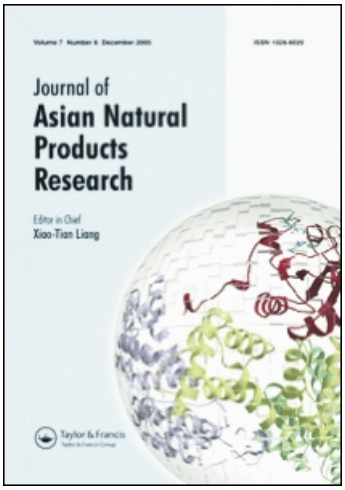

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Total synthesis of scutellarin-7-*O*-Glucuronide

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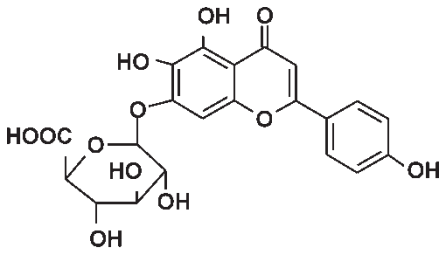
Scutellarin-7-*O*-glucuronide (**1**) has been synthesized from 2-hydroxyl-4,5,6-trimethoxyacetophenone through eight steps, including Michael addition, cyclization, hydrogenation, hydroxyl protection, deprotection, *etc.* The overall yield of 13% is much higher than that reported (0.6%) by L. Farkas, G. Mezey-Vàndor *et al.* in 1974.

Keywords: Scutellarin-7-*O*-glucuronide; Cyclization; Hydroxyl protection; Deprotection

1. Introduction

Scutellarin-7-*O*-glucuronide (**1**) is a flavone that has been isolated from *Erigeron breviscapine* (*van.t*) Hand. Mass., a traditional Chinese medicine widely used to treat cardio-cerebral-vascular diseases [1]. The main source relies on extraction from the plants. Until now, the only synthesis of this compound was reported by L. Farkas *et al.* in 1974, using an Aldol condensation, substitution reaction of bromine and so on from 2,5-dihydroxyl-4,6-dimethoxyacetophenone in eight steps [2–5] in 0.6% total yield. Herewith report a new facile synthetic route to **1**.



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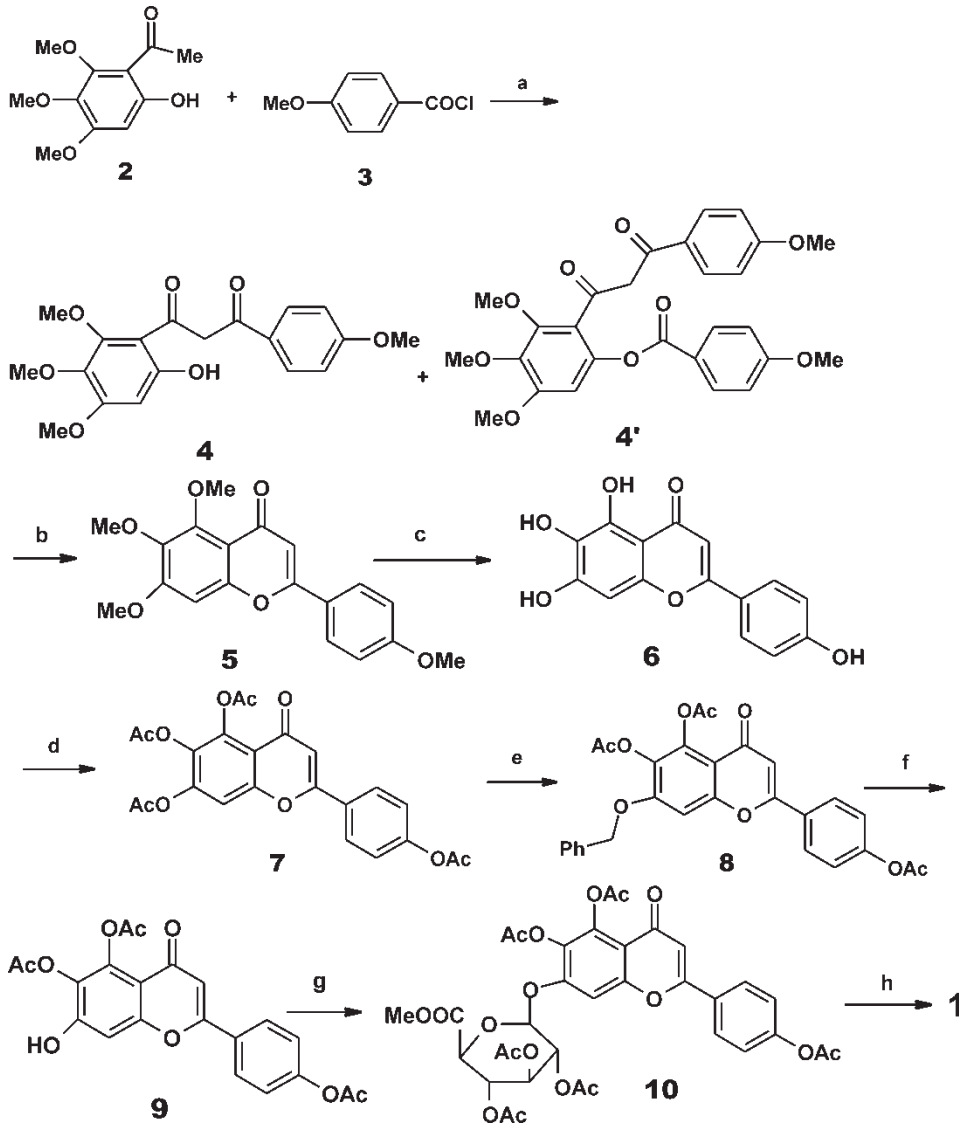
2. Results and discussion

