl]- and 5′-[2-(methoxycarbonyl)-1-(*p*-methoxypheny)-ethyl]-2′,3′,4,4′,6′-pentamethoxychalcone were synthesized. The latter compound was completely identical with the methylated derivative of aglycone of safflomin C, a constituent of safflower (*Carthamus tinctorius L*).

Recently, we isolated a yellow pigment, safflomin C, from safflower yellow, the water soluble yellow constituent of safflower (*Carthamus tinctorius L*), and proposed the structure, **1** or **2**, for this new pigment from its spectral data and the behavior of its derivatives.[1,2]

Safflomin C was hydrolyzed with dilute phosphoric acid and methylated with dimethyl sulfate–potassium carbonate in acetone to give the methylated derivative of its aglycone which seems to have the structure **3** or **4**,[1,2] (Scheme 1).

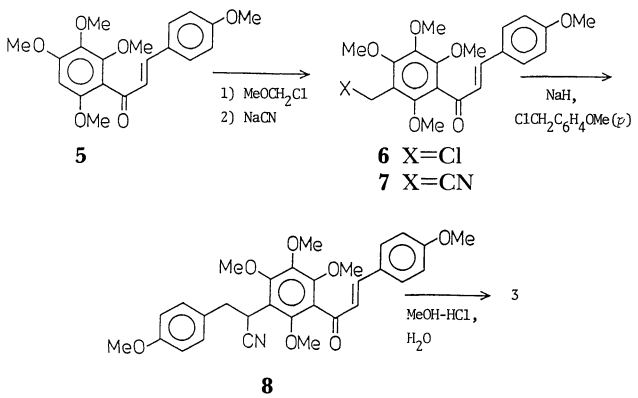



**1** R¹=$CH_2CO_2H$, R²=$C_6H_4OH$ (*p*) **3** R¹=$CO_2Me$, R²=$CH_2C_6H_4OMe$ (*p*)
**2** R¹=$CO_2H$, R²=$CH_2C_6H_4OH$ (*p*) **4** R¹=$CH_2CO_2Me$, R²=$C_6H_4OMe$ (*p*)

Scheme 1.

In this paper, we will report the synthesis of 5′-[1-(methoxycarbonyl)-2-(*p*-methoxyphenyl)ethyl]- and 5′-[2-(methoxycarbonyl)-1-(*p*-methoxyphenyl)ethyl]-2′,3′,4,4′,6′-pentamethoxychalcone (**3** and **4**) and compare these synthetic chalcones with a natural derivative.

First, compound **3** was synthesized by the following method (Scheme 2).

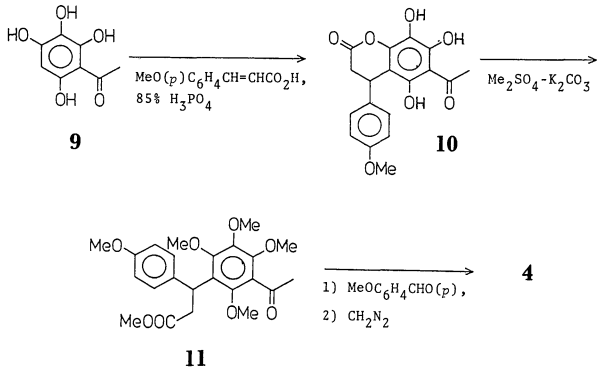



**5** **6** X=Cl **7** X=CN **8**

Scheme 2.

Chloromethylation of 2′,3′,4,4′,6′-pentamethoxychalcone (**5**)[3] with chloromethyl methyl ether in acetic acid gave 5′-chloromethyl-2′,3′,4,4′,6′-pentamethoxychalcone (**6**) in 15% yield. Compound **6** was converted into (cyanomethyl)chalcone (**7**) in 37% yield by treating **6** with sodium cyanide in dimethyl sulfoxide. 5′-[1-Cyano-2-(*p*-methoxyphenyl)ethyl]-2′,3′,4,4′,6′-pentamethoxychalcone (**8**) was obtained by benzylation of **7** with *p*-methoxybenzyl chloride in the presence of sodium hydride in dimethyl sulfoxide in 37% yield. Treatment of **8** with hydrogen chloride in cold methanol followed by the hydrolysis of the resulted imidate hydrochloride gave chalcone **3** in 27% yield.

On the other hand, methoxychalcone **4** was obtained by the following method (Scheme 3).




**9** **10** **11**

Scheme 3.

5-[2-(Methoxycarbonyl)-1-(*p*-methoxyphenyl)ethyl]-2,3,4,6-tetramethoxyacetophenone (**11**) was obtained by methylation of dihydrocoumarin(**10**) prepared by the Friedel–Crafts reaction of 2,3,4,6-tetrahydroxyacetophenone (**9**) with *p*-methoxycinnamic acid in 85% phosphoric acid in 81% yield.

