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Letters in Organic Chemistry, **2013**, *10*, 733-737

Efficient Synthesis of 6-*O*-methyl-scutellarein from Scutellarin *via* Selective Methylation

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Received March 23, 2013: Revised July 22, 2013: Accepted August 07, 2013

Abstract: Scutellarin (**1**) possesses distinguished efficacy in the clinical therapy of cerebral infarction, coronary heart disease, and angina pectoris. Scutellarin (**1**) is readily converted *in vivo*, therefore, synthetic methods for the construction of its metabolites will be very important in the near future. In this work, an efficient and first synthetic method for 6-*O*-methyl-scutellarein (**3**), one metabolite of scutellarin *in vivo*, is developed. Dichlorodiphenylmethane in diphenyl ether is used firstly to protect the dihydroxy groups at C-6 and C-7 in scutellarein (**2**). Then, benzyl bromide is used to selectively protect the hydroxy groups at C-4' and C-7 in **10**. 6-*O*-Methyl-scutellarein (**3**) is obtained in high yield through seven steps.

Keywords: 6-*O*-methyl-scutellarein, metabolite, scutellarin, synthesis, regioselective protection.

1. INTRODUCTION

Ischemic cerebrovascular disease, a common and frequently-occurring disease, seriously endangers human health, and it has been one of the leading causes of death and disability worldwide [1]. Scutellarin (**1**) (Fig. **1**), which is the main effective constituent (>85%) of a natural drug breviscapine consisting of total flavonoids of *Erigeron breviscapus* (Vant.) Hand-Mazz. (Compositae), has been used for the treatment of cerebral infarction, coronary heart disease, and angina pectoris with a large market share in China [2]. Pharmacological studies have demonstrated that scutellarin (**1**) is associated with a wide range of benefits to brain injury caused by cerebral ischemia/reperfusion, these benefits are due to its antioxidant and anticoagulant activities to attenuate neuronal damage [3-5].

Pharmacokinetic studies on scutellarin (**1**) in rats [6-8], dogs [9] and humans [10] showed that the oral bioavailability of scutellarin (**1**) was very poor [11]. One reason was its poor aqueous solubility and low lipophilicity [12]. Its poor ability to penetrate cell membranes has long been a major impediment to its overall effectiveness as an oral drug. The other reason was that scutellarin (**1**) is readily converted into scutellarein (**2**) (Fig. **1**) before absorption *in vivo*. Scutellarein (**2**) is relatively easily absorbed into the blood and can metabolite into glucuronidated, sulfated or methylated forms [13]. Due to the low bioavailability after oral administration, direct administration of scutellarin (**1**) by injection is the most common route in clinical application. Nonetheless, therapeutic effects elicited by breviscapine require repeated injection daily for a long time.

In order to improve the bioavailability of scutellarin, our group has synthesized many scutellarin derivatives [14-16], some compounds demonstrated stronger anticoagulant activity, better water solubility and good antioxidant activity compared with scutellarein. However, very few studies have focused on 6-*O*-methyl-scutellarein (**3**) (Fig. **1**), despite the fact that it was the one of the circulating metabolites of scutellarin *in vivo* and might be responsible for the therapeutic effects. This interesting scutellarin metabolite is not commercially available, as a result, synthetic methods will be very important for the preparation of large amount in order to further study its bioactivity. Because 6-*O*-methyl-scutellarein (**3**) was a metabolite *in vivo*, so the biosynthetic means such as liver microsomal preparation can be used [17,18], but this is not convenient and efficient for the preparation of large quantities [19].

In this work dichlorodiphenylmethane in diphenyl ether is used firstly to protect the dihydroxy groups at C-6 and C-7 in scutellarein (**2**). Then, benzyl bromide is used to selectively protect the hydroxy groups at C-4' and C-7 in **10**, 6-*O*-methyl-scutellarein (**3**) is obtained in high yield through seven steps.

2. RESULTS AND DISCUSSION

Firstly, our aim was to synthesize 6-*O*-methyl-scutellarein (**3**) based on the different reactive activity of hydroxyl groups in the preferential order 7 > 4′ > 6 > 5 [19] in the scutellarein (**2**) skeleton as shown in Scheme **1**.

