## 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.<sup>1–3</sup> Some of these flavanoids have been reported to exhibit hypotensive,<sup>4</sup> antibacterial,<sup>5</sup> and antitumor<sup>6</sup> effects. With respect to the synthesis of geranylflavonoids, only the 8-geranylflavanone skeleton, as found in compounds **1**,<sup>7</sup> **2**,<sup>8</sup> **3**,<sup>9</sup> and **4**,<sup>10</sup> 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,<sup>7</sup> 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 (MO-MCl; 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.<sup>7</sup> Compounds **6b** and **6c** are natural products isolated from *Evodia nerrillii*.<sup>11</sup> Their spectral data were consistent with those in the literature.<sup>10</sup> 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.<sup>12</sup> 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. <sup>1</sup>H NMR spectra were obtained in CDCl<sub>3</sub> solution on a Varian FT-80A instrument, and chemical shifts were recorded in ppm ( $\delta$ ) 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 wellstirred 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 Me<sub>2</sub>CO (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.<sup>11</sup> mp 119–120 °C, according to lit.<sup>12</sup> **6a** is a yellow oil): <sup>1</sup>H NMR  $\delta_{\rm H}$  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)  $\nu_{\text{max}}$  1627 cm<sup>-1</sup>; EIMS m/z(%) [M]<sup>+</sup> 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.,<sup>10</sup> waxy substance). Compound 6d: colorless fine crystals (EtOAc-petroleum ether), mp 71–74 °C, <sup>1</sup>HNMR  $\delta_{\rm H}$  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)  $\nu_{max}$  1644 cm<sup>-1</sup>; EIMS *m*/*z* [M]<sup>+</sup> 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 K<sub>2</sub>CO<sub>3</sub> (966 mg, 7 mmol) in dry Me<sub>2</sub>CO (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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<sup>*a*</sup> Key: (a) geranyl bromide, Me2CO, K<sub>2</sub>CO<sub>3</sub>, reflux; (b) CH<sub>3</sub>OCH<sub>2</sub>Cl, K<sub>2</sub>CO<sub>3</sub>, Me<sub>2</sub>CO, reflux; (c) CH<sub>3</sub>OCH<sub>2</sub>Cl, K<sub>2</sub>CO<sub>3</sub>, acetone, reflux; (d) KOH, H<sub>2</sub>O-EtOH (v/v = 1:1), 0 °C  $\sim$  r.t; (e) NaOAc, EtOH, reflux; (f) 3NHCl, MeOH, reflux.

yield) as a deep red gum: <sup>1</sup>H NMR (400 MHz)  $\delta$  1.58 (3H, s, Me), 1.64 (3H, s, Me), 1.79 (3H, s, Me), 1.90–2.15 (4 H, m, 4″-2H and 5″-2H), 2.66 (3H, s, COMe), 3.32 (2H, d, J = 7.0 Hz, 1″-2H), 3.48 (3H, s, OMe), 3.58 (3H, s, OMe), 5.06 (1 H, t, J = 6.5 Hz, 6″-H), 5.19 (1H, t, J = 7.0 Hz, 2″-H), 5.24 (2H, s, OCH<sub>2</sub>O), 5.27 (2H, s, OCH<sub>2</sub>O), 6.40 (1H, s, ArH), 13.85 (1H, s, OH); IR (KBr)  $\nu_{max}$  1617 cm<sup>-1</sup>; EIMS m/z [M]<sup>+</sup> 392 (4), 347 (10), 273 (7), 269 (3), 225 (3), 69 (10), 45 (100); HREIMS m/z [M]<sup>+</sup> 392.2210 (C<sub>22</sub>H<sub>32</sub>O<sub>6</sub> requires 392.2199); a similar reaction of **8** with MOMCl gave **9** as a white solid, mp 47–48 °C [lit.<sup>11</sup> 48 °C] in 95% yield.

2,4,4',6'-Tetramethoxymethoxy-2'-hydroxy-3'-(1'-geranyl)-chalcone (10). A well-stirred solution of 7 (400 mg, 1.02 mmol) and 9 (231 mg, 1.02 mmol) in EtOH (2 mL) cooled to 5 °C was added dropwise to a mixture of potassium hydroxide (1 g) in 2 mL H<sub>2</sub>O-EtOH (2:3) cooled to 0 °C under argon. The reaction mixture was kept in an ice bath for 3 h, then at room temperature for 33 h. The mixture was poured into iced water, the solution adjusted pH to 3-4 with dilute HCl, and then extracted with Et<sub>2</sub>O. The organic extract was washed with H<sub>2</sub>O and brine, dried over anhydrous MgSO<sub>4</sub>, and evaporated under reduced pressure. The residue was purified by Si gel column chromatography eluting with petroleum ether-EtOAc (10:1) to give chalcone 10 (245 mg, 40%) as a red liquid: <sup>1</sup>H NMR  $\delta$  1.59, 1.66, 1.80 (3H each s, 8"-Me, 9"-Me, and 10"-Me), 1.95-2.15 (4H, m, 4"-H and 5"-H), 3.36 (2H, d, J = 7.3 Hz, 1"-2H), 3.50 (12H, s, 4OMe), 5.00-5.50 (10H, m, 4OCH<sub>2</sub>O, 2"-H and 6"-H), 6.41 (1H, s, 5'-H), 6.84 (1H, dd, J = 8.6 Hz, 2.2 Hz, 5-H), 6.88 (1H, d, J = 2.2 Hz, 3-H), 7.58 (1H, d, J = 8.6 Hz, 6-H), 7.86 (1H, d, J = 15.8 Hz, H<sub>a</sub>), 8.19 (1H, d, J = 15.8 Hz, H<sub> $\beta$ </sub>), 13.69 (1H, s, OH); IR (KBr)  $\nu_{\text{max}}$  1612  $cm^{-1}$ ; EIMS m/z [M]<sup>+</sup> 600 (11), 568 (2), 555 (76), 523 (10), 493 (7), 445 (27), 433 (8), 355 (12), 351 (10), 331 (43), 263 (35), 221(69), 69 (100); HREIMS m/z [M]+ 600.2910 (C<sub>33</sub>H<sub>44</sub>O<sub>10</sub> requires 600.2934

