HETEROCYCLES, Vol. 104, No. 6, 2022, pp. 1123 - 1130. © 2022 The Japan Institute of Heterocyclic Chemistry
Received, 19th January, 2022 Accepted, 28th February, 2022, Published online, 2nd March, 2022
DOI: 10.3987/COM-22-14626

CONCISE SEMI-SYNTHESIS OF A FLAVONE GLYCOSIDE FROM MARINE ANGIOSPERM

Lisha Wu,[1] Shiqiang Yan,[1,2]* and Limei Huang[1]

[1]Weihai Ocean Vocational College, Weihai, 264300, China; [2]Shandong Dyne Marine Biopharmaceutical Limited Corporation, Weihai, 264300, China; E-mail: ysqiang@fudan.edu.cn.

Abstract – Starting from commercially available scutellarin, a natural flavonoid glycoside 6-hydroxyapigenin-7-*O*-(6”-*O*-(*E*)-coumaroyl)-*β*-glucopyranoside was semi-synthesized in a linear 6-step sequence with an overall yield of 31.5%. This work definitely laid the foundation for the further pharmacological study of this natural compound.

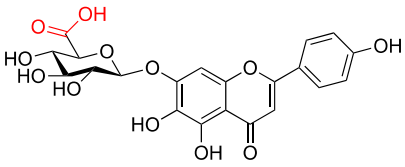
Flavonoids, belonging to the super family of polyphenols, have been found ubiquitously in the human diet, since they are abundant in fruits, vegetables, and a wide variety of other edible plants.[1–3] Interest in flavonoids has bloomed in the last decades because they display many beneficial effects on human health, such as hepatoprotective, antioxidant, antimicrobial, anti-inflammatory, anti-proliferative, antitumor, and anticonvulsant activities, as well as regulatory effects on various enzymes.[4–12] Recently, as another subgroup of flavonoids, flavonoid glucosides also received increasing attention in the research. It was found that glycosylated flavonoids possessing similar stability, bioactivity and improved solubility, and are more efficacious than their aglycones in pharmaceutical studies.[13] However, in contrast to an extensive investigation on flavonoids, flavonoid glycosides have not yet been thoroughly explored, owing to the limited preparative accessibility and the lack of an efficient and convenient synthetic methodology.

Scutellarin (4′,5,6-trihydroxyflavone-7-glucuronide) is a flavonoid glycoside compound isolated from the traditional Chinese medicinal plant *Erigeron breviscapus* (Vant.) Hand. Mazz. Scutellarin exhibits a diverse range of pharmacological and biological properties. It could significantly increase cerebral blood flow, dilate blood vessel, improve microcirculation, protect brain microvascular endothelial cells injury, suppress the increment of intracellular free calcium in vascular smooth muscle cells, and inhibit the platelet aggregation activity in China.[14] *Halophila johnsonii* Eiseman is a threatened shallow-water marine angiosperm endemic to south-eastern Florida coastal lagoons which contains UV-absorbing metabolites. In 2008, 6-hydroxyapigenin-7-*O*-(6”-*O*-(*E*)-coumaroyl)-*β*-glucopyranoside was first isolated

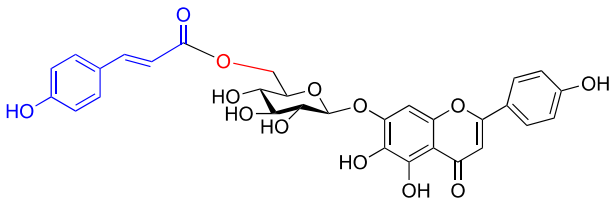
from *Halophila johnsonii* (Hydrocharitaceae).[15]

It is well-known that the usage of content high, extraction and separation easy natural products as scaffolds for the semi-synthesis of larger biological screening libraries is a rather classical approach to create new natural product analogues.[16] Semi-synthesis methods for chemical modification have many advantages, including avoidance of time-consuming, avoidance of the de novo multi-step synthesis, rich in resource and amenable to scale-up.

According to the chemical structure of scutellarin, 6-hydroxyapigenin-7-*O*-(6”-*O*-(*E*)-coumaroyl)-*β*-glucopyranoside has the similar structure (Figure 1). On the basis of these observations and in continuation of our efforts towards the development of bioactive natural glycoconjugates chemical synthesis,[17] herein this research present an efficient method which follows the semi-synthetic route to access 6-hydroxyapigenin-7-*O*-(6”-*O*-(*E*)-coumaroyl)-*β*-glucopyranoside using scutellarin as the starting material.