Condensation of **11** with *p*-methoxybenzaldehyde in the presence of 50% aqueous sodium hydroxide solution in methanol gave 5′-[2-carboxy-1-(*p*-methoxyphenyl)ethyl]-2′,3′,4,4′,6′-pentamethoxychalcone (**12**) which was methylated with diazomethane to give chalcone methyl ester **4** in 90% yield. The IR, $^1H$- and $^{13}C$ NMR spectra of **4** were completely identical with those of a natural derivative so that the structure **1** for safflomin C was strongly supported.

## Experimental

All the melting points were uncorrected. The IR spectra were recorded by a Hitachi 100-50 spectrometer. The $^1H$-

and $^{13}C$ NMR spectra were measured by a Hitachi R-600 and Varian Gemini 200 spectrometer using tetramethylsilane as an internal standard, respectively. The mass spectra were obtained on a Hitachi RMU-6M mass spectrometer.

**5′-Chloromethyl-2′,3′,4,4′,6′-pentamethoxychalcone (6).** To a solution of 2′,3′,4,4′,6′-pentamethoxychalcone (**5**)[3] (3.0 g) in acetic acid (10 ml) was added dropwise a solution of chloromethyl methyl ether (1.5 g) in acetic acid (2 ml) with stirring under cooling with ice-water. The reaction mixture was allowed to stand for 3 days at room temperature; the mixture then poured into cold water and extracted with ethyl acetate. The extract was chromatographed on silica gel with benzene–ethyl acetate (15:1) to give **6** (0.51 g, 15%) as pale yellow crystals. Mp 82—83 °C, MS *m/z* 407 ($M^+$), $^1H$ NMR ($CDCl_3$) $\delta$=3.80 (6H,s), 3.83, 3.92, and 4.01 (each 3H, s), 4.66 (2H, s), 6.83 and 7.34 (each 1H, d, $J$=16.0 Hz), 6.84, and 7.47 (each 2H, d, $J$=8.0 Hz), $^{13}C$ NMR ($CDCl_3$) $\delta$=35.7 (t), 55.3, 60.7, 61.6, 61.7, and 63.6 (each q), 114.3 (d), 121.0, and 124.6 (each s), 126.0 (d), 127.6 (s) 130.2 (d), 142.7 (s), 145.5 (d), 151.7, 152.6, 153.9, 161.7, and 192.8 (each s). Found: C, 62.08; H, 5.74%. Calcd for $C_{21}H_{23}O_6Cl$: C, 61.99; H, 5.70%.

**5′-Cyanomethyl-2′,3′,4,4′,6′-pentamethoxychalcone (7).** A mixed solution of **6** (1.0 g) and sodium cyanide (0.13 g) in anhydrous dimethyl sulfoxide (40 ml) was stirred for 1 h at 35 °C. The reaction mixture was poured into cold water (250 ml) and neutralized with 10% hydrochloric acid and extracted with ethyl acetate. The extract was chromatographed on silica gel with benzene–ethyl acetate (10:1) to give **7** (0.36 g, 37%) as pale yellow crystals. Mp 102—103 °C; MS *m/z* 397 ($M^+$); $^1H$ NMR ($CDCl_3$) $\delta$=3.63 (2H, s), 3.73, 3.78, 3.83, 3.85, and 4.03 (each 3H, s), 6.79 and 7.31 (each 1H, d, $J$=16.0 Hz), 6.83 and 7.46 (each 2H, d, $J$=8.0 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$=12.5 (t), 55.3, 60.8, 61.1, 61.8, and 63.0 (each q), 113.6 (s), 114.4 (d), 118.2, and 124.2 (each s), 125.9 (d), 126.9 (s), 130.3 (d), 142.4 (s), 145.7 (d), 150.7, 151.6, 152.5, 161.8, and 192.6 (each s). Found: C, 66.56; H, 5.86; N, 3.54%. Calcd for $C_{22}H_{23}O_6N$: C, 66.49; H, 5.83; N, 3.52%.