(*R*,*S*)-5,7,2',4'-**Tetramethoxymethoxy-8**-(1'-geranyl)flavanone (11). A solution of 10 (106 mg, 0.176 mmol) and anhydrous NaOAc (100 mg) in EtOH (1 mL) and  $H_2O$  (one drop) was refluxed with stirring for 24 h.  $H_2O$  was added to the reaction mixture, and then the mixture was extracted with  $Et_2O$ . After workup, the extract was purified by column chromatography to give recovered 10 (47 mg) and a yellow gum (11) (51 mg, 86% yield based on unrecovered starting mate-

rial): <sup>1</sup>H NMR  $\delta$  1.61, 1.67, 1.69 (3H each s, 8"-Me, 9"-Me, and 10"-Me), 1.95–2.15 (4H, m, 4"-2H and 5"-2H), 2.86 (2 H, d, J = 7.6 Hz, 3–2H), 3.33 (2H, J 7.1 Hz, 1"-2H), 3.48, 3.41, 3.58 (12H, each s, 4OMe), 5.00–5.30 (10H, m, 2"-H, 6"-H and 4OCH<sub>2</sub>O), 5.70 (1H, t, J = 7.6 Hz, 2-H), 6.58 (1H, s, 6-H), 6.79 (1H, dd, J = 8.3, 2 Hz, 5'-H), 6.85 (1H, d, J = 2 Hz, 3'-H), 7.52 (1H, d, J = 8.3 Hz, 6'-H); IR (KBr)  $\nu_{max}$  1681 cm<sup>-1</sup>; EIMS m/z [M]<sup>+</sup> 600 (1), 555 (3), 477 (2), 383 (1), 331 (3), 221 (3), 69 (9), 45 (100); HREIMS m/z [M]<sup>+</sup> 600.2920 (C<sub>33</sub>H<sub>44</sub>O<sub>10</sub> requires 600.2934).

(R,S)-5,7,2',4'-Tetrahydroxy-8-(1'-geranyl)flavanone (1). A solution of 11 (40 mg, 0.0667 mmol) in MeOH (5 mL) and 3N HCl (1 mL) was refluxed for 30 min, H<sub>2</sub>O (5 mL) was then added and the mixture extracted with EtOAc. After workup. the extract was purified by Si gel column chromatography eluting with petroleum ether-EtOAc (8:1) to afford a yellow oil (R,S)-1 (20 mg, 70% yield); <sup>1</sup>H NMR (acetone- $d_6$ )  $\delta$  1.60, 1.64, 1.66 (3H, each s, 5"-Me, 9"-Me, and 10"-Me), 1.90-2.30 (4H, m, 4"-2H and 5"-2H), 2.80 (1H, dd, J = 17.5, 3.2 Hz,  $3_{eq}$ -H), 3.10 (1H, dd, J = 17.5, 13.3 Hz,  $3_{ax}$ -H), 3.30 (2H, t, J = 7Hz, 1"-2H), 5.06 (1H, t, J = 6.5 Hz, 6"-H), 5.25 (1H, t, J = 7 Hz, 2"-H), 5.70 (1H, dd, J = 13.3, 3.2 Hz, 2-H), 6.05 (1H, s, 6-H), 6.45 (1H, dd, J = 8.3, 2 Hz, 5'-H), 6.49 (1H, d, J = 2 Hz, 3'-H), 7.38 (1H, d, J = 8.3 Hz, 6'-H), 12.42 (1H, s, OH); IR (KBr)  $v_{\text{max}}$  1625 cm<sup>-1</sup>; EIMS m/z [M]<sup>+</sup> 424 (25), 406 (10), 368 (5), 219 (100), 136 (10).

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## **References and Notes**

- Phillips, W. R.; Baj, N. J.; Gunatika, A. A. L.; Kingston, D. G. I. J. Nat. Prod. 1996, 59, 495–497.
- (2) Lincoln, D. E.; Walla M. D. Biochem. Systematics Ecol. 1986, 14, 195– 198.
- (3) Yakushijin, K.; Shibayama, K.; Murata, H. and Fuaukawa, H. *Heterocycles* 1980, 14, 397–401.
- (4) Hnawia, E.; Thoison, O.; Voelein, F. G.; Bourret, O.; Sevenet, T. *Phytochemistry* 1990, 29, 2367–2368.
- (5) Schutz, B. A.; Wright, A. D.; Rali, T.; Sticher, D. Phytochemistry 1995, 40, 1273–1277.

- (9) Bohlmann, F.; Abraham, W. R. *Phytochemistry* 1979, *18*, 1851–1853.
  (10) Linma, M.; Ohyama, M.; Tanaka, T., *Phytochemistry* 1995, 38, 539–
- 543.
- Chou, C. J.; Lin, L. C. J. Nat. Prod. **1992**, 55, 795-799.
  Allelula, I. L.; Braz, F. R.; Goltlieb, O. R.; Magalhes E. G.; Marques, R.; Phytochemistry **1978**, 17, 517-521.
  Montero, J. L.; Winterniz, F. Tetrehedron **1973**, 29, 1243-1252.
  Edwards, R. L.; Mir, L., J. Chem. Soc, Chem. Commun, **1967**, 411-412.
- 411 413.

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