EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201403689

The First Total Synthesis of Sophoflavescenol, Flavenochromane C, and Citrusinol

Van-Son Nguyen,[a,b] Lin-Pei Dong,[a] Sheng-Chun Wang,[a] and Qiuan Wang*[a]

Keywords: Total synthesis / Natural products / Sigmatropic rearrangement / Cyclization / Fused-ring systems / Oxygen heterocycles

The first total syntheses of sophoflavescenol (**1**), flavenochromane C (**2**), and citrusinol (**3**) were achieved. These three naturally occurring prenylated or prenyl-cyclized flavonoids have important biological activities such as cytotoxicity against some cancer cell lines, or are lead compounds for the treatment of erectile dysfunction. Starting from 2,4,6-trihydroxyacetophenone and substituted benzaldehydes, the synthesis involved methoxymethyl protection, aldol condensation, cyclization, oxidation with dimethyldioxirane, *O*-prenylation, microwave-assisted Claisen rearrangement, deprotection, cyclization of the prenyl group, and dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. The overall yields of **1**, **2**, and **3** were 23, 17, and 16 %, respectively. All compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy and MS. The key step of the synthetic route was a regioselective microwave-assisted Claisen rearrangement to form an 8-prenylated flavonoid from a 5-*O*-prenylflavonoid.

Introduction

Prenylated flavonoids are a unique class of naturally occurring flavonoids characterised by the presence of a prenylated side-chain on the flavonoid skeleton. *C*-Prenylation of flavonoids can enhance their binding affinity toward *P*-glycoprotein, and can remarkably improve the biological activity of the flavonoids.[1] Over the past few decades, an impressive number of biological activities and pharmacological effects have been demonstrated for *C*-prenylated flavonoids, including antitumor, anti-inflammatory, and antiosteoporosis activities, enzyme inhibition, and vascular-protective and estrogen regulation activities.[2,3]

Sophoflavescenol (**1**), a C-8-prenylated flavonoid isolated from *S. flavescens*, was the most potent and selective inhibitor of CGMP phosphodiesterase 5 (PDE5; IC_{50} 0.013 μM), and so it was considered as a lead structure for the treatment of erectile dysfunction.[4] Sophoflavescenol (**1**) also showed inhibitory activity against HL-60, LLC, and A549 tumor cells.[5] Flavenochromane C (**2**) is a prenyl-cyclized derivative of sophoflavescenol, and it showed potent cytotoxicity against a panel of five human tumour cell lines with IC_{50} values of 1.0–3.6 μM.[6] It also showed strong cytotoxic activity against lung carcinoma (A549), ovarian carcinoma (1A9), and breast adenocarcinoma (MCF-7) cell lines with IC_{50} values of 1.7–3.6 μM.[7] Citrusinol (**3**), the dimethyl pyrano derivative of C-8-prenylkaempferol, isolated from the stems and leaves of *Desmodium caudatum*, has been shown to have antibacterial and antifungal activities.[8] It has also shown cytotoxicity against KB cells and the HepG2 cell line.[9]

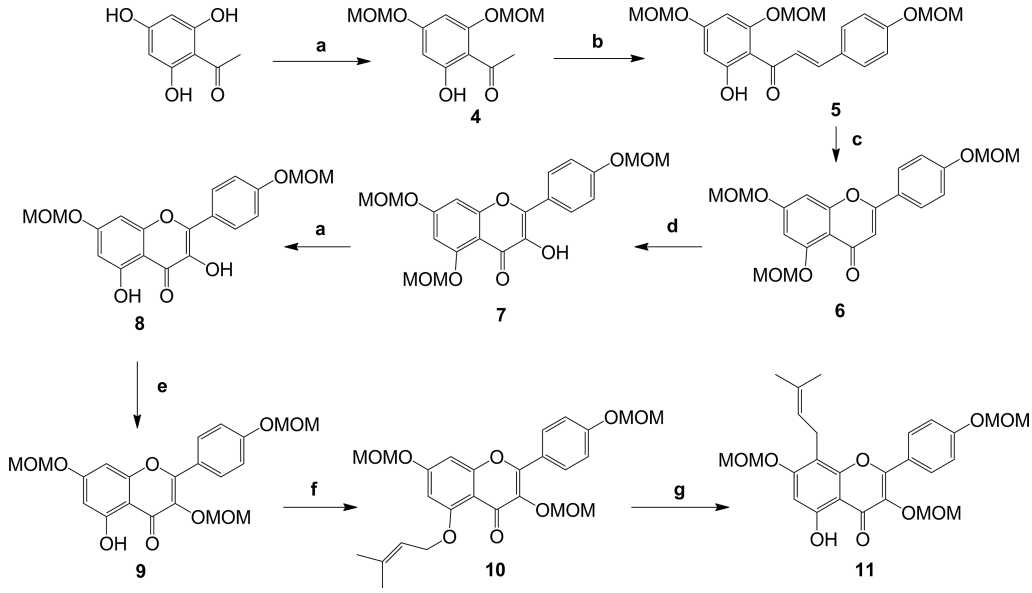
Sophoflavescenol (**1**), flavenochromane C (**2**), and citrusinol (**3**) only occur at low levels in natural plants, and this has negatively influenced further evaluation of their biological activity. Therefore, the chemical synthesis of **1**, **2**, and **3** would be a very important way of addressing the problem of their availability. In this paper, we describe the first total synthesis of sophoflavescenol (**1**), flavenochromane C (**2**), and citrusinol (**3**) in 10–11 steps, starting from commercially available 2,4,6-trihydroxyacetophenone and MOM-protected 4-hydroxybenzaldehyde. The key step is a regioselective microwave-assisted Claisen rearrangement to form an 8-prenylated flavonoid from a 5-*O*-prenylflavonoid. All the compounds synthesized were characterized by ^{1}H and ^{13}C NMR spectroscopy and MS. The synthetic route to sophoflavescenol (**1**), flavenochromane C (**2**), and citrusinol (**3**) is shown in Schemes 1 and 2.

