# 行政院國家科學委員會專題研究計畫　成果報告

## 氯基烯酮在天然物合成的應用

計畫類別：個別型計畫
計畫編號：NSC93-2113-M-041-001-
執行期間：93 年 08 月 01 日至 94 年 07 月 31 日
執行單位：嘉南藥理科技大學醫藥化學系

計畫主持人：戴火木

報告類型：精簡報告

處理方式：本計畫可公開查詢

中　華　民　國 94 年 10 月 27 日

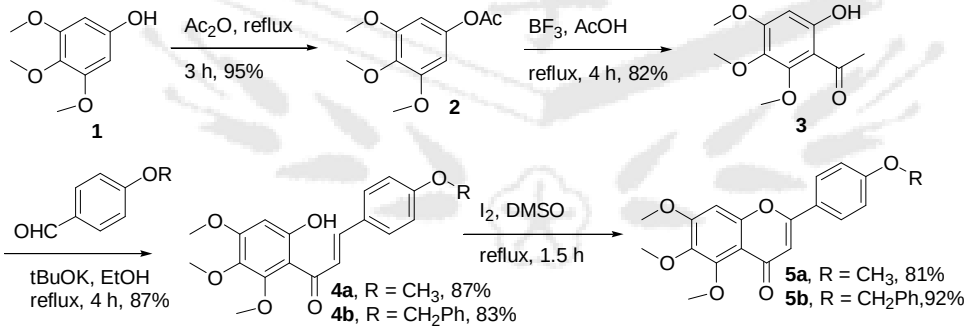
**Abstract:** A total synthesis of the 4'-oxygenated flavonoids and baicalein is described. Intramolecular oxidative cyclization of chalcons is the key step.

**Key words:** baicalein; flavone; chalcone.

Baicalein (5,6,7-trihydroxyflavone),[1] a flavonoid originated from the root of Chinese medicinal herb *Scutellaria baicalensis*, has been shown to exert anti-inflammatory and antioxidant effects,[2] and it is a well-known inhibitor of 12-lipoxygenase.[3] Therefore, the structural characteristics and dives biological activity of these compounds have attracted the attention of chemists and medicinal chemists.[4] In this report, we describe a convenient route to synthesis of 4'-oxygenated flavonoids and baicalein.

Shown as scheme I, 3,4,5-trimethoxyphenol (**1**) underwent an esterification with acetyl anhydride at refluxing temperature for 3 h to give 3,4,5-trimethoxyphenyl acetate (**2**) in 95% yield. Chalcone **4** was readily prepared by treatment of compound **2** with excess acetic acid in the presence of boron trifloride etherate, base promoted aldol condensation of the resulting methyl ketone **3** (82%) and benzaldehydes in refuuxing ethanol afforded chalcone **4** (83-90%).