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1875-6255/13 $58.00+.00

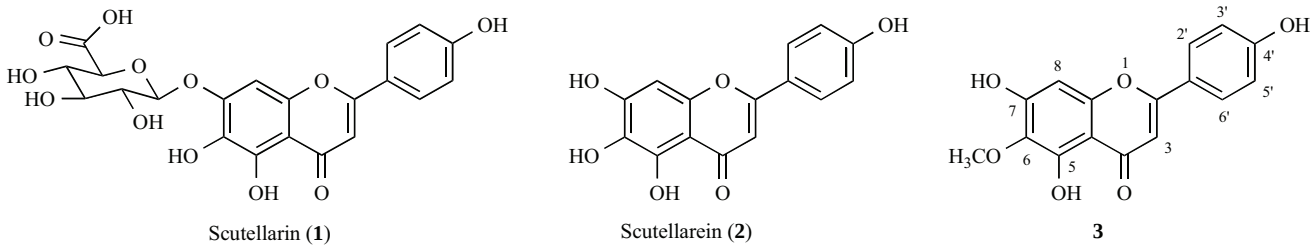
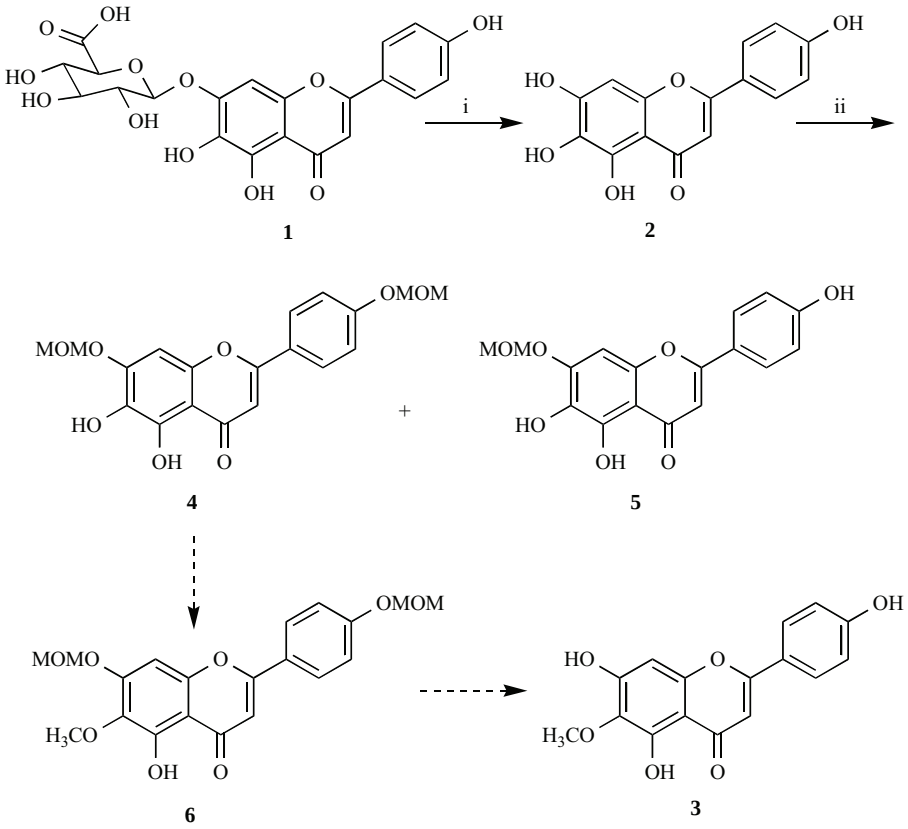


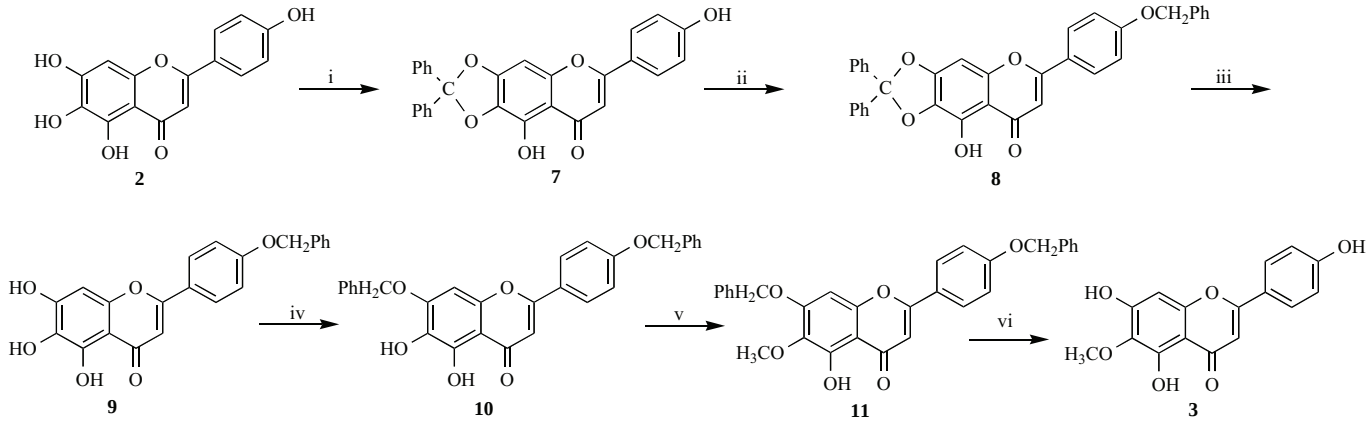
Fig. (1). Chemical structures of scutellarin (**1**), scutellarein (**2**) and 6-*O*-methyl-scutellarein (**3**).



