First total synthesis of two 5-deoxyflavone derivatives from *Albizia odoratissima*

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The first total synthesis of two unusual 5-deoxyflavone derivatives from *Albizia odoratissima*, 7,8-dimethoxy-3',4'-methyleneoxylavone 1 and 7,2',4'-trimethoxy-flavone 2, has been accomplished.

**Keywords:** synthesis, 5-deoxyflavone, derivatives

Flavonoids are widely distributed and are of interest because of their structural diversity, biological and ecological significance, health-promoting and anti-cancer properties. The two new unusual 5-deoxyflavone derivatives, 7,8-dimethoxy-3',4'-methyleneoxylavone 1 and 7,2',4'-trimethoxyflavone 2, were recently isolated from the root bark of a medicinal plant *Albizia odoratissima* (Mimosaceae) which is used in the treatment of leprosy, ulcers and coughs in traditional Indian medicine. We now report the total synthesis (see Scheme 1) of both 1 and 2 to confirm their structures and to provide material for further bioactive studies. The total synthesis of these two compounds has not been reported thus far.

Reagents and conditions: (i) Ac<sub>2</sub>O, conc. H<sub>2</sub>SO<sub>4</sub>, reflux; (ii) CH<sub>3</sub>I, K<sub>2</sub>CO<sub>3</sub>/Me<sub>2</sub>CO, reflux; (iii) KOH, H<sub>2</sub>O-EtOH (1:1, v/v), piperonal for 1 or 2, 4-dimethoxybenzaldehyde for 2; (iv) 1/2/DMO, conc. H<sub>2</sub>SO<sub>4</sub>, 100 °C, reflux.

Acetylation of 3a with Ac<sub>2</sub>O in the presence of traces of concd. H<sub>2</sub>SO<sub>4</sub> under reflux gave 4a.<sup>5</sup> Selective methylation of 4a with CH<sub>3</sub>I in dry acetone and anhydrous K<sub>2</sub>CO<sub>3</sub> on reflux afforded 5a.<sup>5</sup> The key intermediate 5a was condensed with piperonal in the presence of KOH in H<sub>2</sub>O/EtOH to provide 6a.<sup>24</sup> In the presence of traces of conc. H<sub>2</sub>SO<sub>4</sub>, compound 6a was cyclised and oxidised using a catalytic amount of iodine and DMSO to yield 1.<sup>9</sup> Similarly, compound 2 was prepared by the method mentioned above. The spectroscopic data (NMR, MS, and IR) of both synthetic flavonoids 1 and 2 were in agreement with those of the natural metabolites isolated from *Albizia odoratissima*.<sup>4</sup>

**Experimental**

Melting points were obtained on an XRC-1 apparatus and are uncorrected. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker AM-400 spectrometer operating at 400.13 and 100.61 MHz, respectively, with TMS as an internal standard. Mass spectra including HREIMS were recorded on a VG Auto Spec-3000 mass spectrometer at 70eV. IR spectra were recorded in KBr pellets on a Perkin Elmer FT-IR IR spectrophotometer. Column chromatography was performed over silica gel (200-300 mesh) with petroleum ether.

[Scheme 1]

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ethyl acetate. Analytical TLC was carried out on plates precoated with silica gel F254.

2,3,4-Trihydroxyacetophenone (4a) and 2,4-dihydroxyacetophenone (4b), and 2-hydroxy-3,4-dimethoxyacetophenone (5a) and 2-hydroxy-4-dimethoxyacetophenone (5b) were synthesised by the methods described previously.3,5

