Synthesis of Exiguaflavanone K and (±)-Leachianone G

Xianyong Bu and Yulin Li*

State Key Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou 730000, People's Republic of China

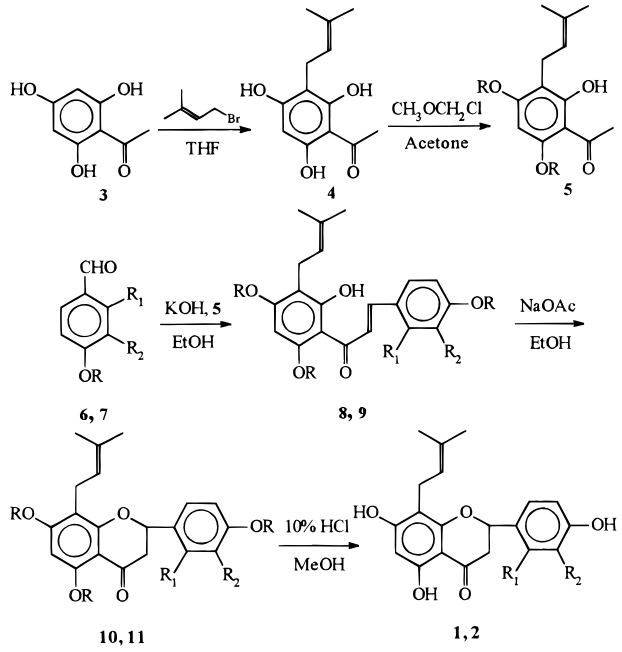
Received January 10, 1996[⊗]

The first total synthesis of two new natural prenylflavonoids, exiguaflavanone K (**1**) and (±)-leachianone G (**2**), has been achieved by condensation of 2-hydroxy-3-prenyl-4,6-dimethoxymethoxyacetophenone (**5**) with hydroxy-protected benzaldehydes **6** and **7**, respectively, followed by cyclization and demethoxymethylation.

Prenylflavonoids are of current interest due to their unique structures and biological activities.[1−5] In continuation of our systematic research on this class of flavonoids, we are now attempting to synthesize a series of new prenylflavonoids with a view to evaluating their biological properties. Herein we present the first total synthesis of two such compounds, exiguaflavanone K (**1**) and (±)-leachianone G (**2**), which were recently isolated from *Sophora exigua* and *Sophora leachiana*, respectively.[6,7]

The synthetic pathway is outlined in Scheme 1. The synthesis started with 2,4,6-trihydroxyacetophenone (**3**), which was prenylated with prenylbromide to furnish **4** according to the reported method.[8] Selective methoxymethylation of **4** with chloromethyl methyl ether and anhydrous K_2CO_3 in dry Me_2CO gave compound **5**.[9] Compounds **6** and **7** were achieved by treating vanillin and 2,4-dihydroxybenzaldehyde, respectively, with chloromethyl methyl ether. Condensation of **5** and **6** (or **7**) proceeded in aqueous alcoholic alkali yielding chalcone **8** or **9**. Compound **8** (or **9**) was cyclized by refluxing in a solution of NaOAc in EtOH to the flavanone **10** (or **11**). Demethoxymethylation of **10** and **11** was carried out in 10% HCl in CH_3OH to obtain the products **1** and **2**, respectively.

Scheme 1



	R_1	R_2
6, 8, 10	H	OMe
7, 9, 11	OMOM	H

	R_1	R_2
1	H	OMe
2	OH	H

Experimental Section

General Experimental Procedures. Mps were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Nicolet 170 XFT-IR spectrophometer in KBr disks. ^{1}H-NMR spectra were recorded at 80 MHz on AC-80 instruments in $CDCl_3$ with internal TMS (δ scale). MS were obtained using a ZAB-HS and HP-5988 mass spectrometer. Elemental analysis was performed with a MOD-1106 elemental analyzer.

Preparation of Chalcones (8,9). To a cold solution of the acetophenone **5** (0.3 mmol) and benzaldehyde **6** or **7** (0.33 mmol) in EtOH, a cooled solution of KOH (3.0 g) in H_2O−EtOH (1.2 mL−2.0 mL) solution was added with stirring. The resulting mixture was stirred under argon at room temperature for 36 h. The whole mixture was poured into ice-H_2O, acidified to pH = 2 with 1 N HCl, and extracted with CH_2Cl_2. The organic phase was washed with saturated $NaHCO_3$ and H_2O, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed over Si gel by elution with petroleum ether−EtOAc (4:1) to give chalcone **8** or **9**.