Results and Discussion

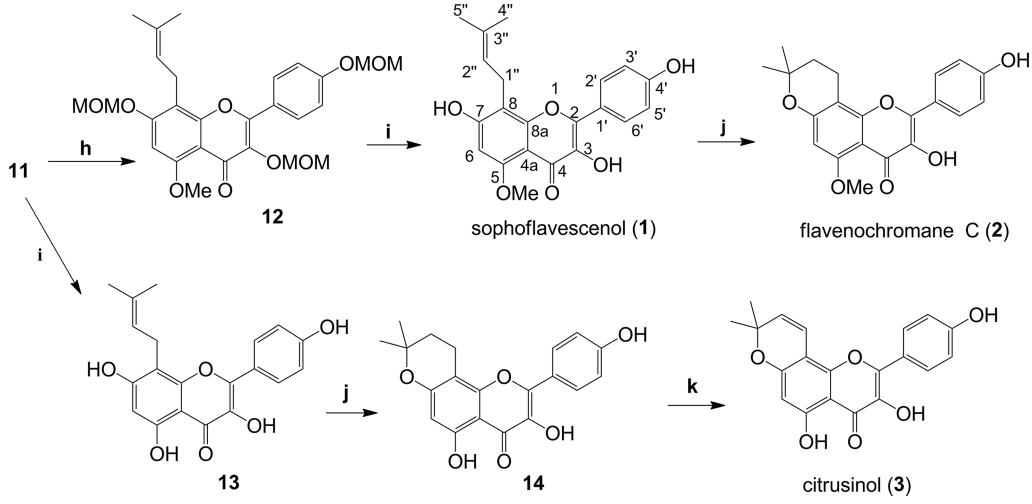
Starting material 2,4,6-trihydroxyacetophenone is commercially available. 2-Hydroxy-4,6-bis(methoxymethoxy)-acetophenone (**4**) and 4-(methoxymethoxy)benzaldehyde were prepared according to literature procedures.[10,11] A

[a] College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, P. R. China
E-mail: wangqa@hnu.edu.cn
http://cc.hnu.cn
[b] Faculty of Chemical Engineering, Industry University of Hochiminh City, Vietnam

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403689.



Scheme 1. Synthesis of **11** by aldol condensation, cyclization, oxidation with dimethyldioxirane (DMDO), selective 5-demethoxymethyl protection, *O*-prenylation, and microwave-assisted Claisen rearrangement. Reagents and conditions: (a) CH_3OCH_2Cl, K_2CO_3, acetone, room temp., 83–90%; (b) 4-MOMO-benzaldehyde, KOH, EtOH, reflux, 85%; (c) I_2, DMSO, reflux, 8 h, 70%; (d) oxone, acetone, CH_2Cl_2/$NaHCO_3$/Na_2CO_3, r.t.; then *p*-toluenesulfonic acid, r.t., 76%; (e) dilute HCl (aq.), EtOH, r.t., 89%; (f) prenyl bromide, K_2CO_3, acetone, reflux, 95%; (g) microwave, $PhNEt_2$, reflux, 82%.