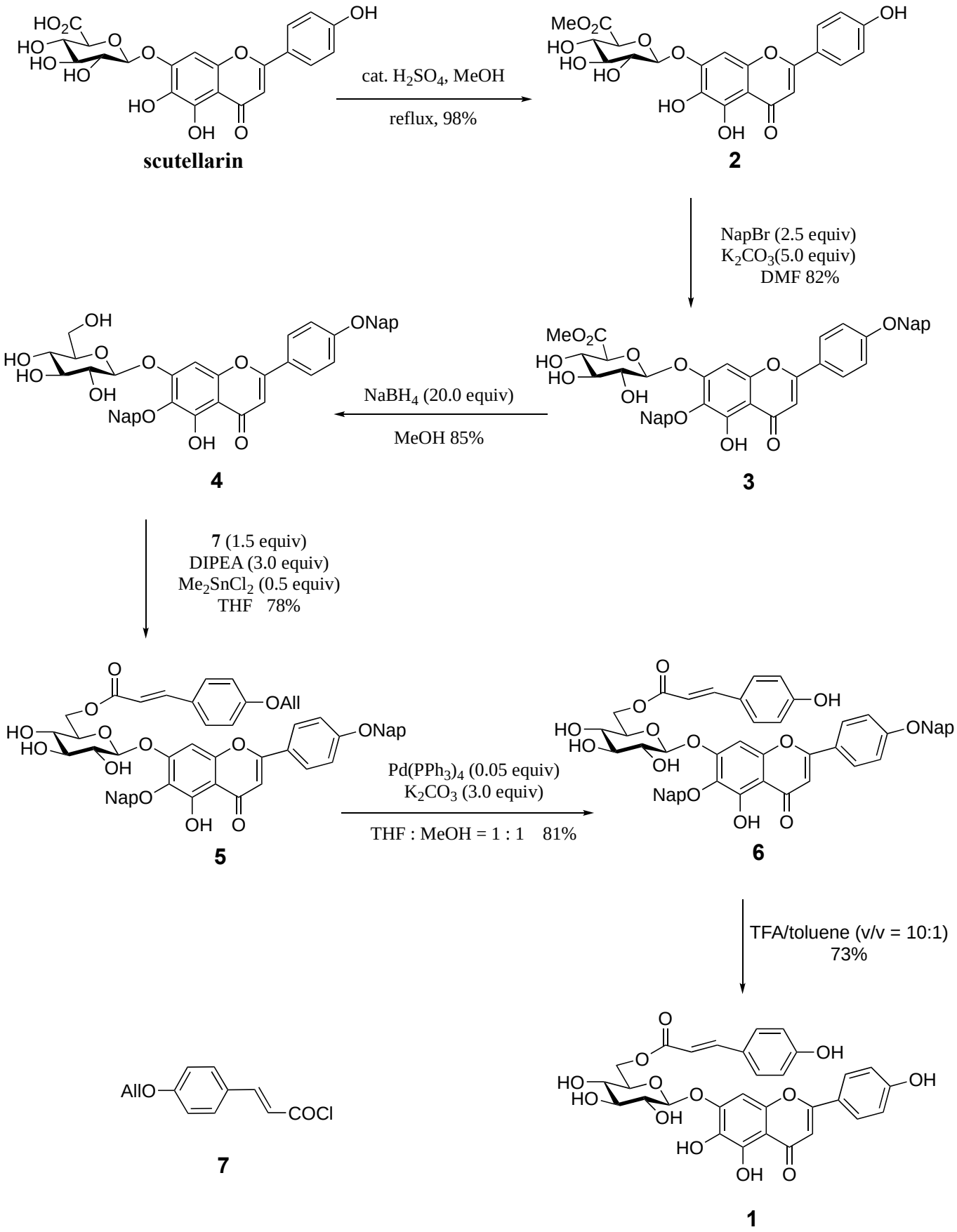
scutellarin



6-hydroxyapigenin-7-*O*-(6"-*O*-(*E*)-coumaroyl)-*β*-glucopyranoside

Figure 1. Structures of scutellarin and 6-hydroxyapigenin-7-*O*-(6”-*O*-(*E*)-coumaroyl)-*β*-glucopyranoside

