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

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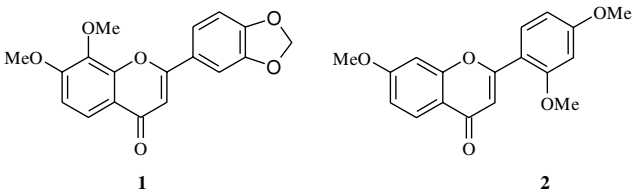
The first total synthesis of two unusual 5-deoxyflavone derivatives from *Albizia odoratissima*, 7,8-dimethoxy-3',4'-methylenedioxyflavone **1** and 7,2',4'-trimethoxy- flavone **2**, has been accomplished.

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.[1-3] Two new unusual 5-deoxyflavone derivatives, 7,8-dimethoxy-3',4'-methylenedioxyflavone (**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.[4] 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_2O, conc. H_2SO_4, reflux; (ii) CH_3I, K_2CO_3/Me_2CO, reflux; (iii) KOH, H_2O-EtOH (1:1, v/v), piperonal for **1** or 2, 4-dimethoxybenzaldehyde for **2**; (iv) I_2/DMSO, conc. H_2SO_4, 100 °C, reflux.

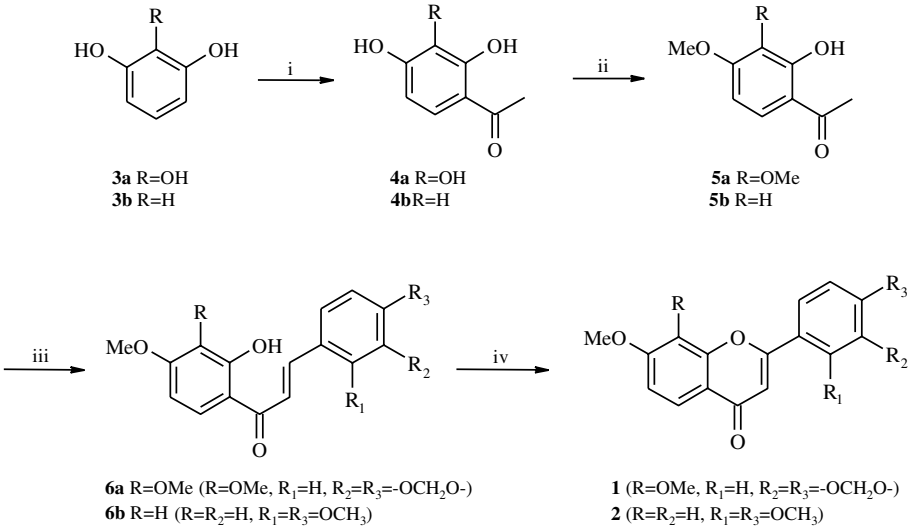
Acetylation of **3a** with Ac_2O in the presence of traces of concd. H_2SO_4 under reflux gave **4a**.[5] Selective methylation of **4a** with CH_3I in dry acetone and anhydrous K_2CO_3 on reflux afforded **5a**.[6] The key intermediate **5a** was condensed with piperonal in the presence of KOH in H_2O/EtOH to provide **6a**.[7,8] In the presence of traces of conc. H_2SO_4, compound **6a** was cyclised and oxidised using a catalytic amount of iodine and DMSO to yield **1**.[9] 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*.[4]



1 **2**

Experimental

Melting points were obtained on an XRC-1 apparatus and are uncorrected. ^{1}H NMR and ^{13}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/



3a R=OH
3b R=H

4a R=OH
4bR=H

5a R=OMe
5b R=H

6a R=OMe (R=OMe, R_1=H, R_2=R_3=-OCH_2O-)
6b R=H (R=R_2=H, R_1=R_3=OCH_3)

1 (R=OMe, R_1=H, R_2=R_3=-OCH_2O-)
2 (R=R_2=H, R_1=R_3=OCH_3)

Scheme 1

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ethyl acetate. Analytical TLC was carried out on plates precoated with silica gel F_{254}.

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.[5-7]

3,4-Methylenedioxy-3',4'-dimethoxy-2'-hydroxychalcone (**6a**): A solution of KOH (3 g, 0.053 mmol) in EtOH/H_2O (5 ml, 1:1, v/v) cooled to 0°C was added dropewise 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 ice 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 H_2O and saturated brine, dried over anhydrous $MgSO_4$, 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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), 13.2 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.1, 60.6, 101.7, 102.9, 106.7, 108.7, 115.7, 118.3, 125.4, 125.8, 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 $C_{18}H_{16}O_6$, 328.1076).

2,4,4'-Trimethoxyflavone-2'-hydroxychalcone (**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, 77. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 6.47-6.57 (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). ^{13}C NMR (100 MHz, $CDCl_3$): 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, 163.2, 165.8, 192.6. IR (KBr/cm^{-1}): 3360, 1650, 1559, 1498. HREIMS *m/z* 314.1042 [M]$^+$ (calcd for $C_{18}H_{18}O_5$, 314.1048).

7,8-Dimethoxy-3',4'-methylenedioxyflavone (**1**): To a solution of **6a** (204 mg, 0.62 mmol) in anhydrous DMSO (4 ml) was added a drop of conc. H_2SO_4. The reaction mixture was heated at 100°C for 10 min. 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. 243–243.5 °C. MS (EI): 326 (M$^+$) (100), 311, 181, 165, 152, 146, 137, 120, 109, 105. ^{1}H NMR(400 MHz, $CDCl_3$): 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), 7.52 (dd, 1H, *J*=8.2, 1.8 Hz), 7.93 (d,1H, *J*=9.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.5, 61.6, 101.9, 106.0, 106.3, 108.8, 110.0, 118.8, 120.9, 121.4, 126.0, 137.0, 148.5, 150.5, 150.6, 156.6, 162.7, 177.9. IR (KBr/cm^{-1}):1650,1611, 1596, 1548, 1450. HREIMS *m/z* 326.0965 [M]$^+$ (calcd for $C_{18}H_{14}O_6$, 326.0969).

7, 2', 4'-Trimethoxyflavone (**2**): Following the same procedure as the preparation of **1**. The only difference in the synthesis of **2** from **6b** was the last purification step. After removal of the ethyl acetate in vacuo, the residue was chromatographed over Si gel by using petroleum ether/ ethyl acetate (3:1, v/v) to afford **2** as pale yellow amorphous powder (53 mg, 55%). M.p. 126.5–128 °C. MS (EI): 312, 295, 281, 269, 226, 211, 163, 162, 151, 142, 119, 107, 91. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 6.54 (d, 1H, J=2.3 Hz), 6.62 (dd, 1H, J=8.7, 2.3 Hz), 6.91 (d, 1H, J=2.3 Hz), 6.95 (dd, 1H, J=8.8, 2.3 Hz), 7.08 (s, 1H), 7.86 (d, 1H, J=8.8 Hz), 8.11 (d, 1H, J=8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5, 55.6, 55.7, 98.9, 100.3, 105.3, 111.1, 113.7, 113.9, 117.7, 126.9, 130.3, 158.1, 159.6, 160.6, 163.1, 163.9, 178.4. IR (KBr/cm^{-1}): 1640, 1600, 1509, 1440, 1376. HREIMS m/z 312.0983 [M]$^+$ (calcd for $C_{18}H_{16}O_5$: 312.0986).

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