A novel synthesis of naringenin and related flavanones

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Efficient methods are reported for the preparation of naringenin (4',5,7-trihydroxyflavanone) which could be easily scaled-up. They have been applied to three other flavanones (6-hydroxyflavanone, 6,4'-dihydroxyflavanone, 6,3',4'-trihydroxyflavanone) suitably.

Keywords: naringenin, flavanone, acetylation, Fries rearrangement, Claisen–Schmidt condensation, demethylation

Naringenin (Fig. 1) (4′,5,7-trihydroxyflavanone) is used in traditional or alternative medicine. Human exposure to naringenin occurs primarily through its presence as a glycoside in many fruits and vegetables.[1] Naringenin acts as antioxidant, free radical scavenger, anti-inflammatory agent, carbohydrate metabolism promoter, and immune system modulator in man. It also has inhibitory effect which can change the pharmacokinetics in a human host of several popular drugs in an adverse manner.[2] It can reduce hepatitis C virus production by infected hepatocytes in cell culture.[3] The antiviral effects of naringenin are currently under investigation.[4] Hence, it is important to find an efficient synthetic route for the preparation of naringenin.[5] Hooper *et al.*[6] have been synthesised naringenin in seven steps with an overall yield of 25% This restricted large-scale production and is open to improvement. Among the published synthesis of naringenin[7–9], none is attractive for large-scale synthesis due to drawbacks such as long reaction times, low yields of the products, harsh reaction conditions, and the use of expensive and environmentally toxic catalysts. A simple and efficient method for the synthesis of naringenin is therefore desirable.

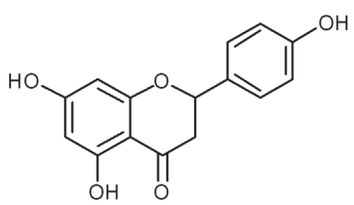

Fig. 1 Structure of naringenin.

We now describe a novel synthesis of naringenin which features better yields is more convenient and should be better for scaling-up. This method was then used for the preparation of other flavanones (Table 1), and we have continued further investigations of this area based on our studies of the structure–activity relationships of active compounds.[10–20] The synthetic route is described in Scheme 1. These flavanones are considered to be of biological and pharmaceutical importance.

Results and discussion

As shown in Scheme 1, compound **3** is an important intermediate for preparing naringenin. It was obtained by a reaction sequence starting from 1,3,5-trimethoxybenzene *via* Friedel–Crafts acylation and selective demethylation. Alternatively it was obtained using *m*-trihydroxybenzene as the starting material *via* acetylation, Fries rearrangement and methylation to protect phenolic hydroxy, but the yield was lower than the first method. Condensation of compound **3** with anisaldehyde using methanol sodium hydroxide resulted in the chalcone **5**, which was then treated with 15% aqueous HCl to afford flavanone **6**. However, further investigations showed that a one-pot reaction by increasing the concentration of KOH could produce compound **6** from compound **3** *via* a Claisen–Schmidt condensation. This method gave good yields. We also considered another route to obtain compound **1** in a one-pot reaction of 2,4,6-trihydroxyacetophenone with 4-hydroxybenzaldehyde under acid conditions. Unfortunately, this method gave low yields of the products and has an inconvenient separation because of the many phenolic hydroxyl groups. It requires further study.

The reaction c2 is the novel step of the synthesis and so the conditions were studied and optimised. Theoretically, the correct concentration of methanolic potassium hydroxide was important for a Claisen–Schmidt condensation. Therefore, we studied the correlation between the yield and the concentration of methanolic potassium hydroxide. The results showed that the reaction gave the highest yield when the concentration of methanol potassium hydroxide was 40% (Fig. 2).