Scheme 1. Reagents and conditions: (i) HCl, EtOH, N_2, reflux, 36h, 17%; (ii) MOMCl (3.5 equiv), K_2CO_3 (3.0 equiv), acetone, reflux, 4h, 45% for **4**, 30% for **5**.

According to our previous method [14, 15], the scutellarein (**2**) was obtained from the hydrolysis of scutellarin (**1**) by refluxing it with 6N HCl in 90% ethanol under N_2 protection. There are four hydroxyl groups in the flavone skeleton, however, the reactive activity of these four hydroxyl groups were different, and the most reactive hydroxyl group were at C-7 and C-4' [19]. So we decided to use the chloromethyl ether to protect the hydroxyl groups at C-7 and C-4' in scutellarein (**2**), and the treatment of **2** with 3.5 equiv. of chloromethyl ether in the presence of K_2CO_3 afforded two products **4** and **5**. The location of MOM groups in these two compounds was confirmed by ^{1}H NMR and ROESY. The ^{1}H NMR signal (in DMSO-d_6) at δ 12.76 of **4** suggested that 5-OH remained unchanged. A cross-peak observed in the ROESY spectrum of **4** between 5.35 (-OCH_2) with 6.69 (8-H) indicated that one of the two MOM groups was at C7, other cross-peaks between 5.22 (-OCH_2) with 7.05 (3′,5′-H) indicated that the second MOM group was at C4'. 7-OMOM in **5** was also confirmed by ROESY cross-peak between 5.35 (-OCH_2) with 6.66 (8-H). However, the polarity of these two compounds was very close, and they were hardly separated over silica gel column. Unfortunately, when we added more or less equiv. of chloromethyl ether in this reaction, the yield of **4** was not improved, furthermore, the tri-MOM substituted and tetra-MOM substituted byproducts appeared with more equiv. of chloromethyl ether, which increased the difficulty of the separate purification of **4**.

Then we turned our attention to the partial synthesis from scutellarein (**2**) as shown in (Scheme **2**), these reactions rely on successive and selective protection of the different hydroxyl groups in scutellarein (**2**). Firstly, we employed the method developed by us [20-22] and treated **2** with 1.5 equiv. of dichlorodiphenylmethane with diphenyl ether as solvent at 175 °C, after only 30 min, the desired product **7** was obtained in 85% yield. Taken into the account that the protecting groups of diphenylmethylene ketal and benzyl groups could be removed by the different reactive condition,



Scheme 2. Reagents and conditions: (i) a) Ph_2CCl_2 (1.5 equiv.), Ph_2O, 175 °C, 30min, 85%; (ii) $PhCH_2Br$ (1.5 equiv), K_2CO_3 (1.75 equiv), DMF, 25 °C, 12h, 93%; (iii) HAc: H_2O (4:1), reflux, 1.5h, 95%; (iv) $PhCH_2Br$ (1.3 equiv), K_2CO_3 (1.5 equiv), DMF, 25 °C, 12h, 93%; (v) CH_3I (1.2 equiv), K_2CO_3 (1.4 equiv), DMF, 25 °C, 6h, 94%; (vi) Pd/C (10 wt%), H_2 (1 atm), THF/EtOH, 8h, 96%.

