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

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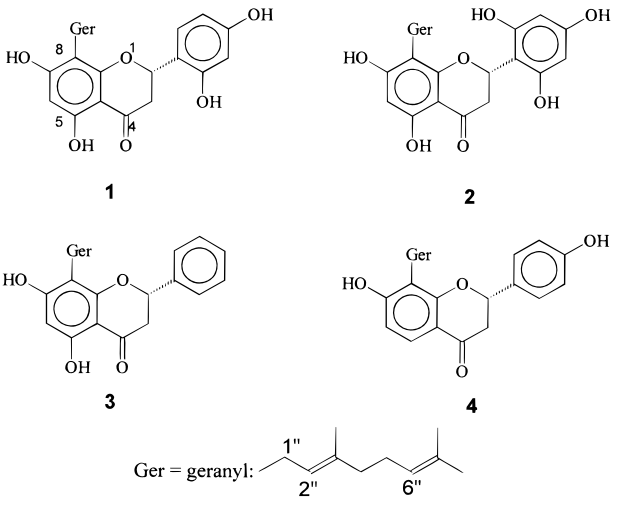
Sophoraflavanone C, a C-8 geranylflavanone natural product originally isolated from *Echinosophora koreensis*, has been synthesized in racemic form in six steps, starting from 2,4,6-trihydroxyacetophenone and 2,4-dihydroxybenzaldehyde.

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 antitumor[6] 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. ^{1}H NMR spectra were obtained in $CDCl_3$ 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 Me_2CO (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): ^{1}H 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, ^{1}HNMR 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 K_2CO_3 (966 mg, 7 mmol) in dry Me_2CO (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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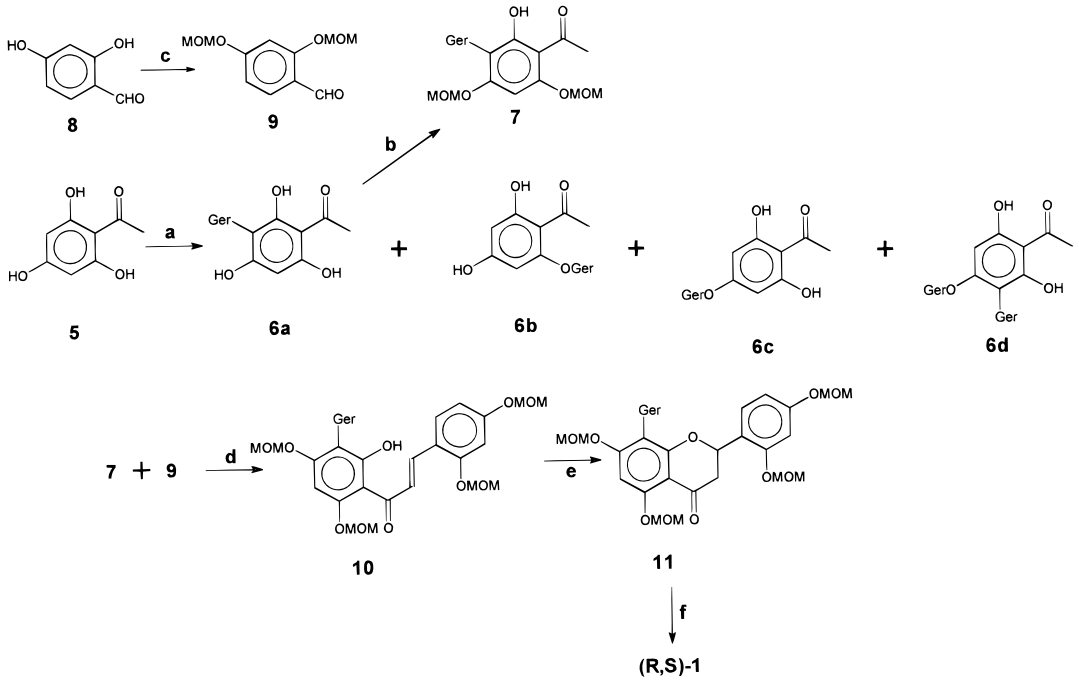
Scheme 1[a]



[a] Key: (**a**) geranyl bromide, Me2CO, K_2CO_3, reflux; (**b**) CH_3OCH_2Cl, K_2CO_3, Me_2CO, reflux; (**c**) CH_3OCH_2Cl, K_2CO_3, acetone, reflux; (**d**) KOH, H_2O-EtOH (v/v = 1:1), 0 °C ~ r.t; (**e**) NaOAc, EtOH, reflux; (**f**) 3NHCl, MeOH, reflux.

yield) as a deep red gum: ^{1}H NMR (400 MHz) δ 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_2O), 5.27 (2H, s, OCH_2O), 6.40 (1H, s, ArH), 13.85 (1H, s, OH); IR (KBr) ν_{max} 1617 cm^{-1}; EIMS m/z [M]$^+$ 392 (4), 347 (10), 273 (7), 269 (3), 225 (3), 69 (10), 45 (100); HREIMS m/z [M]$^+$ 392.2210 ($C_{22}H_{32}O_6$ requires 392.2199); a similar reaction of **8** with MOMCl gave **9** as a white solid, mp 47−48 °C [lit.[11] 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_2O−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_2O. The organic extract was washed with H_2O and brine, dried over anhydrous $MgSO_4$, 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: ^{1}H NMR δ 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_2O, 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_α), 8.19 (1H, d, J = 15.8 Hz, H_β), 13.69 (1H, s, OH); IR (KBr) ν_{max} 1612 cm^{-1}; EIMS m/z [M]$^+$ 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 ($C_{33}H_{44}O_{10}$ 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 material): ^{1}H NMR δ 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_2O), 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) ν_{max} 1681 cm^{-1}; EIMS m/z [M]$^+$ 600 (1), 555 (3), 477 (2), 383 (1), 331 (3), 221 (3), 69 (9), 45 (100); HREIMS m/z [M]$^+$ 600.2920 ($C_{33}H_{44}O_{10}$ 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_2O (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); ^{1}H NMR (acetone-d_6) δ 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 = 7 Hz, 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) ν_{max} 1625 cm^{-1}; EIMS m/z [M]$^+$ 424 (25), 406 (10), 368 (5), 219 (100), 136 (10).

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