**5′-[1-Cyano-2-(*p*-methoxyphenyl)ethyl]-2′,3′,4,4′,6′-pentamethoxychalcone (8).** To a reaction mixture of **7** (0.21 g) and sodium hydride (0.018 g) in anhydrous dimethyl sulfoxide (3 ml) was added *p*-methoxybenzyl chloride (0.11 g) in anhydrous dimethyl sulfoxide (1 ml) under cooling with ice-water; the mixture was then stirred for 2 h at room temperature. The reaction mixture was poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The extract was chromatographed on silica gel with benezene–ethyl acetate (15:1) and with petroleum ether–ethyl acetate (4:1) to give **8** (0.092 g, 34%) as pale yellow viscous oil. MS *m/z* 517 ($M^+$); $^1H$ NMR ($CDCl_3$) $\delta$=3.09 (1H, dd, $J$=13.4 and 7.3 Hz), 3.33 (1H, dd, $J$=8.2 and 13.4 Hz), 3.61, 3.75, 3.84, 3.85, 3.87, and 4.02 (each 3H, s), 4.34 (1H, dd, $J$=7.3 and 8.2 Hz), 6.87 and 8.27 (each 1H, d, $J$=16.1 Hz), 6.82 and 7.50 (each 2H, d, $J$=8.8 Hz), 6.91 and 7.11 (each 2H, d, $J$=8.8 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$=29.5 (d), 38.0 (t), 55.3, 55.4, 60.8, 61.1, 61.9, and 63.0 (each q), 114.0 and 114.5 (each d), 118.1, 121.1, and 123.9 (each s), 126.0 (d), 127.1, and 129.6 (each s), 130.2 and 130.4 (each d), 142.6 (s), 145.9 (d), 150.9, 151.8, 153.3, 158.8, 162.0, and 193.1 (each s). Found: C, 69.38; H, 6.18; N, 2.55%. Calcd for $C_{30}H_{31}O_7N$: C, 69.63; H, 5.99; N, 2.71%.

**5′-[1-(Methoxycarbonyl)-2-(*p*-methoxyphenyl)ethyl]-2′,3′,4,4′,6′-pentamethoxychalcone (3).** To a solution of **8** (34 mg) in anhydrous methanol (10 ml), dry hydrogen chloride gas was passed under cooling with an ice-salt bath. The reaction mixture was allowed to stand for 3 days in a refrigerator; the solvent was then evaporated in vacuo. To the resulting residue was added dilute hydrochloric acid (10 ml) and allowed to stand overnight at room temperature and extracted with ethyl acetate. The extract was chromatographed on silica gel with benzene–ethyl acetate (10:1) to give **3** (10 mg, 28%) as pale yellow viscous oil. MS *m/z* 550 ($M^+$); $^1H$ NMR ($CDCl_3$) $\delta$=3.03 (1H, dd, $J$=13.8 and 9.0 Hz), 3.45 (1H, dd, $J$=6.2 and 13.8 Hz), 3.50 (3H, s), 3.69 (6H, s), 3.79 (3H, s), 3.83 (6H, s), 3.85 (3H, s), 4.21 (1H, dd, $J$=6.2 and 9.0 Hz); 6.72 and 7.00 (each 2H, d, $J$=8.5 Hz), 6.81and 7.18 (each 1H, d, $J$=16.0 Hz), 6.91 and 7.46 (each 2H, d, $J$=8.8 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$=35.9 (t), 43.3 (d), 51.8, 55.1, 55.4, 60.5, 60.7, 61.9, and 62.6 (each q), 113.4 and 114.4 (each d), 122.4 and 123.6 (each s), 126.2 (d), 127.2 (s), 130.2 and 130.4 (each d), 132.1 and 142.3 (each s), 145.8 (d), 150.5, 151.1, 153.1, 157.9, 161.8, 174.0, and 195.8 (each s). Found: C, 67.38; H, 6.05%. Calcd for $C_{31}H_{34}O_9$: C, 67.62; H, 6.22%.

**6-Acetyl-3,4-dihydro-5,7,8-trihydroxy-4-(*p*-methoxyphenyl)-coumarin (10).** A mixed solution of 2,3,4,6-tetrahydroxyacetophenone (**9**)[4] (1.84 g) and *p*-methoxycinnamic acid (1.78 g) in 85% phosphoric acid (60 ml) was stirred for 4 days at room temperature. The reaction mixture was poured into 5% hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous sodium sulfate and evaporated to give **10** (2.8 g, 81%) as pale yellow crystals. Mp 185—186 °C; MS *m/z* 344 ($M^+$); $^1H$ NMR ($CDCl_3$–DMSO-$d_6$) $\delta$=2.78 (3H, s), 3.04 (2H, d, $J$=4.8 Hz), 3.77 (3H, s), 4.65 (1H, t, $J$=4.8 Hz), 6.80 (2H, d, $J$=8.0 Hz), 7.10 (2H, d, $J$=8.0 Hz), 13.58 (1H, s); $^{13}C$ NMR (DMSO-$d_6$) $\delta$=32.5 and 33.0 (each q), 36.4 (t), 54.9 (d), 103.4 and 104.9 (each s), 113.9 and 127.5 (each d), 128.5, 132.9, 145.8, 149.1, 151.6, 157.9, 166.5, and 202.3 (each s). Found: C, 62.63; H, 4.61%. Calcd for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68%.