6-Hydroxyapigenin-7-*O*-(6”-*O*-(*E*)-coumaroyl)-*β*-glucopyranoside **1** was prepared from scutellarin as outlined in Scheme **1**. Based on the reported method,[18] the scutellarin methyl ester **2** was obtained in 98% yield by treating scutellarin with a catalytic amount of concentrated H_2SO_4 in the solution of methanol without purification. There are three alcoholic hydroxy groups and three phenolic hydroxy groups on the key intermediate **2**, the selective etherification of phenolic hydroxy groups could be achieved based on the different reactivity of hydroxy groups on compound **2**. Due to the presence of intramolecular hydrogen bond, the 5-hydroxy group on the flavonoid ring has relatively weak reactivity. Therefore, selective naphthylmethylation of scutellarin methyl ester **2** with 2.4 equiv of 2-naphthylmethyl bromide in the presence of K_2CO_3 led to the formation of dinaphthylmethylated product **3** with the yield of 82%. Subsequently, reduction of compound **3** afforded the desired compound **4** in a 85% yield by employing 10.0 equiv of $NaBH_4$ in MeOH.[17a]



Scheme 1. Synthesis of 6-hydroxyapigenin-7-*O*-(6”-*O*-(*E*)-coumaroyl)-*β*-glucopyranoside

Coumaroyl chloride **7** was prepared in two steps. The hydroxy group in *p*-hydroxybenzaldehyde was protected using allyl bromide. The processed crude and malonic acid were dissolved in a mixture of pyridine and piperidine[19] and refluxed for 2.0 h, and *O*-allyl coumaric acid was obtained in 83% yield. Conversion of *O*-allyl coumaric acid to its coumaroyl chloride **7** was readily achieved in quantitative yield by refluxing with $SOCl_2$ in toluene.

With the compound **4** and coumaroyl chloride **7** in hand, we then examined the directly regioselective *O*-6 acylation of compound **4** using Me_2SnCl_2 as a catalyst.[17c,f] To our delight the desired *O*-6 acylated glucoside **5** was obtained in 78% yield. Then, the compound **6** was achieved in 81% yield after removal of allyl group using $Pd(PPh_3)_4$-K_2CO_3 system.[17c] Finally, the target compound **1** was obtained after the deprotection of the two naphthylmethyl groups by using a mixture of TFA/toluene (v/v = 10:1)[20] with the yield of 73%. The structure of the target compound **1** was confirmed by ^{1}H NMR, ^{13}C NMR and HRMS, and the data matched with the reported one.[15]

In summary, a concise synthetic protocol to access 6-hydroxyapigenin-7-*O*-(6”-*O*-(*E*)-coumaroyl)-*β*-glucopyranoside has been developed involving the simple and readily accessible starting material with an overall yield of 31.5%. The reported synthetic approach is sufficient, facile and may be readily extended to the synthesis of other flavonoid glycosides.

EXPERIMENTAL

All reagents were purchased from Adamas (China), and were used as received without further purification. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with silica gel plates (60F-254) using UV light. Yields refer to pure compounds. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz spectrometer as indicated in the data list. The abbreviations s, d, dd, t, q, br, and m stand for the resonance multiplicity singlet, doublet, doublet of doublets, triplet, quartet, broad and multiplet, respectively.

Methyl (2*S*,3*S*,4*S*,5*R*,6*S*)-3,4,5-trihydroxy-6-((5-hydroxy-6-(naphthalen-1-ylmethoxy)-2-(4-(naphthalen-1-ylmethoxy)phenyl)-4-oxo-4*H*-chromen-7-yl)oxy)tetrahydro-2*H*-pyran-2-carboxylate (3): 2-Naphthylmethyl bromide (1.38 g, 6.25 mmol) and K_2CO_3 (1.04 g, 7.50 mmol) were added to a stirred solution of scutellarin methyl ester **2** (1.19 g, 2.50 mmol) in dry DMF (30 mL), and the mixture was stirred at room temperature for 8.0 h. After the completion of the reaction, the reaction mixture was filtered and poured into 1 M HCl (60 mL) containing broken ice. The residue was extracted with EtOAc (100 mL×2), and washed with saturated brine (150 mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and purified by chromatography on silica gel column to afforded compound **3** (1.55 g, 82%) as yellow solid. Mp: 214 – 217 ºC; $[\alpha]_D^{25}$ -46.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 8.04 (t, *J* = 8.7 Hz, 4H), 7.98 – 7.88 (m, 6H), 7.75 (d, *J* = 8.4 Hz, 1H),