As shown in scheme 1, scutellarin-7-*O*-glucuronide (**1**) has been synthesized from 2-hydroxy-4,5,6-trimethoxyacetophenone (**2**) in eight steps. Acetylation of **2** with **3** affords **4**, which through cyclization yields 5,6,7,4′-tetramethoxyflavone (**5**). Deprotection of **5** with pyridine hydrochloride affords compound **6** in good yield. Protection of the hydroxyl group with acetic anhydride then gives **7** in 94% yield. Protection of the 7-hydroxyl of compound 7 with benzyl chloride affords **8**, and subsequent hydrogenolysis of the benzyl



Scheme 1. Reagents and conditions: (a) (1) pyridine, reflux 3 h and (2) KOH, 60°C, 74%; (b) HAc, NaAc, reflux 3 h, 64%; (c) pyridine HCl, 190–200°C, 4 h, 93%; (d) Ac_2O, pyridine, reflux 2 h, 94%; (e) $PhCH_2Cl$, KI, K_2CO_3, acetone, reflux 4 h, 65%; (f) Pd–C, H_2, room temperature, 70%; (g) AgO, quinoline, $CaSO_4$, methyl (tri-*O*-acetyl-α-D-glucopyranurosyl bromide)-uronate, room temperature, 4 h, 95%; (h) NaOH, acetone, 0°C, 1 h, 70%.

group furnishes compound **9**. Glycosylation of methyl (tri-*O*-acetyl-α-D-glucopyranurosyl bromide)-uronate to compound **9** affords **10** in high yield. Finally, compound **1** is obtained by the hydrolysis of **10**. The total yield is 13%, a marked improvement on the 0.6% of L. Farkas *et al.* in 1974. Especially, the method of synthesis of compound **7** is a new and efficient approach.

3. Experimental

3.1 General experimental procedures

Melting points were obtained on a YRT-3 Temp apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 2401 MC Autopol polarimeter. ^{1}H NMR spectra were recorded on a Varian Mercury-300, Varian Inova-500 NMR spectrometer, and mass spectra on a ZAB-2F Mass spectrometer. TLC was carried out on silica gel layers (Qingdao Haiyang Chemical Co., Ltd).

3.2 2-Hydroxy-4,5,6-trimethoxy-ω-(4-methoxybenzoyl)acetophenone (4)