we used 1.5 equiv. benzyl bromide to selectively protect the hydroxyl group at C-4' in compound **7** in the presence of K_2CO_3 afforded **8**. From compound **8**, we focused on the selection of the deprotection conditions of diphenylmethylene ketal, there are two available different methods for the cleavage of this protecting group: hydrogenolysis or hydrolysis. Fortunately, under hydrolysis conditions the diphenylmethylene ketal was deprotected with HAc in H_2O to give **9** in 95% yield and no side product was detected by TLC analysis. Selective benzylation of **9** with benzyl bromide and K_2CO_3 in DMF led to the di-benzyl ether substituted product **10**. The ROESY cross-peak between 5.03 (-OCH_2Ph) with 6.87 (8-H) indicated that one of the two benzyl group was at C7. The ROESY cross-peak between 5.23 (-OCH_2Ph) with 7.18 (3′,5′-H) indicated that the other benzyl group was at C4'. Treatment of **10** with 1.2 equiv. of iodomethane [19] led selectively to **11** with the desired 6-OH methylated product in 94% yield. Then the deprotection of di-benzyl groups under hydrogenation conditions using 10% palladium on carbon as the catalyst in THF/EtOH afforded **3** in 96% yield.

3. CONCLUSION

In conclusion, we have firstly succeeded in synthesizing 6-*O*-methyl-scutellarein (**3**) from scutellarin (**1**). Our strategy relies on the selective protection of the catechol group with dichlorodiphenylmethane using diphenyl ether as a solvent, and on the selective protection of the different hydroxyl groups at C-4' and C-7 with benzyl bromide. This efficient method could be applied to the selective synthesis of other *O*-methylflavonoids as well as the other flavonoid sulfate- and glucuronide-metabolites. These metabolites will assist the research on the structure activity relationship studies of flavonoids, and their easily obtained labeled form will give access to isotopic dilution dosage by LC–MS, and so will help in the identification of unknown flavonoid metabolites.

4. EXPERIMENTAL SECTION

Reagents and solvents were purchased from commercial sources and used without further purification unless otherwise specified. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at approximately 20 mm Hg. All non-aqueous reactions were carried out under anhydrous conditions using flame-dried glassware in an argon atmosphere in dry, freshly distilled solvents, unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.15–0.20 mm Yantai silica gel plates (RSGF 254) using UV light as the visualizing agent. Chromatography was performed on Qingdao silica gel (160–200 mesh) with petroleum ether (60–90) and ethyl acetate mixtures as eluant. ^{1}H NMR spectra were obtained with a Bruker AV-300 (300 MHz). Chemical shifts are recorded in ppm downfield from tetramethylsilane. *J* values are given in Hz. Abbreviations used are s (singlet), d (doublet), t (triplet), q (quartet), b (broad) and m (multiplet). ESI-MS spectra were recorded on a Waters Synapt HDMS spectrometer.

5,6,7-Trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (2)

To a stirring mixture of **1** (10.0 g, 20.6 mmol) and concentrated hydrochloric acid (120 mL) in ethanol (120 mL) was added water (10 mL), the reaction mixture was refluxed under a N_2 atmosphere for 36 h. After cooled down to the room temperature, the mixture was poured into water. The solid obtained was filtered followed by silica gel column chromatographic purification of the residue using 50% ethyl acetate in petroleum ether afforded the compound **2** in 17.0% yield as yellow solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.78 (s, 1H, 5-OH), 10.44 (s, 1H, 4'-OH), 10.29 (s, 1H, 7-OH), 8.71 (s, 1H, 6-OH), 7.90 (d, *J* = 8.8 Hz, 2H, 2',6'-H), 6.91 (d, *J* = 8.8 Hz, 2H, 3',5'-H), 6.74 (s, 1H, 3-H), 6.57 (s, 1H, 8-H); ESI-MS: m/z 287 $[M+H]^+$.

Synthesis of di-MOM Substituted Product 4 and mono-MOM Substituted Product 5

To a stirring mixture of **2** (2 g, 7 mmol) and K_2CO_3 (2.90 g, 21 mmol, 3 equiv) in dry acetone at room temperature was added chloromethyl ether (1.86 mL, 24.5 mmol, 3.5 equiv),

the reaction mixture was refluxed gently for 4 h. After cooling to room temperature, the reaction mixture was filtered. Removal of the solvent in vacuo followed by purification by column chromatography on silica gel of the residue with 20% ethyl acetate in petroleum ether afforded **4** (1.14g, 45%) and **5** (693mg, 30%) as yellow solids.

