

Total Synthesis of Heliannone A and (*R,S*)-Heliannone B, Two Bioactive Flavonoids from *Helianthus annuus* Cultivars

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The total synthesis of heliannone A (**1**) and (*R,S*)-heliannone B (**2**), two bioactive flavonoids originally isolated from *Helianthus annuus* cultivars, is described.

Helianthus annuus L. var VYP (Compositae) is a source of allelopathic flavonoids, viz., heliannone A (**1**), heliannone B (**2**), and heliannone C.¹ In the present study we undertook the total synthesis of heliannone A and (*R,S*)-heliannone B to confirm their structures and to provide material for further bioactive studies.

2'-Hydroxychalcones are isomeric with the corresponding flavanones, and these are interconverted using either acid or base. A common approach for the synthesis of chalcones and flavanones is to condense the respective 2-hydroxyacetophenone and benzaldehyde to give the corresponding 2'-hydroxychalcone and then isomerize it to the flavanone in acid medium.²

Heliannone A (**1**) and (*R,S*)-heliannone B (**2**) were synthesized via the key intermediate 2-hydroxy-3,4-dimethoxyacetophenone (**4**). To prepare **4**, pyrogallol was first acetylated in the presence of Ac₂O and traces of concentrated H₂SO₄ to give gallocetophenone (**5**) in 92% yield.³ Selective methylation of **5** with MeI gave **4** in 68% yield. The key intermediate **4** was condensed with *p*-hydroxybenzaldehyde (**6**) in the presence of 50% aqueous KOH to afford **1** in 48% yield.⁴ Attempted cyclization of **1** under acidic conditions such as 20% HOAc, 20 or 50% aqueous H₃PO₄, and 30% HBr in HOAc,⁵ at temperatures between 30 and 70 °C failed to yield the corresponding flavanone (**2**). Decomposition of the chalcone occurred above 70 °C. However, treatment of **1** with KF in MeOH under reflux for 20 h yielded **2** in 64% yield⁶ (Scheme 1). The spectral data (UV, IR, NMR, and MS) of synthetic **1** and **2** were identical to those of heliannone A and heliannone B, respectively, reported earlier from *H. annuus* cultivars.¹

Experimental Section

General Experimental Procedures. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 283B double-beam spectrophotometer and UV spectra on a Shimadzu 240 double-beam spectrophotometer. ¹H and ¹³C NMR spectra were recorded on a Bruker 400 MHz instrument, and EIMS was obtained on a VG Micromass 7070F instrument at 70 eV.

Gallocetophenone (5). Equimolar quantities of pyrogallol (**3**) (2.5 g; 19.8 mmol) and Ac₂O (1.9 mL; 20.14 mmol) were refluxed with a drop of concentrated H₂SO₄ for about 1 h. The contents were cooled and poured into 10 mL of H₂O containing 2 mL of EtOH. Then 2 drops of concentrated HCl was added, and the solution was refluxed for 45 min to decompose excess Ac₂O. The reaction mixture on concentration under reduced pressure yielded a yellow solid, which on crystallization from hexane–EtOAc gave **5** as a yellow crystalline solid (3.1 g, 92%), mp 169–172 °C (lit.⁷ mp 173 °C).

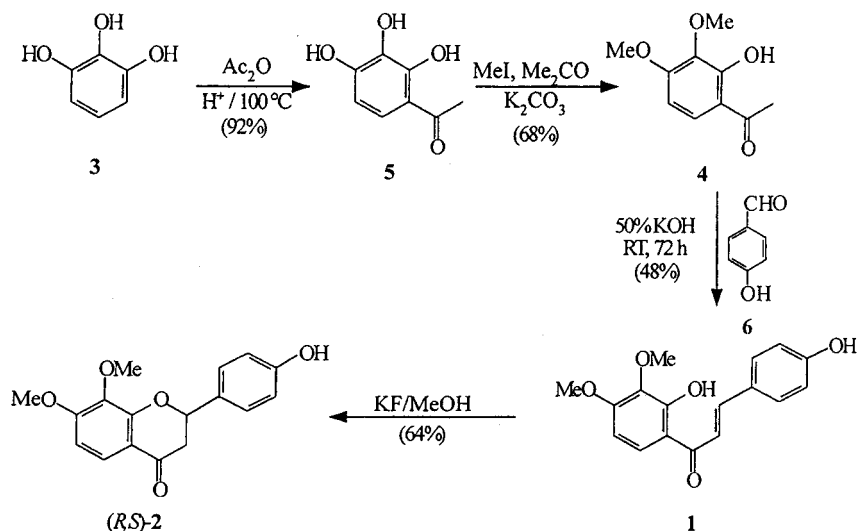
2-Hydroxy-3,4-dimethoxyacetophenone (4). A mixture of **5** (1.5 g; 8.9 mmol) and MeI (0.6 mL; 9.6 mmol) in dry Me₂CO (15 mL) and anhydrous K₂CO₃ (1.4 g; 10.1 mmol) was well stirred under reflux for 2 h. The reaction mixture was cooled and filtered. The filtrate on evaporation afforded 1.19 g of **4** (68%) as a pale cream-colored solid: mp 62–64 °C; EIMS *m/z* [M]⁺ 196; IR (KBr) ν_{\max} 3400, 1636 cm⁻¹; ¹H NMR (CDCl₃) δ 2.58 (3H, s, COMe), 3.92 (3H, s, OMe-3), 3.98 (3H, s, OMe-4), 6.50 (1H, d, *J* = 9 Hz, H-5), 7.50 (1H, d, *J* = 9 Hz, H-6), 12.98 (1H, s, OH-2).