A dry round-bottomed flask equipped with a reflux condenser charged with compound **2** (127 g, 0.56 mol), *p*-methoxybenzoyl chloride (127 g, 0.74 mol), and dry pyridine (402 mL) was heated at 120°C for 3 h. The mixture was then poured into a mixture of ice and hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and aqueous sodium carbonate and dried over sodium sulfate. The solvent was then evaporated under reduced pressure to give the crude product. To a solution of the crude product in pyridine (400 mL) was added freshly powdered potassium hydroxide (160 g), and the resultant mixture was vigorously stirred at 60°C for 4 h and then poured into a mixture of ice and hydrochloric acid and extracted with ethyl acetate. The extract was washed with diluted hydrochloric acid and aqueous sodium carbonate, and the solvent was evaporated. The residue was recrystallized from methanol to give 2-hydroxy-4,5,6-trimethoxy-ω-(4-methoxy-benzoyl)acetophenone (**4**) as yellow crystals (150 g, 74%); mp 110–112°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 15.74 (s, 1H, $-CH_2-$), 13.26 (s, 1H, $-CH_2-$), 12.88 (s, 1H, –OH), 7.88–7.96 (dd, 2H, Ar–H, $J = 9$ Hz), 6.95–6.98 (d, 2H, Ar–H, $J = 8.4$ Hz), 6.24–6.28 (d, 1H, Ar–H, $J = 13.2$ Hz), 3.93–3.64 (m, 12H, $4 \times -OCH_3$); MS *m/z* (%): 360 (M^+, 30), 329 ($M^+ - OCH_3$, 20), 210 ($M^+ - CH_2CO-C_6H_4-OCH_3$, 19), 135 ($CH_3O-C_6H_4 - CO^{\cdot}$, 100).

3.3 5,6,7,4′-Tetramethoxyflavone (5)

A mixture of compound **4** (131 g, 0.36 mol) and anhydrous sodium acetate (122 g, 1.49 mol) in acetic acid (900 mL) was heated at 140–145°C for 3–4 h, diluted with water, and then extracted with ethyl acetate. The extract was washed with aqueous sodium carbonate, and the solvent was evaporated. The resultant residue was recrystallized from methanol to give compound 5 (80 g, 64%); mp 158–161°C (Lit. [3] 158–160°C]; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.79, 7.82 (d, 2H, $C_2'C_6'$-H, $J = 8.7$ Hz), 6.96, 6.99 (d, 2H, $C_2'C_6'$-H, $J = 8.7$ Hz),

6.78 (s, 1H, C_3-H), 6.61 (s, 1H, C_8-H), 3.97 (s, 6H, $2 \times -OCH_3$), 3.90 (s, 3H, $-OCH_3$), 3.86 (s, 3H, $-OCH_3$); MS *m/z* (%): 342 (M^+, 19), 327 ($M^+ - CH_3$, 100).

3.4 5,6,7,4′-Tetrahydroxyflavone (6)

A three-necked round-bottomed flask equipped with a reflux condenser was charged with excess pyridine hydrochloride (97 g, 0.84 mol) and compound **5** (18 g, 0.05 mol) under an N_2 atmosphere. The mixture was then heated at 190–200°C, and refluxed for 5–6 h. The resultant hot dark mixture was poured into 12 M HCl (300 mL), and the reaction mixture was stirred for 1 h and then filtered. The so-obtained solid was washed with dilute hydrochloric acid to give a yellow solid (**6**) (14 g, 93%); mp 290–293°C (Lit. [4] 158–160°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 12.37 (s, 1H, C_4'-OH), 10.44 (s, 1H, C_5-OH), 10.31 (s, 1H, C_7-OH) 8.74 (s, 1H, C_6-OH), 8.01, 7.98 (d, 2H, $C_2'C_6'$-H, $J = 8.7$ Hz), 6.92, 6.89 (d, 2H, $C_3'C_5'$-H, $J = 8.7$ Hz), 6.73 (s, 1H, C_3-H), 6.24 (s, 1H, C_8-H); ^{1}H NMR (300 MHz, $D_2O + CDCl_3$): 7.99, 7.96 (d, 2H, $C_2'C_6'$-H, $J = 9$ Hz), 6.93, 6.90 (d, 2H, $C_3'C_5'$-H, $J = 9$ Hz), 6.70 (s, 1H, C_3-H), 6.25 (s, 1H, C_8-H); FABMS *m/z* (%): 287 ($M^+ + 1$, 7), 223 ($287 - CO - 2 \times H_2O$, 17).