Scheme I

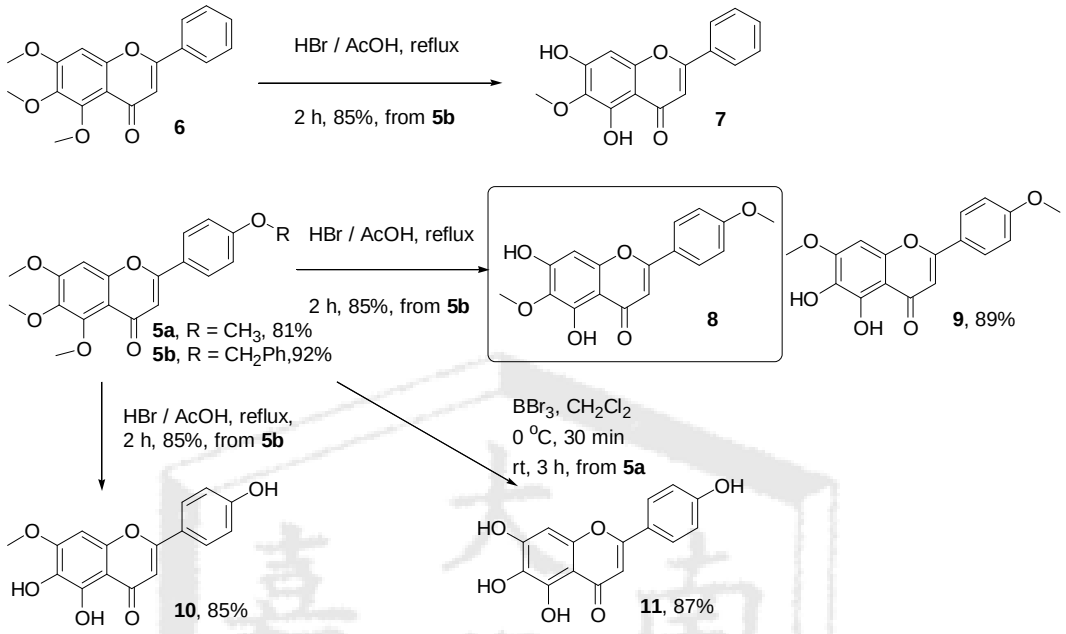



With chalcones **4** in hand, intramolecular oxidative cyclization of chalcones **4** to flavones **5** was accomplished in DMSO solution at refluxing temperature catalyzed by catalytic amount of iodine for 30 min in excellent yields (81-93%).

Demethylation of flavone **6** with HBr/AcOH in refluxing temperature for 2 h gave oroxylin A (**7**), proposed by Lee (Chem. Pharm. Bull. **2003**, *51*, 339). In this approach, demethylation of 4'-methoxyl flavone **5a** in the same condition would be furnished compound **8**. However, the $^{1}H$ and $^{13}C$ NMR data of the product in this reaction, we got, could not satisfy the proposed structure. The structure of this compound is assigned as **9**, since a cross peak was evidenced in the NOESY spectrum between the methoxyl and H8 resonance. If the methoxyl group was located in C6 position, there was no interaction in NOESY experiment. The other evidence is the $^{1}H$ and $^{13}C$ NMR spectra data are identical

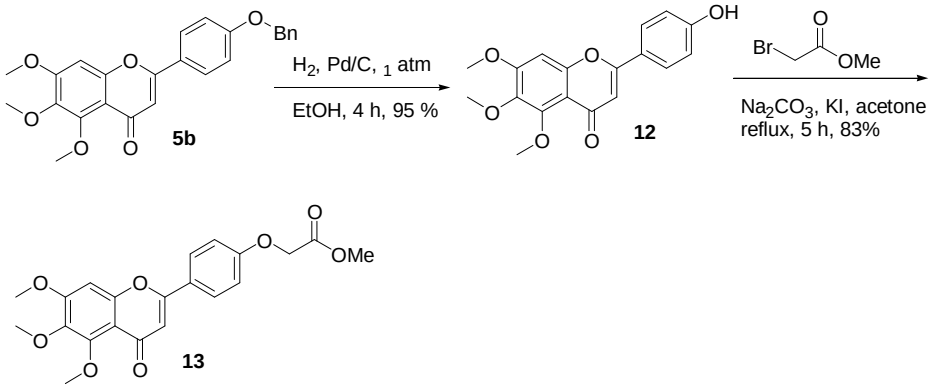
to those of the literature reported (*Phytochemistry* **1995**, *40*, 287). In the same reason, compound **5b** was converted to **10**. The stereochemistry of compound **10** was also confirmed by cosy and noesy experiment. The demethylation of **5** with brorn tribromide in methylene chloride at –23 $^{o}$C furnished tetrahydroxyflavone **11**.

Scheme II




The chemial modification of 4'-oxygenated flavonoids was shown as scheme II. Catalytic hydrogenation of compound **5b** yielded **12** in 95% yield. Successive treatment of **12** with bromoacetate in ethanol in the presence of potassium carbonate gave ester **13** in 83%.

Scheme II




In conclusion, we have successfully synthesized 4'-oxygenated flavonoids. Further synthesis of the flavonoids and their pharmacological effect are now under investigations in our laboratory.