7.60 (d, *J* = 8.4 Hz, 1H), 7.52 (dd, *J* = 9.1, 6.7 Hz, 4H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.15 (s, 1H), 6.94 (s, 1H), 5.75 (d, *J* = 5.2 Hz, 1H), 5.56 (d, *J* = 5.3 Hz, 1H), 5.47 (d, *J* = 7.5 Hz, 1H), 5.45 – 5.37 (m, 3H), 5.28 (d, *J* = 11.2 Hz, 1H), 5.14 (d, *J* = 11.2 Hz, 1H), 4.26 (d, *J* = 9.5 Hz, 1H), 3.66 (s, 3H), 3.46 (ddd, *J* = 14.0, 10.6, 5.7 Hz, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 182.37, 169.24, 163.86, 161.56, 156.12, 152.87, 152.27, 135.21, 134.09, 132.77, 132.72, 132.65, 132.62, 131.32, 128.43, 128.19, 127.90, 127.83, 127.68, 127.64, 127.56, 126.85, 126.55, 126.41, 126.27, 126.12, 126.06, 125.74, 123.00, 115.52, 105.94, 103.51, 99.33, 93.88, 75.77, 75.34, 74.25, 72.98, 71.37, 69.73, 52.02; ESI-HRMS *m/z* $[M+H]^+$ calcd for $C_{44}H_{37}O_{12}$: 757.2280; found: 757.2286.

5-Hydroxy-6-(naphthalen-1-ylmethoxy)-2-(4-(naphthalen-1-ylmethoxy)phenyl)-7-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)-4*H*-chromen-4-one (4):

Compound **3** (1.20 g, 1.59 mmol) was suspended in MeOH (30 mL) and cooled to 0 ºC. Then $NaBH_4$ (0.91 g, 23.85 mmol) was added portionwise, after the addition was complete, the mixture was stirred for an additional 3.0 h at room temperature and then quenched with 25 mL of 10% AcOH/H_2O. The solution was extracted with EtOAc (100 mL×2) and evaporated under vacuum to obtain the crude product as a yellow solid. The residue was suspended in EtOAc (50 mL), and heated for 30 min at reflux. The suspension was cooled to room temperature, filtered and washed with EtOAc. The product was dried in vacuo for 12.0 h at 50 ºC to yield compound **4** (0.98 g, 85%) as a light yellow solid. Mp: 174 – 178 ºC; $[\alpha]_D^{25}$ -60.7 (*c* 0.5, MeOH); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 13.00 (s, 1H), 8.17 – 7.85 (m, 10H), 7.76 (d, *J* = 7.3 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.52 (s, 4H), 7.25 (d, *J* = 7.5 Hz, 2H), 7.09 (s, 1H), 6.95 (s, 1H), 5.60 (s, 1H), 5.40 (s, 2H), 5.22 (dt, *J* = 36.7, 14.3 Hz, 5H), 4.68 (s, 1H), 3.74 (s, 1H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ 182.42, 163.88, 161.60, 156.70, 152.71, 152.35, 135.34, 134.15, 132.82, 132.78, 132.70, 132.67, 131.39, 128.51, 128.25, 127.97, 127.89, 127.72, 127.61, 126.94, 126.65, 126.59, 126.48, 126.34, 126.18, 126.11, 125.78, 123.04, 115.58, 105.82, 103.50, 100.17, 94.40, 77.34, 76.88, 74.30, 73.42, 69.76, 69.65, 60.71, 54.95; ESI-HRMS *m/z* $[M+H]^+$ calcd for $C_{43}H_{37}O_{11}$ 729.2330, found 729.2314.

((2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-Trihydroxy-6-((5-hydroxy-6-(naphthalen-1-ylmethoxy)-2-(4-(naphthalen-1-ylmethoxy)phenyl)-4-oxo-4*H*-chromen-7-yl)oxy)tetrahydro-2*H*-pyran-2-yl)methyl (*E*)-3-(4-(allyloxy)phenyl)acrylate (5):

