

Total Synthesis of (*R,S*)-Sophoraflavanone C

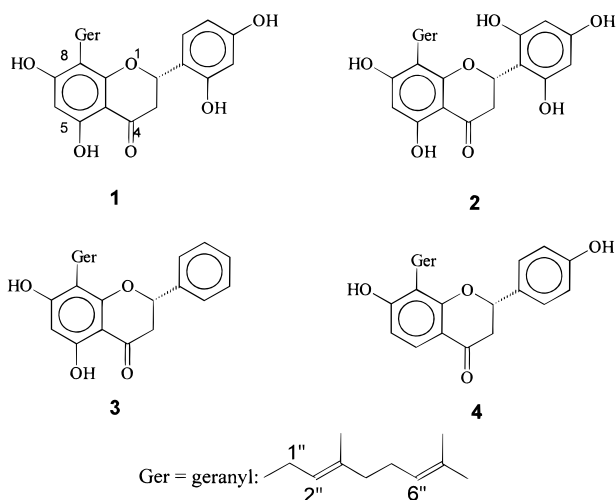
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Sophoraflavanone C, a C-8 geranylflavanone natural product originally isolated from *Echinosophora koreensis*, has been synthesized in racemic form in six steps, starting from 2,4,6-trihydroxyacetophenone and 2,4-dihydroxybenzaldehyde.

Geranylflavonoids are interesting natural products isolated in recent years from some traditional medicinal plants.^{1–3} Some of these flavanoids have been reported to exhibit hypotensive,⁴ antibacterial,⁵ and antitumor⁶ effects. With respect to the synthesis of geranylflavonoids, only the 8-geranylflavanone skeleton, as found in compounds **1**,⁷ **2**,⁸ **3**,⁹ and **4**,¹⁰ has not been yet prepared.



The development of a general synthetic method for this class of compound would facilitate further studies relating biological activity to structure. In this paper, we describe the first total synthesis of sophoraflavanone C,⁷ a compound isolated from *Echinosophora koreensis* and identified on the basis of its spectral data as 5,7,2',4'-tetrahydroxy-8-geranylflavanone (**1**). This work provides a general synthesis method for the 8-geranylflavanones. The synthetic route is outlined in Scheme 1.

Treatment of 2,4,6-trihydroxyacetophenone (**5**) and geranyl bromide with anhydrous potassium carbonate in dry acetone under reflux yielded four geranyl acetophenones **6a**, **6b**, **6c**, and **6d** in 78%, 5%, 5%, and 1% yield, respectively (**6a**:**6b** = 15.6:1). Compound **6a** was regioselectively protected with chloromethyl methyl ether (MOMCl; DANGER carcinogenic reagent) to give compound **7** in 65% yield. A similar treatment of **8** with MOMCl gave compound **9** in 95% yield. The condensation of **7** and **9** was achieved in a mixture of aqueous potassium hydroxide and ethanol at 0 °C to room temperature for 36 h to give chalcone **10** in 40% yield. Compound **10** was refluxed in a

solution of sodium acetate in ethanol for 24 h to form **11** in 86% yield, followed by hydrolysis with 3N HCl in methanol to afford (*R,S*)-**1** in 70% yield. The spectral data (MS, NMR) of (*R,S*)-**1** was comparable to those reported.⁷ Compounds **6b** and **6c** are natural products isolated from *Evodia nerrillii*.¹¹ Their spectral data were consistent with those in the literature.¹⁰ Compound **6a** has been prepared in 1% yield by the reaction of **5** with geraniol in a mixture of ascorbic acid and 5% aqueous citric acid at 80 °C for 11 h.¹² The method described in this paper (78%) is a considerable improvement over the older procedure.

Experimental Section

General Experimental Procedures. Melting points were measured on Kofler hot stage and are uncorrected. IR spectra were obtained on an FT-170-SX spectrometer. ¹H NMR spectra were obtained in CDCl₃ solution on a Varian FT-80A instrument, and chemical shifts were recorded in ppm (δ) units using TMS as internal standard. MS were measured on ZAB-HS and MAT44S spectrometers by direct inlet at 70eV.

2,4,6-Trihydroxy-3-geranylacetophenone (6a). A well-stirred mixture of phloracetophenone (**5**) (1.000 g, 6 mmol), geranyl bromide (0.876 g, 4.80 mmol), and anhydrous potassium carbonate (0.415 g, 3.00 mmol) in dry Me₂CO (3.5 mL) was refluxed for 6 h. The reaction mixture was filtered and evaporated under reduced pressure to give an oily residue that was purified by flash column chromatography on Si gel (petroleum ether–EtOAc, 10:1) to afford recovered **5** (228 mg) and **6a** (1.100 g), **6b** (71 mg), **6c** (75 mg), and **6d** (25 mg) in 78%, 5%, 5%, and 1% yields (based on unrecovered starting material), respectively. Compound **6a**, a light yellow powder, mp 105–106 °C (lit.¹¹ mp 119–120 °C, according to lit.¹² **6a** is a yellow oil): ¹H NMR δ_H 1.60 (3 H, s, Me), 1.67 (3 H, s, Me), 1.82 (3 H, s, Me), 1.80–2.20 (m, 4 H, 4''-2H and 5-2H), 2.68 (3H, s, COMe), 3.32 (2H, d, *J* = 7.0 Hz, 1''-2H), 5.17 (1H, t, *J* = 6.8 Hz, 6''-H), 5.26 (1H, t, *J* = 7.0 Hz, 2''-H), 5.90 (1H, s, ArH), 6.97 (1H, s, OH), 9.55 (1H, s, OH), 11.67 (1H, s, OH); IR (KBr) ν_{max} 1627 cm⁻¹; EIMS *m/z*(%) [M]⁺ 304 (38), 289 (3), 261 (9), 235 (25), 219 (22), 181 (100). Compound **6b**; colorless fine crystals (EtOAc–Petroleum ether), mp 145–147 °C (lit.¹¹ 147–150 °C). Compound **6c**: a white waxy substance (lit.,¹⁰ waxy substance). Compound **6d**: colorless fine crystals (EtOAc–petroleum ether), mp 71–74 °C. ¹H NMR δ_H 1.62 (6H, s, 2Me), 1.70 (6H, s, 2Me), 1.74 (3H, s, Me), 1.83 (3H, s, Me), 1.90–2.20 (8H, m), 2.65 (3H, s, COMe), 3.41 (2H, d, *J* = 7.0 Hz), 4.56 (2H, d, *J* = 6.6 Hz), 5.05–5.60 (4H, m), 5.92 (1H, s, ArH), 6.25 (1H, s, OH), 14.41 (1H, s, OH); IR (KBr) ν_{max} 1644 cm⁻¹; EIMS *m/z* [M]⁺ 440 (1), 304 (30), 261 (3), 235 (6), 181 (100), 137 (2), 69 (25).

4,6-Dimethoxymethoxy-2-hydroxy-3-(1'-geranyl)acetophenone (7). A mixture of **6a** (304 mg, 1 mmol), MOMCl (200 mg, 2.5 mmol), and anhydrous K₂CO₃ (966 mg, 7 mmol) in dry Me₂CO (20 mL) was well stirred under reflux for 1.5 h. Evaporation of the filtered solution afforded **7** (255 mg, 65%

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