**Acknowledgement** We thank the National Science Council of the Republic of China and Chia Nan University of Pharmacy and Science for financial support.

# Experimental section:

**3,4,5-Trimethoxyphenyl acetate (2)** A solution of 3,4,5-trimethoxyphenol (5.52 g, 30 mmol) in acetic anhydride (15 mL) was refluxed for 4 h. The reaction mixture was poured onto crushed ice (50 g). The resulting precipitate was filtered and washed with water. The residue was dried in vacuum at 50 ℃ for 24 h to afford white crystals (6.31 g, 93%). Without purification, the purity of these crystals is higher than 95%: mp 74-75 ℃; $^{1}$H NMR ($CDCl_3$, 200 M Hz) δ 6.34 (s, 2 H), 3.83 (s, 6 H), 3.82 (s, 3 H), 2.29 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 50 M Hz) δ 169.6 (s), 153.5 (s, 2C), 146.7 (s), 135.8 (s), 99.1 (d, 2C), 60.9 (q), 56.1 (q, 2C), 21.1 (q).

**1-(6-Hydroxy-2,3,4,-trimethoxyphenyl)ethanone (3)** To a solution of 3,4,5-trimethoxyphenyl acetate (6.78 g, 30 mmol) in glacial acetic acid (10 mL) was added dropwise of boron trifluride etherate (13.0 mL). The mixture was stirred at 70 ℃ for 2 h. Then the mixture was poured onto crushed ice (80 g). The light brown oil was separated and distilled under reduced pressure to furnish light yellow oil (5.56g, 82%); $^{1}$H NMR ($CDCl_3$, 200 M Hz) δ 13.42 (br s, 1 H), 6.23 (s, 3 H), 3.82 (s, 3 H), 3.99 (s, 3 H), 3.88 (s, 3 H), 3.79 (s, 3 H), 2.65 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 50 M Hz) δ 203.3 (s), 161.8 (s), 160.0 (s), 155.2 (s), 134.7 (s), 108.4 (s), 96.0 (d), 60.9 (q, 2C), 56.0 (q), 31.8 (q).

**Chalcone 4** To a solution of 1-(6-hydroxy-2,3,4,-Trimethoxyphenyl)ethanone (3) (2.26 g, 10 mmol), 4-methoxybenzaldehyde (1.63 g, 12 mmol) and $^{t}$BuOK (2.11 g 22 mmol) in ethanol (30 mL) was refluxed for 4 h. The reaction mixture was poured onto crushed ice (100 g). The resulting precipitate was filtered and washed with water. The residue was air-dried at room temperature. The crude product was recrystallized from ethyl acetate to afford chalcone as orange crystals (2.99 g, 87%): **4a**, $^{1}$H NMR ($CDCl_3$, 200 M Hz) δ 11.75 (br s, 1 H), 7.84 (s, 2 H), 7.60 (d, *J* = 8.8 Hz, 2 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 6.29 (s 1 H), 3.93 (s 3 H), 3.90 (s, 3 H), 3.85 (s, 3 H), 3.84 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 50 M Hz) δ 192.7 (s), 162.6 (s), 161.5 (s), 159.9 (s), 154.9 (s), 143.3 (d), 135.2 (s), 130.1 (d, 2C), 128.0 (s), 124.0 (d), 114.4 (d, 2C), 108.7 (s), 96.5 (d), 61.8 (q), 61.2 (q), 56.0 (q), 55.3 (q). **4b** (orange crystals), $^{1}$H NMR ($CDCl_3$, 200 M Hz) δ 13.79 (s, 1 H), 7.83 (s, 2 H), 7.58 (d, *J* = 8.8 Hz, 2 H), 7.50-7.30 (m, 5H), 7.00 (d, *J* = 8.8 Hz, 2 H), 6.28 (s 1 H), 5.09 (s, 2 H), 3.92 (s 3 H), 3.87 (s, 3 H), 3.83 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 50 M Hz) δ 192.7 (s), 162.6 (s), 160.6 (s), 159.9 (s), 154.9 (s), 143.2 (d), 136.4 (s), 135.2 (s), 130.1 (d, 2C), 128.5 (d, 2C), 128.2 (s), 128.0 (d), 127.4 (d, 2C), 124.1 (d), 115.2 (d, 2C), 108.7 (s), 96.5 (d), 70.0 (t), 61.8 (q), 61.2 (q), 55.9 (q).