3.5 5,6,7,4′-Tetraacetoxyflavone (7)

A dry round-bottomed flask equipped with a reflux condenser was charged with compound **6** (14 g, 0.05 mol) and acetic anhydride (260 mL) in pyridine (180 mL). The mixture was then boiled under reflux for 4 h at 140–145°C and the excess acetic anhydride and pyridine was evaporated. The residue was recrystallized with methanol to give **7** (21 g, 94%); mp 250–252°C (Lit. [4] 252–253°C); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.88, 7.86 (d, 2H, $C_2'C_6'$-H, $J = 5.4$ Hz), 7.49 (s, 1H, C_3-H), 7.27, 7.26 (d, 2H, $C_3'C_5'$-H, $J = 1.8$ Hz), 6.61 (s, 1H, C_8-H), 2.44–2.34 (m, 12H, $-COCH_3$); FABMS *m/z* (%): 455 ($M^+ + 1$, 5), 413 ($M^+ + 1 - COCH_2$, 12), 341 ($413 - CO - COCH_2 + H$, 29), 313 ($341 - CO$, 12).

3.6 7-Benzyloxy-5,6,4′-triacetoxyflavone (8)

A round-bottomed flask equipped with a reflux condenser was charged with the **7** (21 g, 0.05 mol), K_2CO_3 (52.5 g, 0.38 mol), KI (2.1 g, 12.6 mmol) and $PhCH_2Cl$ (23 mL) in dry acetone (600 mL). The mixture was then heated at 40–45°C for 4 h, diluted with water and extracted with CH_2Cl_2. The extract was dried and evaporated, and the residue was recrystallized from ethanol to give a white solid **8** (15 g, 65%); mp 190–193°C; (Lit [4] 189–192°C); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.87, 7.85 (d, 2H, $C_2'C_6'$-H, $J = 5.1$ Hz), 7.42–7.38 (m, 5H, 7-OCH_2–Ar–H), 7.38–7.26 (d, 2H, $C_3'C_5'$-H, $J = 5.1$ Hz), 6.60–6.56 (d, 1H, C_8-H, $J = 12.6$ Hz), 7.81–7.79 (d, 1H, C_3-H, $J = 5.4$ Hz), 5.21–5.19 (d, 2H, $-CH_2-$, $J = 3.9$), 2.45–2.31 (m, 9H, $-COCH_3$); FABMS *m/z* (%): 503 ($M^+ + 1$, 83), 461 ($503 - COCH_2$, 65), 419 ($461 - COCH_2$, 17), 91 ($C_6H_5-CH_2$, 100).

3.7 7-Hydroxy-5,6,4′-triacetoxyflavone (9)

Compound **8** (14 g, 0.03 mol) and 10% Pd–C (1.5 g) were added in CH_2Cl_2 (600 mL). The mixture was then hydrogenized at room temperature and normal pressure until no more

hydrogen was absorbed. After filtration, the solvent was then evaporated under reduced pressure, and the resultant residue was recrystallized to give compound **9** (8 g, 70%); mp 230–235°C (Lit. [4] 234–236°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.92, 7.89 (d, 2H, $C_2'C_6'$-H, $J = 8.7$ Hz), 7.32, 7.29 (d, 2H, $C_3'C_5'$-H, $J = 6.9$ Hz), 6.96 (s, 1H, C_3-H), 6.70 (s, 1H, C_3-H), 2.41–2.34 (m, 9H, $3 \times -COCH_3$), 1.55 (s, bro, 1H, –OH); ^{1}H NMR (300 MHz, $D_2O + CDCl_3$) δ (ppm): 7.92, 7.89 (d, 2H, $C_2'C_6'$-H), 7.31,7.29 (d, 2H, $C_3'C_5'$-H), 6.96 (s, 1H, C_3-H), 6.69 (s, 1H, C_3-H), 2.41–2.34 (m, 9H, $3 \times -COCH_3$), 1.55 (s, bro, − 1H, –OH); FABMS *m/z* (%): 413 ($M^+ + 1$, 10), 371 ($M^+ + 1 - COCH_2$, 7.5), 329 ($371 - COCH_2$, 11), 288 ($413 - 3 \times COCH_2 + H$, 100).