Table 1 Related flavanones

Entry	Flavanone	Yield/%	M.p. (lit.)/°C
9A	6-Hydroxyflavanone	72	214–215 (213–214)[28]
10B	6,4'-Dihydroxyflavanone	71	231–232 (230)[30]
10C	6,3',4'-Trihydroxyflavanone	75.5	216–217 (218–220)[31]

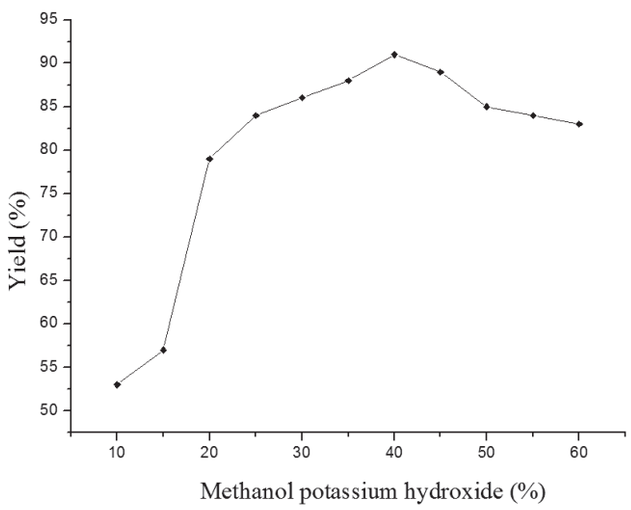

Fig. 2 Correlations between yields and the concentration of methanol KOH.

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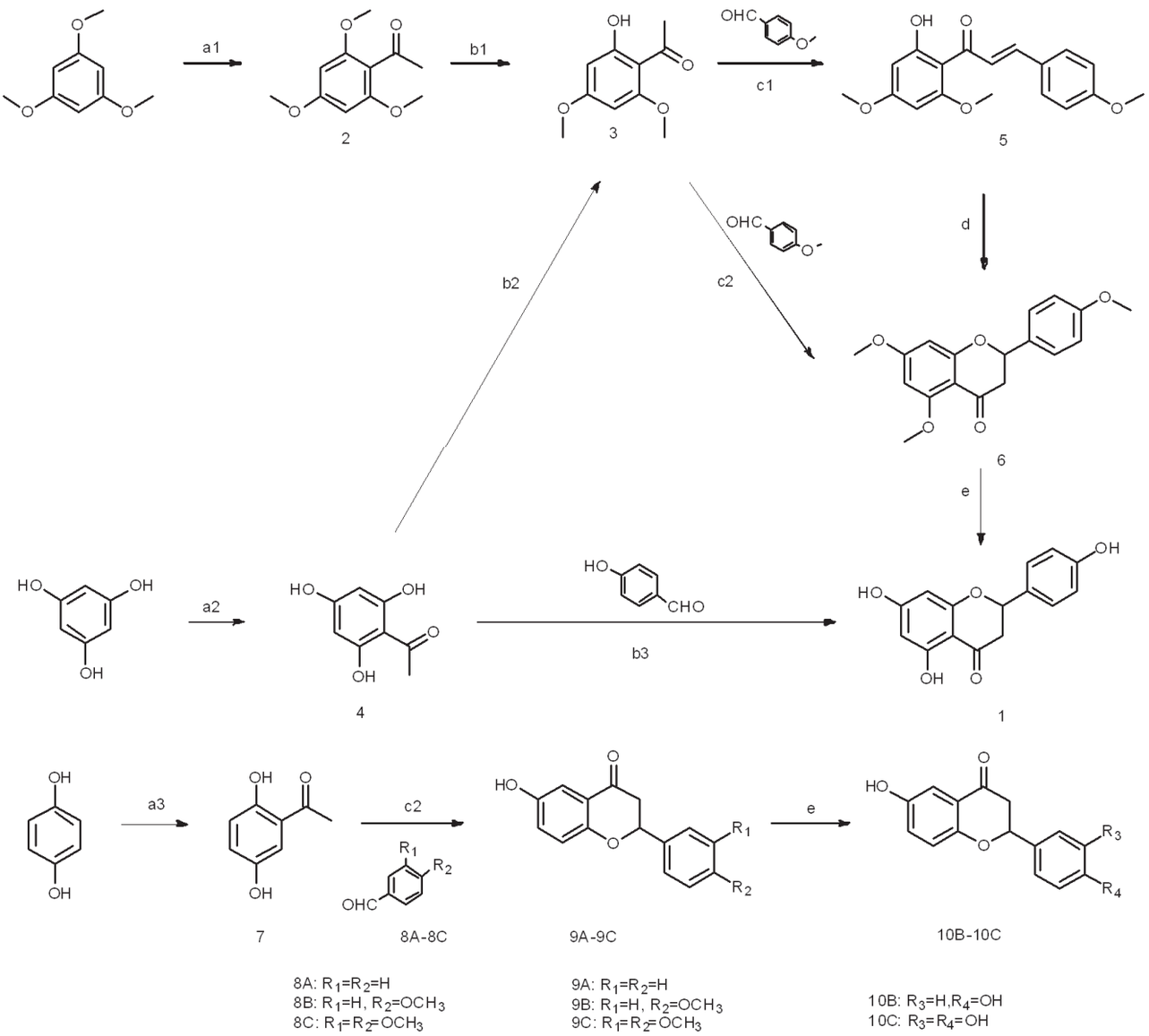