To a solution of **4** (0.73 g, 1.0 mmol) in THF (15 mL) was added Me_2SnCl_2 (33.0 mg, 0.15 mmol), DIPEA (530 μL, 3.0 mmol) under strong stirring. After stirring for 15 min at room temperature, the mixture was treated with coumaroyl chloride **7** (0.33 g, 1.5 mmol). After stirred for 3.0 h, the mixture was added MeOH and concentrated under reduced pressure. The residue was then extracted with EtOAc (50 mL×2), washed with 1 M HCl (20 mL) and saturated brine (30 mL) in turn. The combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure and purified by silica gel column chromatography to obtain **5** (0.71 g, 78%) as a white solid. Mp: 209 – 211 ºC; $[\alpha]_D^{25}$ -38.8 (*c* 0.5,

$CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (s, 1H), 8.10 – 7.85 (m, 10H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.52 (dt, *J* = 24.2, 12.4 Hz, 6H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.04 (s, 1H), 6.85 (s, 1H), 6.63 (d, *J* = 8.3 Hz, 2H), 6.32 (d, *J* = 16.0 Hz, 1H), 6.06 – 5.89 (m, 1H), 5.73 (t, *J* = 6.9 Hz, 1H), 5.50 (d, *J* = 5.1 Hz, 1H), 5.42 (d, *J* = 4.7 Hz, 1H), 5.39 – 5.10 (m, 6H), 4.59 (d, *J* = 10.9 Hz, 1H), 4.45 (d, *J* = 4.7 Hz, 2H), 4.25 – 4.11 (m, 1H), 3.92 (d, *J* = 7.6 Hz, 1H), 3.61 – 3.50 (m, 2H), 3.32 (dd, *J* = 14.1, 9.1 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 182.33, 166.33, 163.70, 161.48, 159.87, 156.42, 152.75, 152.24, 144.51, 135.26, 134.09, 133.29, 132.80, 132.75, 132.69, 132.66, 131.33, 129.76, 128.22, 127.93, 127.85, 127.70, 127.68, 127.58, 126.97, 126.67, 126.52, 126.45, 126.31, 126.13, 126.08, 125.72, 125.72, 122.86, 117.68, 115.37, 114.87, 114.71, 105.83, 103.27, 99.66, 94.14, 76.57, 74.29, 74.05, 73.22, 70.11, 69.69, 68.23, 63.53; ESI-HRMS *m/z* $[M+H]^+$ calcd for $C_{55}H_{47}O_{13}$: 915.3011; found: 915.3016.

((2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-Trihydroxy-6-((5-hydroxy-6-(naphthalen-1-ylmethoxy)-2-(4-(naphthalen-1-ylmethoxy)phenyl)-4-oxo-4*H*-chromen-7-yl)oxy)tetrahydro-2*H*-pyran-2-yl)methyl (*E*)-3-(4-hydroxyphenyl)acrylate (6):

To a solution of **5** (482 mg, 0.50 mmol) in MeOH (10 mL) and THF (10 mL) was added $Pd(PPh_3)_4$ (28.8 mg, 0.025 mmol) under N_2 atmosphere at room temperature. The solution was stirred for 5 min and then K_2CO_3 (207 mg, 1.50 mmol) was introduced. After stirring at room temperature for 2.0 h, the solution was neutralized with ion-exchange resin (H^+) and then filtered and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH) to afford **6** (354 mg, 81%) as a white solid. Mp: 186 – 189 ºC; $[\alpha]_D^{25}$ -55.9 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.99 (s, 1H), 9.97 (s, 1H), 8.02 (t, *J* = 9.1 Hz, 5H), 7.92 (dd, *J* = 14.0, 7.2 Hz, 5H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.57 – 7.48 (m, 4H), 7.44 (d, *J* = 15.9 Hz, 1H), 7.17 (t, *J* = 8.2 Hz, 4H), 7.05 (s, 1H), 6.88 (s, 1H), 6.54 (d, *J* = 8.4 Hz, 2H), 6.25 (d, *J* = 15.9 Hz, 1H), 5.67 (d, *J* = 5.4 Hz, 1H), 5.45 (d, *J* = 5.3 Hz, 1H), 5.40 – 5.33 (m, 3H), 5.32 – 5.26 (m, 2H), 5.14 (d, *J* = 11.2 Hz, 1H), 4.53 (d, *J* = 11.0 Hz, 1H), 4.22 – 4.10 (m, 1H), 3.89 (d, *J* = 7.9 Hz, 1H), 3.50 (dd, *J* = 13.9, 7.8 Hz, 1H), 3.17 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 182.35, 166.49, 163.79, 161.53, 159.73, 156.44, 152.73, 152.24, 145.01, 135.24, 134.10, 132.80, 132.73, 132.67, 131.30, 130.01, 128.27, 128.21, 127.92, 127.86, 127.68, 127.57, 126.95, 126.65, 126.59, 126.44, 126.30, 126.13, 126.07, 125.79, 124.76, 122.90, 115.57, 115.43, 113.58, 105.82, 103.32, 99.72, 94.20, 76.55, 74.26, 73.97, 73.18, 70.01, 69.73, 63.40; ESI-HRMS *m/z* $[M+H]^+$ calcd for $C_{52}H_{43}O_{13}$: 875.2698; found: 875.2703.