3.8 5,6,4′-Triacetoxy-7-hydroxyflavon-7-o-(2,3,4-tri-o-acetyl-β-D-glucopyranosiduronsauremethylester) (10)

In a dry round-bottomed flask compound **9** (8 g, 0.02 mol), methyl (tri-*O*-acetyl-α-D-glucopyranurosyl bromide) uronate (17.6 g, 0.04 mol), dry $CaSO_4$ (8 g, 59 mmol), AgO (11.2 g, 0.04 mol) and quinoline (160 mL) were added. The so-obtained mixture was then stirred at room temperature for 5 h, and then diluted with $CHCl_3$, and filtrated. The organic layer was then separated and washed with dilute sulfuric acid, and the solvent was dried and evaporated to give crude product. Recrystallization from C_2H_5OH–$CHCl_3$ (7/3) gave compound **10** (14 g, 96%); mp 270–272°C (Lit. [5] 272–274°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.89–7.88 (d, 2H, $C_2'C_6'$-H, $J = 5.1$ Hz), 7.28–7.26 (d, 2H, $C_3'C_5'$-H, $J = 5.4$ Hz), 7.04 (s, 1H, C_3-H), 6.58 (s, 1H, C_3-H), 5.38–5.29 (m, 4H, $-C_6H_9O_6$), 4.35–4.33 (d, 1H, $-C_6H_9O_6$, $J = 5.1$ Hz), 3.77 (s, 3H, $-C_6H_9O_6$-OCH_3), 2.43–2.05 (m, 18H, $6 \times -COCH_3$); MS *m/z* (%): 728 (M^+, 15), 644 ($M^+ - 2 \times COCH_2$, 22), 584 ($M^+ - 3 \times COCH_2 - CO$, 21), 328 ($M^+ - C_6H_9O_6 - 2 \times COCH_2$, 72), 286 ($328 - COCH_2$, 51), 257 ($-C_6H_9O_6 - 2 \times OCOCH_3$, 47), 215 ($257 - COCH_3 + H$, 18), 155 ($215 - CH_3COOH$, 100).

3.9 Scutellarin-7-o-glucuronide (1)

A three-necked round-bottomed flask equipped with a dropping funnel and thermometer was charged with **10** (24 g, 7 mmol) and acetone (500 mL). The mixture was then cooled to 0°C with ice under a N_2 atmosphere. A solution of sodium hydroxide (2.5 M, 300 mL) was added dropwise to maintain the temperature below 0°C; the mixture was stirred under 0°C for 1 h. Dilute hydrochloric acid was then added dropwise at the same temperature. The resultant mixture was stirred under 0°C for 0.5 h, and then the solvent was evaporated. The yellow precipitate was separated and dried to give sutellarin-7-*O*-glucuronide (10 g, 69%). mp 298–300°C (Lit. [5] 300°C); $[\alpha]_D^{25} = -123$ ($c = 0.5$, pyridine) [Lit. [5] $[\alpha]_D^{25} = -123$ ($c = 0.5$, pyridine)]; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 12.73 (s, 1H, –COOH), 10.36 (s, 1H, C_4'-OH), 8.58 (s, 1H, C_5-OH), 7.93, 7.91 (d, 2H, $C_3'C_5'$-H, $J = 8.7$ Hz), 7.10–6.91 (m, 3H, $C_3'C_5'$-H and C_3-H), 6.83 (s, 1H, C_8-H), 5.41 (s, bro, 2H), 5.22–5.20 (d, 1H, C_7-OH, $J = 6.9$ Hz), 4.05–4.02 (d, 1H, $J = 9$ Hz), 3.45–3.30 (m, 4H); ^{1}H NMR (500 MHz, D_2O + DMSO-d_6) δ (ppm): 7.91–7.88 (d, 2H, $C_3'C_5'$-H, $J = 8.7$ Hz), 6.95–6.91 (m, 3H, $C_3'C_5'$-H and C_3-H), 6.75 (s, 1H, C_8-H), 5.20–5.18 (d, 1H, C_7-OH, $J = 6.9$ Hz), 4.05–4.02 (d, 1H, $J = 9.3$ Hz), 3.42–3.35 (m, 4H); FABMS *m/z* (%): 463 ($M + 1$, 26), 288 ($463 - C_6H_9O_6$, 100).

References

[1] Institute of Materia Medica of Yunnan Province, Zhongcaoyao Tongxun, **11** (1976), 11–14.
[2] G. Zemplén, L. Farkas, R. Rakusa. *Acta Chim. Hung.*, **14**, 471–473 (1958).
[3] G. Zemplén, L. Farkas, R. Rakusa. *Acta Chim. Aca. Sci. Hung.*, **16**, 445–448 (1958).
[4] L. Farkas, G. Mezey-Vàndor, M. Nógràdi. *Chem. Ber.*, **104**, 2646–2647 (1971).
[5] L. Farkas, G. Mezey-Vàndor, M. Nógràdi. *Chem. Ber.*, **107**, 3878–3882 (1974).