5,6-Dihydroxy-7-(methoxymethoxy)-2-(4-(methoxymethoxy)phenyl)-4H-chromen-4-one (4)

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.76 (s, 1H, 5-OH), 8.01 (d, 2H, J = 8.6 Hz, 2′,6′-H), 7.05 (d, 2H, J = 8.6 Hz, 3′,5′-H), 6.69 (s, 1H, 8-H), 6.61 (s, 1H, 3-H), 5.35 (s, 2H, -OCH_2), 5.22 (s, 2H, -OCH_2), 3.61 (s, 3H, -OCH_3), 3.52 (s, 3H, -OCH_3); ESI-MS: *m/z* 373 $[M-H]^-$.

5,6-Dihydroxy-2-(4-hydroxyphenyl)-7-(methoxymethoxy)-4H-chromen-4-one (5)

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.40 (s, 1H, 5-OH), 10.33 (s, 1H, 4′-OH), 8.02 (d, 2H, J = 8.6 Hz, 2′,6′-H), 7.04 (d, 2H, J = 8.6 Hz, 3′,5′-H), 6.66 (s, 1H, 8-H), 6.60 (s, 1H, 3-H), 5.35 (s, 2H, -OCH_2), 3.50 (s, 3H, -OCH_3); ESI-MS: *m/z* 329 $[M-H]^-$.

9-Hydroxy-6-(4-hydroxyphenyl)-2,2-diphenyl-8H-[1,3]dioxolo[4,5-g]chromen-8-one (7)

To a stirring mixture of scutellarein (**2**) (10 g, 35 mmol) in diphenyl ether (200 ml) was added dichlorodiphenylmethane (18 g, 52.5 mmol, 1.5 equiv), and the reaction mixture was heated at 175 °C for 30 min. The mixture was cooled to room temperature and petroleum ether (1000 ml) was added to give a solid compound. Then the solid was filtered and purified by column chromatography (25% ethyl acetate in petroleum ether) to yield **7** (13.35 g, 85%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.99 (s, 1H, 5-OH), 10.41 (s, 1H, 4′-OH), 7.94 (d, 2H, J = 8.7 Hz, 2′,6′-H), 7.58-7.61 (m, 4H, -Ph), 7.47-7.50 (m, 6H, -Ph), 6.96 (d, 2H, J = 8.7 Hz, 3′,5′-H), 6.82 (s, 1H, 8-H), 6.69 (s, 1H, 3-H); ESI-MS: m/z 449 $[M-H]^-$.

6-(4-(Benzyloxy)phenyl)-9-hydroxy-2,2-diphenyl-8H-[1,3]dioxolo[4,5-g]chromen-8-one (8)

To a stirring solution of **7** (200 mg, 0.44 mmol) in DMF (10 ml) was added K_2CO_3 (107 mg, 0.78 mmol, 1.75 equiv) and benzyl bromide (0.078 ml, 0.66 mmol, 1.5 equiv). After stirring at 0 °C for 2 h, the reaction mixture was allowed to warm to room temperature and the stirring was maintained for 12 h. Then the reaction mixture was partitioned between 100 ml ethyl acetate and 100 ml water, and the organic layer was washed with brine (100 ml), dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (33% ethyl acetate in petroleum ether) to yield the tribenzylether **8** (221 mg, 93% yield) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.10 (s, 1H, 5-OH), 10.40 (s, 1H, 4′-OH), 8.04 (d, 2H, J = 8.7 Hz, 2′,6′-H), 7.55-7.61(m, 4H, -Ph), 7.32-7.48 (m, 11H, -Ph), 7.22 (d, 2H, J = 8.7 Hz, 3′,5′-H), 7.08 (s, 1H, 8-H), 6.95 (s, 1H, 3-H), 5.22 (s, 2H, -OCH_2); ESI-MS: *m/z* 541 $[M+H]^+$.

2-(4-(Benzyloxy)phenyl)-5,6,7-trihydroxy-4H-chromen-4-one (9)

The solid **8** (150 mg, 0.28 mmol) was dissolved in 20 ml of HOAc/H_2O (4:1) solution and the reaction mixture was refluxed under a N_2 atmosphere for 1.5 h. After cooled down to the room temperature, the mixture was poured into 100 ml water, extracted with ethyl acetate (50 ml×3), then the organic layer was washed with brine (100 ml), dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (25% ethyl acetate in petroleum ether) to yield the **9** (100 mg, 95% yield) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.69 (s, 1H, 5-OH), 10.35 (s, 1H, 7-OH), 8.74 (s, 1H, 6-OH), 7.94 (d, 2H, J = 8.7 Hz, 2′,6′-H), 7.51-7.54 (m, 2H, -Ph), 7.35-7.45 (m, 3H, -Ph), 7.00 (s, 1H, 8-H), 6.92 (d, 2H, J = 8.7 Hz, 3′,5′-H), 6.81 (s, 1H, 3-H), 5.28 (s, 2H, -OCH_2); ESI-MS: *m/z* 375 $[M-H]^-$.