**5-[2-(Methoxycarbonyl)-1-(*p*-methoxyphenyl)ethyl]-2,3,4,6-tetramethoxyacetophenone (11).** A mixed solution of **10** (1.72 g), dimethyl sulfate (12.0 g), and potassium carbonate (21.0 g) in acetone containing a small amount of water was refluxed for 30 h. The reaction mixture was filtered; the filtrate was evaporated in vacuo and the residue was poured into water (90 ml) and stirred for 6 h at room temperature and extracted with ethyl acetate. The ethyl acetate layer was washed with 10% aqueous sodium carbonate solution and with water, dried over anhydrous sodium sulfate, and then evaporated in vacuo. The residue was chromatographed on silica gel with benzene–ethyl acetate (10:1) to give **11** (1.19 g, 55%) as pale yellow viscous oil. MS *m/z* 432 (M+); $^1H$ NMR ($CDCl_3$) $\delta$=2.51 (3H, s), 3.26 (2H, d, $J$=8.0 Hz), 3.58 (3H, s), 3.61 (6H, s), 3.76, 3.82, and 3.86 (each 3H, s), 4.99 (1H, t, $J$=8.0 Hz), 6.80 and 7.21 (each 2H, d, $J$=9.0 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$=32.5 and 36.2 (each q), 37.8 (t), 51.5 (q), 55.2 (d), 60.5, 61.8, and 63.2 (each q), 75.3 and 77.3 (each s), 113.5 (d), 127.0 (s), 128.3 (d), 128.6, 135.2, 150.3, 153.6, 157.7, 172.9, and 201.5 (each s). Found: C, 64.06; H, 6.64%. Calcd for $C_{23}H_{28}O_8$: C, 63.88; H, 6.53%.

**5′-[2-(Methoxycarbonyl)-1-(*p*-methoxyphenyl)ethyl]-2′,3′,4,4′,6′-pentamethoxychalcone (4).** To a mixed solution of **11** (2.4 g) and *p*-anisaldehyde (0.78 g) in methanol (11 ml) was added 50% aqueous sodium hydroxide solution (4.8 g) and the mixed solution was allowed to stand for 4 days at room temperature. The reaction mixture was poured into 6 M (M=mol dm$^{-3}$) hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous sodium sulfate. The ethyl acetate was evaporated in vacuo to give 5′-[2-carboxy-1-(*p*-methoxyphenyl)ethyl]-2′,3′,4,4′,6′-pentamethoxychalcone (**12**) (2.62 g, 90%) as pale yellow crystals. Mp 134—135 °C; MS *m/z* 536 ($M^+$); IR (KBr) $\nu$ 3450 (br.), 1705, 1624, and 1600 cm$^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=3.25 (2H, m), 3.48, 3.67, and 3.77 (each 3H, s), 3.82, (9H, s), 5.06 (1H, t, $J$=6.0 Hz), 6.80 and 7.52 (each 2H, d, $J$=8.5 Hz), 6.85 and 7.34 (each 1H, d, $J$=16.0 Hz), 6.90 and 7.23 (each 2H, d, $J$=8.0 Hz). To a solution of **12** in ether was added a solution of diazomethane in ether with stirring at room temperature. By evaporating

ether in vacuo **4** was obtained as pale yellow viscous oil in quantitative yield. MS *m/z* 550 ($M^+$); IR ($CCl_4$) $\nu$ 1740, 1645, and 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=3,24 (2H, m), 3.52, 3.62, 3.66, 3.77, 3.83, 3.84, and 3.85 (each 3H, s), 5.02 (1H, t, $J$=7.9 Hz), 6.83 and 6.90 (each 2H, d, $J$=9.0 Hz), 6.89 and 7.32 (each 1H, d, $J$=16.2 Hz), 7.22 and 7.51 (each 2H, d, $J$=8.5 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$=36.3 (d), 37.8 (t), 51.8, 55.4, 55.6, 60.8, 62.0, and 63.1 (each q), 113.8 and 114.7 (each d), 124.6 (s), 126.4 (d), 127.1 and 127.7 (each s), 128.7 and 130.8 (each d), 132.8 and 135.8 (each s), 143.4 (d), 146.5, 150.6, 151.6, 154.1, 158.3, 162.3, 173.7, and 194.7 (each s). Found: C, 67.50; H, 6.09%. Calcd for $C_{31}H_{34}O_9$: C, 67.62; H, 6.22%.

The IR, $^1H$-, and $^{13}C$ NMR spectra of this compound were completely identical with those of natural derivative **4**.

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