Scheme 1 Reagents and conditions: (a1) BF_3–Et_2O, Ac_2O, r.t., 4 h, 93%; (a2) BF_3–Et_2O, Ac_2O, 75 °C, 15 h, 67%; (a3) BF_3–Et_2O, Ac_2O, 120 °C, 3 h, 92%; (b1) BCl_3, CH_2Cl_2, 0 °C, r.t., 4 h, 90%; (b2) K_2CO_3, DMC, DMSO, 120 °C, 69%; (b3) 15% aqueous HCl, ethanol, r.t., 72 h, 45%; (c1) NaOH, methanol, r.t., 72 h, 83%; (c2) 40% aqueous KOH, methanol, r.t.,72 h; (d) 15% aqueous HCl, ethanol, r.t., 48 h, 73%; (e) pyridine HCl, 180 °C, 7 h.

In conclusion, we have found a better route for the synthesis of the compound **1** which proceeded overall with approximately 68% yield. This method not only has the advantages of mild conditions, easily accessible starting materials and facile separation, but it is also less expensive, more practical, and environmentally friendly. The most important feature is that it could be a promising method for the industrial synthesis of flavanone series and it should provide a general route for preparing higher analogues.

Experimental

All reactions were monitored by TLC and TLC was performed on silica gel GF254. Melting points were measured on a YRT-3 temperature apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DRX 500 NMR spectrometer and chemical shifts are reported in ppm (δ) relative to TMS as internal standard. IR spectra were recorded on Impact 400 FTIR instrument. All reagents were purchased from Aladdin-reagent, China, and used without further purification.

2,4,6-Trimethoxyacetophenone (**2**): A mixture of 1,3,5-trimethoxybenzene (6.7 g, 0.04 mol) and acetic anhydride (6 mL, 0.06 mol) in ethyl acetate (25 mL), was treated with BF_3–Et_2O (2.5 mL, 0.02 mol) dropwise. The reaction mixture was stirred at room temperature for 4 h. Then, H_2O (40 mL) was added and the reaction mixture was extracted with ethyl acetate (50 mL × 2). The combined extracts were washed sequentially with H_2O (100 mL × 2), saturated sodium bicarbonate (100 mL × 2) and H_2O (100 mL × 1) and then dried with anhydrous sodium sulfate overnight. Removal of the solvent *in vacuo* gave a solid residue, which was recrystallised from ethanol to give the compound **2** as white crystals (7.8 g), yield: 93%, m.p. 100–102 °C (lit.[21] 101–103 °C) ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 2.48 (s, 3H, $COCH_3$), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.12 (s, 1H, ArH), 6.13 (s, 1H, ArH). IR ν_{max} (KBr/cm^{-1}): 1704 (C=O).