2',4-Dihydroxy-3',4'-dimethoxychalcone (1). To a solution of 2-hydroxy-3,4-dimethoxyacetophenone (**4**) (98 mg; 0.5 mmol) and *p*-hydroxybenzaldehyde (**6**) (61 mg; 0.5 mmol) in EtOH (10 mL) was added dropwise 10 mL of 50% aqueous KOH. The resulting mixture was stirred at room temperature for 72 h. The reaction mixture was poured into ice cold H₂O, and the pH of the solution was adjusted to 3–4 with 10% aqueous HCl and then extracted with Et₂O (4 × 20 mL). The organic extract was washed with H₂O and brine, dried over anhydrous MgSO₄, and evaporated under reduced pressure. The resulting residue was purified over a Si gel column eluting with hexane–EtOAc (7:3) to give chalcone **1** (72 mg, 48%) as a yellow crystalline solid (hexane–EtOAc, 8:2): mp 144–146 °C; UV (MeOH) λ_{\max} (log ϵ) 300 sh (3.38), 363 (4.30) nm; (MeOH+AlCl₃) 248 sh, 425 nm; (MeOH+AlCl₃+HCl) 248 sh, 341, 405 nm; (MeOH+NaOMe) 278 sh, 430 nm; (MeOH+NaOAc) 295, 370, 424 sh nm; (MeOH+NaOAc+H₃BO₃) 297, 365 nm; IR (KBr) ν_{\max} 3363 (OH), 1633 (C=O), 1605 (C=C), 1562 cm⁻¹; ¹H NMR (CDCl₃) δ 3.92 (3H, s, OMe-3'), 3.95 (3H, s, OMe-4'), 5.62 (1H, s, OH-4), 6.53 (1H, d, *J* = 9.1 Hz, H-5'), 6.89 (2H, d, *J* = 8.6 Hz, H-3, H-5), 7.45 (1H, d, *J* = 15.4 Hz, H- α), 7.57 (2H, d, *J* = 8.6 Hz, H-2, H-6) 7.68 (1H, d, *J* = 9.1 Hz, H-6'), 7.86 (1H, d, *J* = 15.4 Hz, H- β), 13.33 (1H, s, OH-2'); ¹³C NMR (CDCl₃) δ 56.1 (OMe-4'), 60.7 (OMe-3'), 102.8 (C-6'), 115.6 (C-5'), 116.1 (C-3, C-5), 117.5 (C- α), 126.0 (C-1'), 127.3 (C-1), 130.7 (C-2, C-6), 136.5 (C-3'), 144.8 (C- β) 158.1 (C-4), 158.4 (C-2'), 158.6 (C-4'), 192.6 (C- β'); EIMS *m/z* 300 [M]⁺ (60), 181 (50), 180 (55), 152 (100), 151 (30), 149 (25), 148 (15), 120 (40); HREIMS *m/z* [M]⁺ 300.0995 (calcd for C₁₇H₁₆O₅, 300.0997).

(*R,S*)-4'-Hydroxy-7,8-dimethoxyflavanone (2). Chalcone (**1**) (45 mg; 0.15 mmol) was added to a stirred solution of KF (10 mg) in MeOH (5 mL), and the reaction mixture was refluxed for 20 h. The reaction mixture was diluted with H₂O (5 mL) and extracted with Et₂O (4 × 5 mL). The combined ethereal extracts were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated to give a syrupy residue. Purification of this residue over a Si gel column using hexane–EtOAc (8:2) afforded **2** (29 mg, 64%) as colorless needles (hexane–EtOAc, 9:1): mp 130–132 °C; UV (MeOH) λ_{\max} (log ϵ) 280 (4.28), 323 sh (3.18) nm; (MeOH+AlCl₃) 280, 324 sh nm; (MeOH+AlCl₃+HCl) 281, 323 sh nm; (MeOH+NaOMe) 281 sh, 430 nm; (MeOH+NaOAc) 281, 324 sh nm; (MeOH+NaOAc+H₃BO₃) 282, 324 sh nm; IR (KBr) ν_{\max} 3340 (OH), 1652 (C=O) cm⁻¹; ¹H NMR (CDCl₃) δ 2.83 (1H, dd, *J* = 17.5, 3.2 Hz, H-3_{eq}), 3.02 (1H, dd, *J* = 17.5, 13.3 Hz, H-3_{ax}), 3.88 (3H, s, OMe-8), 3.94 (3H, s, OMe-7), 5.44 (1H, dd, *J* =

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Scheme 1



13.3, 3.2 Hz, H-2), 6.68 (1H, d, $J = 8.6$ Hz, H-6), 6.88 (2H, d, $J = 8.5$ Hz, H-3', H-5'), 7.36 (2H, d, $J = 8.5$ Hz, H-2', H-6'), 7.66 (1H, d, $J = 8.6$ Hz, H-5); ^{13}C NMR (CDCl_3) δ 44.5, (C-3), 56.8 (OMe-7), 61.1 (OMe-8), 79.5 (C-2), 110.2 (C-6), 111.0 (C-4a), 115.8 (C-3', C-5'), 128.6 (C-2', C-6'), 128.8 (C-5), 129.8 (C-1'), 130.4 (C-8), 158.2 (C-7), 158.4 (C-4), 159.7 (C-8a), 194.5 (C-4); EIMS m/z 300 $[\text{M}]^+$ (75), 299 (10), 181 (25), 180 (70), 151 (54), 120 (28); HREIMS m/z $[\text{M}]^+$ 300.0993 (calcd for $\text{C}_{17}\text{H}_{16}\text{O}_5$, 300.0997).

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References and Notes

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