Compound 8 (84%): a yellow solid; mp 47−48 °C; IR 3112, 2995, 1624, 1581, 1155 cm^{-1}; ^{1}H NMR 1.77, 1.82 (each 3H, s, CH_3), 3.51 (3H, s, OCH_3), 3.54 (6H, s, OCH_3 × 2), 3.95 (3H, s, OCH_3), 4.58 (2H, d, J = 7 Hz, CH_2), 5.22 (2H, s, OCH_2O), 5.30 (4H, s, OCH_2O × 2), 5.60 (1H, t, J = 7 Hz, CH=), 6.08 (1H, s, H-5′), 6.23 (1H, d, J = 7 Hz, H-5), 7.14 (1H, d, J = 7 Hz, H-6), 7.19 (1H, s, H-2), 7.75 (1H, d, J = 16 Hz, CH_α=), 7.94 (1H, d, J = 16 Hz, CH_β=), 14.27 (1H, br s, OH); EIMS *m/z* $[M]^+$ 502, 457, 425, 381, 357, 325, 263, 221, 191, 165; *Anal.* calcd for $C_{27}H_{34}O_9$, C 64.53, H, 6.82; found C 64.46, H 6.75.

Compound 9 (84%): a yellow oil; IR 3326, 2956, 2925, 1609, 1557 cm^{-1}; ^{1}H NMR 1.69, 1.81 (each 3H, s, CH_3), 3.36 (2H, d, J = 7 Hz, CH_2), 3.52 (12H, br s, OCH_3 × 4), 5.08−5.26 (1H, m, CH=), 5.27 (8H, s, OCH_2O × 4), 6.42 (1H, s, H-5′), 6.78−6.91 (2H, m, H-3 and H-5), 7.59 (1H, d, J = 8 Hz, H-6), 7.88 (1H, d, J = 16 Hz, CH_α=), 8.17 (1H, d, J = 16 Hz, CH_β=), 13.88 (1H, br s, OH); EIMS *m/z* $[M]^+$ 532, 487, 455, 425, 387, 355, 309, 263, 219, 179; *Anal.* calcd for $C_{28}H_{36}O_{10}$, C 63.15, H 6.81; found C 63.23, H 6.88.

[⊗] Abstract published in *Advance ACS Abstracts,* September 1, 1996.

S0163-3864(96)00169-3 CCC: $12.00

Cyclization of 8 and 9. A solution of **8** (100 mg, 0.2 mmol) and NaOAc (300 mg) in EtOH (4.0 mL) with 3 drops of H_2O was refluxed for 24 h. The reaction mixture was diluted with cold H_2O (20 mL) and extracted with CH_2Cl_2. The organic layer was washed with H_2O and saturated NaCl solution and then dried (Na_2SO_4). The solution was evaporated to dryness, and the residue was chromatographed over Si gel. Elution with petroleum ether−EtOAc (4:1) gave 83 mg (82%) of flavanone **10** as a pale yellow solid: mp 68−69 °C; IR 2925, 1681, 1599, 1155 cm^{-1}; ^1H NMR 1.67 (6H, br s, $CH_3 \times 2$), 2.95 (2H, d, $J = 7$ Hz, H-3), 3.34 (2H, d, $J = 7$ Hz, H-1″), 3.49 (3H, s, OCH_3), 3.55 (6H, s, $OCH_3 \times 2$), 3.93 (3H, s, OCH_3), 5.02−5.20 (1H, m, H-2″), 5.48 (1H, t, $J = 7$ Hz, H-2), 5.28 (6H, s, $OCH_2O \times 3$), 6.59 (1H, s, H-6), 6.98 (1H, d, $J = 8$ Hz, H-5′), 7.03 (1H, s, H-2′), 7.21 (1H, d, $J = 8$ Hz, H-6′); FABMS *m/z* $[M]^+$ 502; *Anal*. calcd for $C_{27}H_{34}O_9$, C 64.53, H 6.82; found C 64.39, H 6.88.

Compound 11: using the previous procedure, cyclization of **9** (106 mg, 0.2 mmol) gave **11** (86 mg, 81%) as a yellow amorphous powder; IR 2958 (sh), 2910, 1682, 1598, 1154 cm^{-1}; ^1H NMR 1.68 (6H, br s, $CH_3 \times 2$), 2.86 (2H, d, $J = 8$ Hz, H-3), 3.33 (2H, d, $J = 7$ Hz, H-1″), 3.48, 3.49, 3.52, 3.56 (each 3H, s, OCH_3), 5.03−5.22 (1H, m, H-2″), 5.20 (4H, s, $OCH_2O \times 2$), 5.27 (4H, s, $OCH_2O \times 2$), 5.70 (1H, t, $J = 8$ Hz, H-2), 6.58 (1H, s, H-6), 6.69−6.88 (2H, m, H-3′ and H-5′), 7.52 (1H, d, $J = 8$ Hz, H-6′); EIMS *m/z* $[M]^+$ 532, 487, 456, 387, 355, 293, 263, 231, 209, 179; *Anal*. calcd for $C_{28}H_{36}O_{10}$, C 63.15, H 6.81; found C 63.07, H 6.74.