3,4-Methylenedioxy-3',4'-dimethoxy-2'-hydroxychalcone (6a): A solution of KOH (3 g, 0.035 mmol) in EtOH/H2O (5 ml: 1, 1/1 v/v) cooled to 0°C was added dropwise to a stirred ice cooled mixture of 5a (501 mg, 2.25 mmol) and piperonal (574 mg, 3.16 mmol) in EtOH (10 ml). The resulting mixture was stirred in an ice bath for 3 h, then for 42 h at room temperature. The reaction mixture was poured into iced water, and the pH of the solution was adjusted to 3−4 with 2 N HCl, then extracted with ethyl acetate (3 × 5 ml). The combined organic layers were washed with H2O and saturated brine, dried over anhydrous MgSO4, and evaporated under reduced pressure. The residue was purified by column chromatography on Si gel with petroleum ether/ethyl acetate (6:1, v/v) as eluent to afford chalcone 6a (503 mg, 60%) as a yellow solid. MS (EI): 328, 180, 165, 152, 148, 137, 135, 120, 106, 91, 89.1H NMR (400 MHz, CDCl3): δ 3.91 (s, 3H), 3.94 (s, 3H), 6.02 (s, 2H), 6.51 (d, 1H, J=9.1 Hz), 6.84 (d, 1H, J=8.0 Hz), 7.10 (d, 1H, J=1.6 Hz), 7.14 (dd, 1H, J=7.0, 1.6 Hz), 7.38 (d, 1H, J=15.3 Hz), 7.64 (d, 1H, J=9.1 Hz), 7.92 (d, 1H, J=15.3 Hz), 12.2 (s, 1H). 13C NMR (100 MHz, CDCl3): δ 56.1, 60.6, 101.7, 102.9, 106.7, 108.7, 115.7, 118.3, 125.4, 122.8, 129.3, 136.9, 144.5, 148.5, 150.1, 158.3, 158.5, 192.3. IR (KBr/cm−1): 3365, 1638, 1559, 1498. HREIMS m/z 328.1070 [M]+ (calcd for C19H18O3 328.1076).

3,4'-Trimethoxyfluavone-2'-hydrochalcone (6b): The synthesis of 6b was achieved by the same procedure as 6a. After the removal of the ethyl acetate under reduced pressure, the residue was crystallised from MeOH to give chalcone 6b as yellow amorphous powder (192 mg, 65%). MS (EI): 314, 283, 164, 152, 151, 138, 135, 121, 108, 95, 57. 1H NMR (400 MHz, CDCl3): δ 3.88 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 6.47-6.77 (m, 4H), 7.57 (d, 1H, J=8.6 Hz), 7.61 (d, 1H, J=15.5 Hz), 7.84 (dd, 1H, J=13.6, 8.9 Hz), 8.12 (d, 1H, J=15.5 Hz). 13C NMR (100 MHz, CDCl3): δ 55.3, 55.4, 55.5, 98.5, 100.9, 105.6, 107.3, 110.0, 114.3, 113.9, 118.3, 127.5, 131.2, 140.2, 160.5, 164.2, 165.2, 192.5. IR (KBr/cm−1): 3360, 1635, 1568, 1498. HREIMS m/z 314.1042 [M]+ (calcd for C19H16O3 314.1048).

7,8-Dimethoxy-3',4'-methylenedioxylavone (1): To a solution of 6a (204 mg, 0.62 mmol) in anhydrous DMSO (4 ml) was added a drop of conc. H2SO4. The reaction mixture was heated at 100°C for 10 h. After a catalyst amount of iodine (4 mg) was added, the mixture was refluxed for 8 h at 100°C, and then was quenched with ice-cold water (40 ml), filtered, washed with brine, and purified by crystallisation from acetone to afford 1 as pale yellow needles (133 mg, 65%). M.p. 243–245.5 °C. MS (EI): 326 (M+1) (100), 276, 181, 165, 152, 146, 137, 120, 109, 105. 1H NMR (400 MHz, CDCl3): δ 4.00 (s, 3H), 4.03 (s, 3H), 6.06 (s, 2H), 6.63 (s, 1H), 6.93 (d, 1H, J=8.2 Hz), 7.02 (d, 1H, J=9.0 Hz), 7.39 (d, 1H, J=1.8 Hz), 7.45 (dd, 1H, J=8.2, 1.8 Hz), 7.49 (d, 1H, J=9.0 Hz). 13C NMR (100 MHz, CDCl3): δ 56.5, 61.6, 101.9, 106.3, 106.8, 110.1, 118.8, 120.9, 121.4, 126.0, 137.0, 148.5, 150.5, 150.6, 156.6, 167.2, 177.9. IR (KBr/cm−1): 1650, 1611, 1596, 1548, 1450. HREIMS m/z 326.0965 [M]+ (calcd for C19H16O6, 326.0969).

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