6-Hydroxyapigenin-7-*O*-(6”-O-*(E)*-coumaroyl)-*β*-glucopyranoside (1):

Compound **6** (175 mg, 0.2 mmol) was dissolved in a mixture of TFA/toluene (v/v = 10:1, 11 mL) at 0 ºC and the reaction mixture was stirred at 0 ºC for 30 min. Next, the reaction was warmed to room temperature and stirred for an additional 3.0 h. The mixture was then diluted with toluene (15 mL) and concentrated under reduced pressure and the resulting residue was purified by Sephadex LH-20 size

exclusion chromatography (CH_2Cl_2/MeOH) to afford compound **1** as a white powder (86 mg, 73%). The physical data matched those previously reported. Mp: 158 – 162 ºC; $[\alpha]_D^{25}$ -19.2 (*c* 0.05, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.72 (s, 1H, 5-OH) , 10.41 (s, 1H, 4”-OH) , 10.03 (s, 1H, 4’-OH), 8.59 (s, 1H, 6-OH), 7.93 (s, 2H, H-2’, H-6’), 7.48 (d, *J* = 16.2 Hz, 1H, H-7’’’), 7.27 (s, 2H, H-2’’’, H-6’’’), 6.94 (d, *J* = 9.4 Hz, 3H, H-8, H-3’, H-5’), 6.79 (s, 1H, H-3), 6.59 (s, 2H, H-3’’’, H-5’’’), 6.30 (d, *J* = 16.0 Hz, 1H, H-8’’’), 5.52 (s, 1H, OH from sugarring), 5.43 (s, 1H, OH from sugarring), 5.31 (s, 1H, OH from sugarring), 5.12 (d, *J* = 8.0 Hz, 1H, H-1’’), 4.47 (d, *J* = 11.4 Hz, 1H, H-6’’b), 4.24 (s, 1H, H-6’’a), 3.87 (s, 1H, H-5’’); ^{13}C NMR (150 MHz, DMSO-d_6) δ 182.34 (C-4), 166.54 (C-9’’’), 164.07 (C-2), 161.28 (C-6’), 159.81 (C-4’’’), 151.26, 149.04 (C-7), 146.72 (C-9), 145.08 (C-7’’’), 130.44 (C-2), 130.36 (C-6’’’), 130.04 (C-6), 128.31 (C-2’, C-6’), 124.73 (C-1’’’), 121.19 (C-1’’), 116.00 (C-3’, C-5’), 115.84 (C-3’’’), 115.63 (C-5’’’), 113.50 (C-8’’’), 105.78 (C-10), 102.37 (C-3), 100.32 (C-1’’), 93.59 (C-8), 75.66 (C-3’’), 73.79 (C-5’’), 72.95 (C-2’’), 70.06 (C-4’’), 63.45 (C-6’’); ESI-HRMS *m/z* $[M+H]^+$ calcd for $C_{30}H_{27}O_{13}$: 595.1451; found: 595.1428.

ACKNOWLEDGEMENTS

We gratefully acknowledge the financial support from Natural Science Foundation of Shandong Province (Grant No. ZR2020KH002).