**Flavone 5** A solution of chalcone (1.72 g, 5 mmol) and iodine (catalytic amount) in dimethyl sulfoxide (6 mL) was reflux for 30 min, and then the reaction mixture was poured onto crushed ice (50 g). The resulting precipitate was filtered and washed with 5% sodium thiosulfate solution (30 mL) and water. Recrystallization from ethanol afforded flavone (1.38 g, 81%) as bright yellow crystals: **5a**, $^{1}$H NMR ($CDCl_3$, 200 M Hz) δ 7.81 (d, *J* = 9.0 Hz, 2 H), 6.98 (d, *J* = 9.0 Hz, 2 H), 6.79 (s 1 H), 6.57 (s, 1 H), 3.99 (s 3 H), 3.98 (s, 3 H), 3.92 (s, 3 H), 3.87 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 50 M Hz) δ 177.1 (s), 162.0 (s), 161.0 (s), 157.5 (s), 154.3 (s), 152.4 (s), 140.2 (s), 127.5 (d, 2C), 123.6 (s), 114.2 (d, 2C), 122.7 (s), 106.8 (d), 96.1 (d), 62.0 (q), 61.4 (q), 56.1 (q), 55.3 (q). **5b** (from **4b** as the same procedure for synthesis of **5a**), $^{1}$H NMR ($CDCl_3$, 200 M Hz) δ 7.82 (d, *J* = 8.7 Hz, 2 H), 7.50-7.35 (m, 5H), 7.08 (d, *J* = 8.7 Hz, 2 H), 6.80 (s 1 H), 5.15 (s, 2 H), 3.99 (s 3 H), 3.98 (s, 3 H), 3.92 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 50 M Hz) δ 177.1 (s), 162.2 (s), 161.0 (s), 157.6 (s), 154.4 (s), 152.5 (s), 140.2 (s), 136.2 (s), 128.6 (d, 2C), 128.2 (d), 127.6 (d, 2C), 127.4 (d, 2C), 124.0 (s), 115.2 (d, 2C), 122.8 (s), 107.0 (d), 96.2 (d), 70.1 (t), 62.1 (q), 61.5 (q), 56.2 (q).

**5,6-Dihydroxy-7,4'-dimethoxyflavone (9)** Compound **9** (407 mg) was prepared by the same procedure as above from **5a** (500 mg, 1.46 mmol) in 89% yield as yellow crystals: $^{1}$H NMR (DMSO, 200 M Hz) δ 12.59 (br s, 1 H), 8.70 (br s, 1 H), 8.02 (d, *J* = 8.6 Hz, 2 H), 7.08 (d, *J* = 8.6 Hz, 2 H), 6.90 (s 1 H), 6.85 (s 1 H), 3.91 (s, 3 H), 3.84 (s, 3 H); $^{13}$C NMR (DMSO, 50 M Hz) δ 182.2 (s), 163.3 (s), 161.3 (s), 154.4 (s), 149.7 (s), 146.2 (s), 130.0 (s), 128.2 (d, 2C), 123.0 (s), 114.6 (d, 2C), 105.1 (s), 103.1 (d), 91.2 (d), 56.3 (q), 55.6 (q). The stereochemistry of compound **9** was conformed by cosy and noesy experiments.