2-Hydroxy-4,6-dimethoxyacetophenone (**3**): *Method (b1)*: A solution of compound **2** (4.2 g, 0.02 mol) in dichloromethane (20 mL) was treated dropwise at approximately 0 °C, with 1 mol L^{-1} BCl_3 in dichloromethane (24 mL, 0.024 mol) for about 0.5 h. Once the addition was completed, the reaction mixture was stirred at room temperature

for another 4 h. After completion of the reaction, H_2O (100 mL) was added and the mixture was stirred for another 1 h and extracted with dichloromethane (50 mL × 2). The organic layers were combined and washed sequentially with H_2O (100 mL × 2), saturated sodium bicarbonate (100 mL × 2) and H_2O (100 mL × 1). Then the extracts were dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give a solid. The residue was recrystallised from ethanol to give compound **3** (3.5 g), yield 90%, white crystals, m.p. 81–82 °C (lit.[22] 80–81 °C) ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 2.60 (s, 3H, $COCH_3$), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.92 (s, 1H, ArH), 6.05 (s, 1H, ArH), 14.02 (s, 1H, OH). IR ν_{max} (KBr/cm^{-1}): 3461 (OH), 1619 (C=O).

Method (b2): Compound **4** (2.5 g, 0.015 mol), K_2CO_3 (1.7 g, 0.01 mol), and DMC (7.5 mL, 0.09 mol) in DMSO (20 mL) were heated at 120 °C until TLC showed that compound **4** had disappeared. Then the mixture was cooled to room temperature and H_2O (30 mL) was added. The reaction mixture was neutralised to pH 3–4 with 10% aqueous HCl and the precipitate was filtered and recrystallised from methanol to give compound **3** (2.0 g), yield 69%, white crystals, m.p. 81–82 °C (lit.[22] 80–81 °C) ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 2.60 (s, 3H, $COCH_3$), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.92 (s, 1H, ArH), 6.05 (s, 1H, ArH), 14.02 (s, 1H, OH). IR ν_{max} (KBr/cm^{-1}): 3461 (OH), 1619 (C=O).

2,4,6-Trihydroxyacetophenone (**4**): *m*-Trihydroxybenzene (2.5 g, 0.02 mol) and acetic anhydride 4.5 mL (0.045 mol) were dissolved in ethyl acetate (10 mL), and BF_3–Et_2O 4 mL (0.032 mol) was added dropwise. The reaction mixture was heated at 75 °C for 15 h. Then, H_2O (20 mL) was added and the reaction mixture was extracted with ethyl acetate. After evaporation of the solvent, the crude products were purified by a silica-gel column chromatography with petroleum ether and CH_2Cl_2 (3 : 1) as eluent to give the desired compound **4** (2.25 g); yield 67%, yellow crystals, m.p. 222–223 °C (lit.[23] 221 °C) ^{1}H NMR (500 MHz, DMSO-d_6): 12.23 (s, 2H, OH), 10.38 (s, 1H, OH), 5.79 (s, 2H, ArH), 2.50 (s, 3H, $COCH_3$). IR ν_{max} (KBr/cm^{-1}): 3201 (OH), 1616 (C=O).

2′-Hydroxy-4,4′,6′-trimethoxychalcone (**5**): A mixture of compound **3** (0.98 g, 0.005 mol), anisaldehyde (0.85 g, 0.006 mol) and methanol (35 mL) was placed in a dry round-bottomed flask. Sodium hydroxide (4 g, 0.10 mol) was slowly added and the solution was stirred for approximately 72 h at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was neutralised to pH 3–4 with 10% aqueous HCl. The precipitate was filtered off, washed with water and recrystallised from ethanol to give compound **5** (1.3 g) as yellow crystals; yield 83%, m.p. 114–115 °C (lit.[24] 113–114 °C) ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 14.40 (s, 1H, OH), 7.83–7.77 (m, 2H, ArH), 7.57 (d, J = 8.5 Hz, 2H, ArH), 6.93 (d, J = 8.5 Hz, 2H, ArH), 6.11 (s, 1H, CH), 5.97 (s, 1H, CH), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3). IR ν_{max} (KBr/cm^{-1}): 3648 (OH), 1622 (C=O), 1580 (C=C).