7-(Benzyloxy)-2-(4-(benzyloxy)phenyl)-5,6-dihydroxy-4H-chromen-4-one (10)

To a stirring solution of **9** (200 mg, 0.53 mmol) in dry DMF (20 ml) was added K_2CO_3 (109 mg, 0.80 mmol, 1.5 equiv.) and benzyl bromide (0.08 mL, 0.68 mmol, 1.3 equiv.) at 0 °C, then the mixture was warmed to room temperature. After 12 h, the reaction mixture was partitioned between 100 ml ethyl acetate and 100 ml water. The ethyl acetate layer was then washed with brine (100 ml), dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (25% ethyl acetate in petroleum ether) to yield dibenzylether **10** (230 mg, 93% yield) as yellow solids. ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.11 (s, 1H, 5-OH), 10.82 (s, 1H, 6-OH), 8.04 (d, 2H, J = 8.6 Hz, 2′,6′-H), 7.31-7.53 (m, 10H, -Ph), 7.18 (d, 2H, J = 8.6 Hz, 3′,5′-H), 6.87 (s, 1H, 8-H), 6.62 (s, 1H, 3-H), 5.23 (s, 2H, -OCH_2), 5.03 (s, 2H, -OCH_2); ESI-MS: *m/z* 465 $[M-H]^-$.

7-(Benzyloxy)-2-(4-(benzyloxy)phenyl)-5-hydroxy-6-methoxy-4H-chromen-4-one (11)

To a stirring solution of **10** (84 mg, 0.18 mmol) in dry DMF (20 ml) was added K_2CO_3 (48 mg, 0.35 mmol, 1.4 equiv.) and iodomethane (0.014 ml, 0.22 mmol, 1.2 equiv.) at room temperature. After 12 h, the reaction mixture was then partitioned between 100 ml ethyl acetate and 100 ml water. The ethyl acetate layer was then washed with brine (100 ml), dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (25% ethyl acetate in petroleum ether) to yield **11** (81 mg, 94% yield) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.69 (s, 1H, 5-OH), 7.94 (d, 2H, J = 8.6 Hz, 2′,6′-H), 7.44-7.54 (m, 4H, -Ph), 7.32-7.42 (m, 6H, -Ph), 7.00 (s, 1H, 8-H), 6.94 (d, 2H, J = 8.6 Hz, 3′,5′-H), 6.62 (s, 1H, 3-H), 5.28 (s, 2H, -OCH_2), 4.95 (s, 2H, -OCH_2), 4.00 (s, 3H, -OCH_3); ESI-MS: *m/z* 481 $[M+H]^+$.

5,7-Dihydroxy-2-(4-hydroxyphenyl)-6-methoxy-4H-chromen-4-one (3)

To a solution of **11** (100 mg, 0.21 mmol) dissolved in ethanol (10 ml) and THF (10 ml) was added 10% Pd/C (2 mg) with vigorous stirring. The reaction vessel was then

evacuated and the atmosphere replaced with hydrogen. After 8 h, the reaction mixture was filtered and the filtrate was concentrated. The crude material was purified by column chromatography (50% ethyl acetate in petroleum ether) to yield **3** (60 mg, 96%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.76 (s, 1H, 5-OH), 10.72 (s, 1H, 7-OH), 10.19 (s, 1H, 4′-OH), 7.87 (d, 2H, J = 8.6 Hz, 2′,6′-H), 6.89 (d, 2H, J = 8.6 Hz, 3′,5′-H), 7.11 (s, 1H, 8-H), 6.58 (s, 1H, 3-H), 3.72 (s, 3H, -OCH_3); ESI-MS: *m/z* 299 $[M-H]^-$.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by National Natural Science Foundation of China (No. 81001382, 81274058, 21302225), the Program for New Century Excellent Talents by the Ministry of Education (NCET-12-0741), 333 High-level Talents Training Project Funded by Jiangsu Province, Program by the Fundamental Research Funds for the Central Universities (JKQ2011001), National Key Technology R&D Program (2008BAI51B01), Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (ysxk-2010), and Construction Project for Jiangsu Engineering Center of Innovative Drug from Blood-conditioning TCM Formulae.

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