**5,6,4'-Trihydroxy-7-methoxyflavone (10)** A solution of **5b** (500 mg, 1.20 mmol) in 48% HBr (5 mL) and glacial acetic acid (10 mL) was refluxed for 2 h. Then, the reaction mixture was poured onto crushed ice (ca. 100 g). The resulting precipitate was filtered and washed with water. Recrystallization from ethanol furnished compound **10** (305 mg, 85%) as yellow crystals: $^{1}$H NMR (DMSO, 200 M Hz) δ 12.63 (br s, 1 H), 10.30 (br s, 1 H), 8.70 (br s, 1 H), 7.93 (d, *J* = 8.8 Hz, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.88 (s 1 H), 6.78 (s 1 H), 3.90 (s, 3 H); $^{13}$C NMR (DMSO, 50 M Hz) δ 182.2 (s), 163.8 (s), 161.1 (s), 154.3 (s), 149.6 (s), 146.2 (s), 129.9 (s), 128.4 (d, 2C), 121.4 (s), 116.0 (d, 2C), 105.0 (s), 102.5 (d), 91.1 (d), 56.3 (q). The stereochemistry of compound **11** was conformed by cosy and noesy experiments.

**5,6,7,4'-Tetrahydroxyflavone (11)** To a solution of flavone **5a** (68.4 mg, 0.2 mmol) in dichloromethane (3 mL) was added dropwise of boron tribromide (0.7 mL) at 0 ℃. The mixture was allowed to warm to room temperature after 30 min and stirred at room temperature for 20 h. Then the mixture was poured into ice water (20 mL). The organic layer was separated and concentrated under reduce pressure. The aqueous layer was poured onto the organic residue. After stirring, the precipitate was filtered and washed with water. Recrystallization from ethanol afforded **11** (50 mg, 88%) as yellow crystals: $^{1}$H NMR (DMSO, 200 M Hz) δ 10.20 (br s, 2 H), 7.90 (d, *J* = 8.7 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 6.72 (s 1 H), 6.57 (s 1 H), 3.75 (br s, 2 H); $^{13}$C NMR (DMSO, 50 M Hz) δ 182.1 (s), 163.6 (s), 161.0 (s), 153.3 (s), 149.7 (s), 147.1 (s), 129.2 (s), 128.4 (d, 2C), 121.5 (s), 116.0 (d, 2C), 104.1 (s), 102.3 (d), 93.9 (d).

**4'-Hydroxy-5,6,7-trimethoxyflavone (12)** To a suspension of **5b** (120 mg, 0.29 mmol) and catalytic amount of palladium on charcoal (10 %) in ethanol (15 mL) was hydrogenated at atmosphere for 4 h. Then, the catalyst was filtered off and the solvent was stripped off to produce compound **12** (89 mg, 95%) as slight yellow crystals. Without purification, the purity of this compound is higher than 95%. $^{1}$H NMR (DMSO, 200 M Hz) δ 7.88 (d, *J* = 8.6 Hz, 2 H), 7.16 (s, 1H), 6.90 (d, *J* = 8.6 Hz, 2 H), 6.60 (s 1 H), 3.93 (s 3 H), 3.93 (s, 3 H), 3.78 (s, 3 H), 3.75 (s, 3 H);

**Compound 13** To a suspension of **12** (100 mg, 0.30 mmol), methyl bromoacetate (150 mg, 1.0 mol), potassium carbonate (300 mg), and potassium iodide (200 mg) in acetone (15 mL) was refluxed for 5 h. Then the reaction mixture was concentrated. The residue was added water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was chromatographied on silica to afford compound **13** (101 mg, 83%) as white solids. $^{1}$H NMR ($CDCl_3$, 200 M Hz) δ 7.83 (d, *J* = 9.0 Hz, 2 H), 7.01 (d, *J* = 9.0 Hz, 2 H), 6.79 (s 1 H), 6.57 (s, 1H), 4,72 (s, 2 H), 3.99 (s 3 H), 3.98 (s, 3 H), 3.92 (s, 3 H), 3.83 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 50 M Hz) δ 177.1 (s), 168.7 (s), 160.7 (s), 160.0 (s), 157.6 (s), 154.4 (s), 152.5 (d), 140.3 (s), 127.6 (d, 2C), 124.9 (s), 114.9 (d, 2C), 112.8 (s), 107.3 (d), 96.2 (d), 65.0 (t), 62.1 (q), 61.4 (q), 56.2 (q), 52.3 (q).

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