4′,5,7-Trimethoxyflavanone (**6**): *Method (d)*: Compound **5** (2 g, 0.006 mol) and ethanol (10 mL) was placed in a dry round-bottomed flask, then 15% aqueous HCl (10 mL) was slowly added and the solution was stirred for 48 h at room temperature. The precipitate was filtered off and solvent was removed *in vacuo*. The crude material was recrystallised from H_2O to give compound **6** (1.37 g); yield 73%; almost white crystals, m.p. 122–123 °C (lit.[25] 124 °C) ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 7.70 (d, 2H, ArH), 7.01 (d, 2H, ArH), 6.14 (s, 1H, CH_2), 6.12 (d, 1H, ArH), 6.09 (d, 1H, ArH), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3).

Method (c2): A mixture of compound **3** (0.02 mol) and anisaldehyde (0.022 mol) was dissolved in methanol (20 mL), and 40% aqueous KOH 100 mL was added dropwise at approximately 0 °C. The solution was vigorously stirred for 72 h at room temperature. Then the reaction mixture was neutralised to pH 5 with 37% aqueous HCl. The precipitate was filtered off, washed with water and recrystallised from ethanol to give compound **6** (5.7 g); yield 91%; almost white crystals, m.p. 122–123 °C (lit.[25] 124 °C) ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 7.70 (d, 2H, ArH), 7.01 (d, 2H, ArH), 6.14 (s, 1H, CH_2), 6.12 (d, 1H, ArH), 6.09 (d, 1H, ArH), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3).

4′,5,7-Trihydroxyflavanone (**1**): *Method (e)*: A mixture of compound **6** (6.28 g, 0.02 mol) and excess pyridine hydrochloride (22.8 g, 0.20 mol) was heated at 180–190 °C for 7 h under an N_2 atmosphere. Then the mixture was cooled to room temperature and ethanol (25 mL) and H_2O (80 mL) were added. The reaction mixture was stirred for another 10 min. The precipitate was filtered off, washed with ethanol and recrystallised from ethanol to give compound **1** (4.84 g); yield 89%, yellow crystals, m.p. 253–254 °C (lit.[26] 247–250 °C) ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 12.15 (s, 1H, CH), 10.80 (s, 1H, ArH), 9.60 (s, 1H, ArH), 7.73–7.64 (m, 4H, ArH), 5.87 (s, 2H, OH), 5.48–5.37 (m, 1H, OH), 3.27 (dd, J = 17.2, 12.9 Hz, 1H, CH_2), 2.66 (dd, J = 17.0, 3.0 Hz, 1H, CH_2).

Method (b3): A mixture of compound **4** (3.36 g, 0.02 mol) and 4-hydroxybenzaldehyde (2.7 g, 0.022 mol) was dissolved in ethanol (20 mL), and 15% aqueous HCl 15 mL was added dropwise. The solution was vigorously stirred for 72 h at room temperature. The precipitate was washed with water and the crude product was purified by a silica-gel column chromatography with petroleum ether and EtOAc (8 : 1) as eluent to give the desired title compound (2.45 g); yield 45%, yellow crystals, m.p. 253–254 °C (lit.[26] 247–250 °C) ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 12.15 (s, 1H, CH), 10.80 (s, 1H, ArH), 9.60 (s, 1H, ArH), 7.73–7.64 (m, 4H, ArH), 5.87 (s, 2H, OH), 5.48–5.37 (m, 1H, OH), 3.27 (dd, J = 17.2, 12.9 Hz, 1H, CH_2), 2.66 (dd, J = 17.0, 3.0 Hz, 1H, CH_2).

2,5-Dihydroxyacetophenone (**7**): 1,4-Dihydroxybenzene (5.5 g, 0.05 mol) and dichloroethane (10 mL) were placed in a dry round-bottomed flask, then Ac_2O (10 mL, 0.1 mol) was slowly added. The solution was stirred for 4 h at 100 °C until TLC showed that 1,4-dihydroxybenzene had disappeared. BF_3–Et_2O (9 mL, 0.07 mol) was then added dropwise and the reaction mixture was heated to 120 °C and stirred for another 2–3 h. H_2O (40 mL) was then added and the reaction mixture was extracted with ethyl acetate (50 mL × 2). The combined extracts were washed sequentially with H_2O (100 mL × 2), saturated sodium bicarbonate (100 mL × 2) and H_2O (100 mL × 1) and then dried with anhydrous sodium sulfate overnight. Removal of the solvent *in vacuo* to give a solid residue, which was recrystallised from ethanol to give compound **7** as yellow crystals (7.0 g), yield: 92%, m.p. 195–198 °C (lit.[27] 197–199 °C) ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 2.6 (s, 3H, CH_3), 6.9 (s, 1H, OH), 7.2–7.3 (m, 3H, ArH), 11.8 (s, 1H, OH).