Demethoxymethylation of OH-Protected Flavanones 10 and 11. To a solution of **10** (50 mg, 0.1 mmol) in CH_3OH (5.0 mL), was added 10% HCl (1.0 mL). The resulting mixture was refluxed for 30 min, then poured into cold H_2O and extracted with CH_2Cl_2. The organic phase was washed with saturated $NaHCO_3$ solution and H_2O and then dried (Na_2SO_4). After removal of the solvent, the residue was chromatographed over Si gel. Elution with petroleum ether−EtOAc (4:1) gave 31 mg of **1** (84%), as a colorless amorphous powder; mp 140−141 °C; IR 3409 (br), 2931, 1643, 1586, 1157 cm^{-1}; ^1H NMR 1.76, 1.85 (each 3H, s, CH_3), 2.84−2.92 (2H, m, H-3), 3.32 (2H, d, $J = 6$ Hz, H-1″), 3.95 (3H, s, OCH_3), 5.36 (1H, dd, $J = 13$, 3 Hz, H-2), 5.66 (1H, m, H-2″), 5.98 (1H, s, H-6), 6.97 (2H, s, H-5′ and H-6′), 7.28 (1H, s, H-2′), 7.46, 11.78, 11.96 (each 1H, br s, OH); EIMS *m/z* $[M]^+$ 370, 355, 327, 315, 271, 221, 205, 192, 165, 150; *Anal*. calcd for $C_{21}H_{22}O_6$, C 68.10, H 5.99; found C 68.24, H 6.05.

Demethoxymethylation of **11** via the same procedure led to **2** (85%) as a colorless amorphous powder; mp 146−148 °C; IR 3218 (br), 2927, 1682, 1604, 1163 cm^{-1}; ^1H NMR 1.71, 1.80 (each 3H, s, CH_3), 2.91−3.14 (2H, m, H-3), 3.32 (2H, br d, $J = 7$ Hz, H-1″), 5.24 (1H, m, H-2″), 5.59 (1H, dd, $J = 13$, 3 Hz, H-2), 6.12 (1H, s, H-6), 6.44−6.54 (2H, m, H-3′ and H-5′), 7.28 (1H, d, $J = 8$ Hz, H-6′), 8.87, 12.01, 12.38 (each 1H, br s, OH); EIMS *m/z* $[M]^+$ 356, 338, 323, 295, 283, 270, 205, 177, 165, 136; *Anal*. calcd for $C_{20}H_{20}O_6$, C 67.41, H 5.66; Found C 67.50, H 5.76.

Acknowledgment. This project was financially supported by the Natural Science Foundation of China.

References and Notes

(1) Nikaido, T.; Ohmoto, T.; Fukai, T.; Sankawa, V. *Chem. Pharm. Bull.* **1984**, *32*, 4929−4934.
(2) Mitscher, L. A.; Park, Y. H.; Clark, D. *J. Nat. Prod.* **1980**, *43*, 259−269.
(3) Masao, C.; Shunn, S.; Kunio, H.; Hiroshi, M. *Jpn Kokai Tokkyo Koho* **1989**, 0113, 019; *Chem. Abstr.* **1989**, *111*, 214230j.
(4) Kunio, H.; Masao, C.; Hiroshi, M. *Jpn. Kokai Tokkyo Koho* **1987**, *62*, 185, 037; *Chem. Abstr.* **1988**, *108*, 74984u.
(5) Yukio, K.; Shigeshumi, T.; Kunio, H.; Hiroshi, M.; Toshihiko, W. *PCT Int. Appl. Wo88/8804* **1988**, *288*; *Chem. Abstr.* **1989**, *110*, 23539m.
(6) Iinuma, M.; Yokoyama, J.; Ohyama, M.; Tanaka, T.; Ruangrungsi, N. *Phytochemistry* **1994**, *35*, 785−789.
(7) Iinuma, M.; Ohyama, M.; Tanaka, T. *J. Nat. Prod.* **1993**, *56*, 2212−2215.
(8) Jakupovic, J.; Kuhnke, J.; Schuster, A.; Metawally, M. A.; Bohlmann, F. *Phytochemistry* **1986**, *25*, 1133−1142.
(9) Li, Y. L.; Zhao, L. Y. *Chin. Chem. Lett.* **1994**, *5*, 935−938; *Chem. Abstr.* **1995**, *122*, 105470u.

NP960169J