REFERENCES

1. M. Katalinić, G. Rusak, J. D. Barović, G. Šinko, D. Jelić, R. Antolović, and Z. Kovarik, *Eur. J. Med. Chem.*, 2010, **45**, 186.
2. W. Huang, Q. Chen, W. C. Yang, and G. F. Yang, *Eur. J. Med. Chem.*, 2013, **66**, 161.
3. A. Scalbert and G. Williamson, *J. Nutr.*, 2000, **130**, 2073S.
4. T. P. T. Cushnie and A. J. Lamb, *Int. J. Antimicrob. Agents*, 2005, **26**, 343.
5. P. G. Pietta, *J. Nat. Prod.*, 2000, **63**, 1035.
6. L. P. Guan and B. Y. Liu, *Eur. J. Med. Chem.*, 2016, **121**, 47.
7. F. A. Ragab, T. A. Yahya, M. M. El-Naa, and R. K. Arafa, *Eur. J. Med. Chem.*, 2014, **84**, 506.
8. M. Singh, M. Kaur, and O. Silakari, *Eur. J. Med. Chem.*, 2014, **84**, 206.
9. D. Grassi, G. Desideri, and C. Ferri, *Nutrients*, 2010, **2**, 889.
10. M. Serafini, I. Peluso, and A. Raguzzini, *Proc. Nutr. Soc.*, 2010, **69**, 273.
11. T. Sawa, M. Nakao, T. Akaike, K. Ono, and H. Maeda, *J. Agric. Food Chem.*, 1999, **47**, 397.
12. D. Ravishankar, A. K. Rajora, F. Greco, and H. M. Osborn, *Int. J. Biochem. Cell Biol.*, 2013, **45**, 2821.
13. Y. Chen, H. Hui, H. Yang, K. Zhao, Y. Qin, C. Gu, X. Wang, N. Lu, and Q. Guo, *Blood*, 2013, **121**,

3682.

14. (a) Z. W. Pan, T. M. Feng, L. C. Shan, B. Z. Cai, W. F. Chu, H. L. Niu, Y. J. Lu, and B. F. Yang, *Phytother. Res.*, 2008, **22**, 1428; (b) H. F. Zhang, X. M. Hu, L. X. Wang, S. Q. Xu, and F. D. Zeng, *Planta Med.*, 2009, **75**, 121; (c) J. T. Zhu, R. C. Choi, J. Li, H. Q. Xie, C. W. Bi, A. W. Cheung, T. T. Dong, Z. Y. Jiang, J. J. Chen, and K. W. Tsim, *Planta Med.*, 2009, **75**, 1489; (d) H. Yao, S. Li, J. Hu, L. Huang, J. Lin, G. Li, and X. Lin, *Planta Med.*, 2011, **77**, 388.
15. Y. H. Meng, A. J. Krzysiak, M. J. Durako, J. I. Kunzelman, and J. L. C. Wright, *Phytochemistry*, 2008, **69**, 2603.
16. (a) F. Nussbaum, M. Brands, B. Hinzen, S. Weigand, and D. Habich, *Angew.Chem. Int. Ed.*, 2006, **45**, 5072; (b) A. M. Szpilman and E. M. Carreira, *Angew. Chem. Int. Ed.*, 2010, **49**, 9592; (c) R. M. Wilson and S. J. Danishefsky, *J. Org. Chem.*, 2006, **71**, 8329; (d) E. C. Barnes, R. Kumar, and R. A. Davis, *Nat. Prod. Rep.*, 2016, **33**, 372.
17. (a) S. Q. Yan, M. X. Xie, Y. J. Wang, Q. Xiao, N. Ding, and Y. X. Li, *Tetrahedron*, 2020, **76**, 130950; (b) S. Q. Yan, Y. Y. Zhu, Y. J. Wang, Q. Xiao, N. Ding, and Y. X. Li, *Tetrahedron Lett.*, 2020, **61**, 151886; (c) S. Q. Yan, S. M. Ren, N. Ding, and Y. X. Li, *Carbohydr. Res.*, 2018, **460**, 41; (d) S. Q. Yan and Y. X. Li, *Chin. J. Org. Chem.*, 2019, **39**, 561; (e) S. Q. Yan, M. X. Xie, Y. J. Wang, and Y. X. Li, *Chin. J. Org. Chem.*, 2019, **39**, 412; (f) S. Q. Yan, Y. Y. Zhu, L. S. Wu, L. Q. Chi, and W. Zhang, *Heterocycles*, 2021, **102**, 1791.
18. G. H. He, Y. Gao, C. L. Li, G. L. Wu, Y. Z. Li, L. R. Dong, C. C. Huang, and H. J. Chen, *Tetrahedron Lett.*, 2016, **57**, 2001.
19. X. Yang, Q. Wen, T. Zhao, J. Sun, X. Li, M. Xing, X. Lu, and H. Zhu, *Bioorg. Med. Chem.*, 2012, **20**, 1181.
20. D. M. Yao, Y. C. Liu, Q. Gao, Q. Sui, X. P. Liu, and N. Ding, *J. Carbohydr. Chem.*, 2017, **36**, 173.