Synthesis of **9A**, **9B**, **9C**; *general procedure*

Method (c2): A mixture of compound **7** (0.02 mol) and compound **8** (0.022 mol) were dissolved in methanol (20 mL), and 40% aqueous KOH (100 mL) was added dropwise at approximately 0 °C. The solution was vigorously stirred for 72 h at room temperature. Then the reaction mixture was neutralised to pH 5 with 37% aqueous HCl. The precipitate was filtered off, washed with water and recrystallised from ethanol to give compound **9**.

6-Hydroxyflavanone (**9A**): White solid (4.3 g), yield: 89%, m.p. 214–215 °C (lit.[28] 213–214 °C) ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 7.49–7.31 (m, 5H, ArH), 7.09–6.51 (m, 3H, ArH), 5.43 (dd, 1H, CH), 4.96 (s, 1H, OH), 3.07 (dd, 1H, CH_2), 2.87 (dd, 1H, CH_2).

6-Hydroxy-4′-methoxyflavanone (**9B**): Light white solid (4.75 g), yield: 88%, m.p. 142–144 °C (lit.[29] 138 °C) ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 7.42–6.93 (m, 7H, ArH), 5.38 (dd, 1H, CH), 5.18 (s, 1H, OH), 3.84 (s, 3H, CH_3), 3.06 (dd, 1H, CH_2), 2.86 (dd, 1H, CH_2).

6-Hydroxy-3′,4′-dimethoxyflavanone (**9C**): Light white solid (5.52 g), yield: 92%, m.p. 284–285.5 °C ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 7.33–6.90 (m, 6H, ArH), 5.36 (dd, 1H, CH), 5.02 (s, 1H, OH), 3.93 (d, 6H, CH_3), 3.09 (dd, 1H, CH_2), 2.87 (dd, 1H, CH_2).

Synthesis of **10B**, **10C**; *general procedure*

Method (e): A mixture of compound **9** (0.02 mol) and excess pyridine hydrochloride (22.8 g, 0.20 mol) was heated at 180–190 °C for 7 h under a nitrogen atmosphere. Then the mixture was cooled to room temperature and ethanol (25 mL) and H_2O (80 mL) were added. The

reaction mixture was stirred for another 10 min. The precipitate was filtered off, washed with ethanol and recrystallised from ethanol to give compound **10**.

6,4′-Dihydroxyflavanone (**10B**): White solid (4.66 g), yield: 91%, m.p. 231–232 °C (lit.[30] 230 °C) ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 7.85–6.81 (m, 7H, ArH), 4.34 (dd, 1H, CH), 3.75 (dd, 2H, OH), 3.18 (dd, 1H, CH_2), 2.68 (dd, 1H, CH_2).

6,3′,4′-Trihydroxyflavanone (**10C**): Light white solid (5.1 g), yield: 93%, m.p. 216–217 °C (lit.[31] 218–220 °C) ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 7.99–5.83 (m, 6H, ArH), 3.77 (dd, 1H, CH), 2.79 (dd, 1H, OH), 2.59 (dd, 2H, OH), 2.04 (dd, 1H, CH_2), 1.93 (dd, 1H, CH_2).

This work was supported by National Natural Science Foundation of China (NSFC) (No.21062009), the Natural Science Foundation of Yunnan Province (No. 2011FZ059), and Science Foundation of Department of Education of Yunnan Province (No. 2011J077), which are gratefully acknowledged.

Received 20 September 2014; accepted 20 October 2014
Paper 1402900 doi: 10.3184/174751914X14145820775908
Published online: 13 November 2014

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