Scheme 2. The last steps in the total synthesis of sophoflavescenol (**1**), flavenochromane C (**2**), and citrusinol (**3**): 5-*O*-methylation, deprotection, cyclization of the prenyl group, and dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Reagents and conditions: (h) $(Me)_2SO_4$, NaOH, r.t., 80%; (i) HCl (aq.), EtOH, r.t., 96%; (j) H_2SO_4 (20% aq.), CH_3OH, reflux, 86%; (k) DDQ, 1,4-dioxane, reflux, 76%.

methoxymethyl (MOM) group was chosen to protect the hydroxy group because it is stable under the basic conditions, and is easily removed by acidic treatment. Base-catalysed aldol condensation of **4** with 4-(methoxymethoxy)-benzaldehyde gave chalcone **5** in 85% yield after a simple purification. Chalcone **5** was cyclized in the presence of catalytic iodine in dimethyl sulfoxide at 140 °C to give MOM-protected flavone **6** in high yield.

The oxidation of the flavone to the flavonol was achieved by following our previously published procedures.[12] Thus, a 3-OH group was introduced by treatment with dimethyldioxirane (DMDO), generated in situ from Oxone and acetone[13] at low temperature, followed by opening of the resulting epoxide with catalytic *p*-toluenesulfonic acid to give flavonol **7** in 76% yield.

The MOM protecting group of 5-OH was selectively removed by a catalytic amount of dilute HCl in EtOH at room temperature to give compound **8**. Treatment of **8** with chloromethyl methyl ether and K_2CO_3 in acetone give the intermediate 3,7,4′-tri-*O*-(methoxymethoxyl)kaempferol

(**9**). *O*-Prenylation of the free 5-hydroxy group of **9** using prenyl bromide as the electrophile gave **10**.

Once prenyl ether **10** was available, our attention was focussed on the formation of an 8-prenylated flavonoid from the 5-*O*-prenylflavonoid. A microwave-assisted Claisen rearrangement was the key step of our synthetic strategy. *O*-Prenylated Claisen precursor **10** was subjected to microwave-assisted Claisen rearrangement in *N*,*N*-diethylaniline to give the desired *C*-prenylated flavonoid (i.e., **11**). The effects of microwave irradiation versus conventional heating on the regioselectivity of the Claisen rearrangement and the reactivity of **10** in the reaction were investigated. Using conventional heating, the *ortho*-rearranged product was found to be the major product (70% yield) in *N*,*N*-diethylaniline at 190 °C, and only 15% of the *para*-rearranged product (i.e., **11**) was obtained. However, using microwave irradiation, the *para*-rearranged product (i.e., **11**) was obtained selectively in 82% yield under otherwise identical conditions, and it was the only product observed in the ^{1}H NMR spectrum of the crude reaction mixture [signals for the –CH_2–CH=C(CH_3)$_2$ group in **11** at δ = 3.04 (d, 2 H) ppm, and loss of H-8 (C-8 position)]. These results also show that microwave irradiation can greatly accelerate the reaction rate of the Claisen rearrangement. The reaction rates under microwave irradiation (700 W) are 72 times higher than those using conventional heating at 190 °C. Thus, we confirmed that the microwave-assisted procedure was suitable for the synthesis of MOM-protected 8-prenylflavonoids.

The next step involved the introduction of the desired methyl functionality onto the reexposed 5-hydroxy group in **11**. This was accomplished by using dimethyl sulfate in the presence of potassium carbonate to produce **12**. Removal of the MOM protecting groups was achieved by stirring **12** in HCl (3 M) and EtOH for 2 h, carefully monitoring the reaction by TLC to avoid concomitant cyclization to **2**. Indeed, heating **12** at pH 3–5 largely resulted in the cyclized product. Alternatively, lowering the pH to slightly less than 1 and avoiding elevated temperature by stirring at room temperature for 2 h allowed the gradual removal of the MOM groups without cyclization. After aqueous work-up and purification by silica gel flash column chromatography, we obtained sophoflavescenol (**1**). The optimized yield for this step was 72%, and the overall yield for the entire 10-step synthesis became about 23%. The prenyl group in compound **1** underwent cyclization with the neighbouring hydroxy group upon treatment with H_2SO_4 (20% aq.) in CH_3OH to give flavenochromane C (**2**) as shown by the characteristic NMR signals at δ = 1.83 and 2.82 (2 t, 4 H, J = 6.7 Hz, –CH_2–), and 1.33 [s, 6 H, (CH_3)$_2$C=] ppm. Removal of the MOM protecting group of **11** to give 8-prenylkaempferol (**13**) was achieved using same conditions as were used for the synthesis of **1** from **12**. Compound **13** underwent acid-catalysed cyclization to give **14**, under the same conditions as were used for the conversion of **1** into **2**. Compound **14** was subjected to dehydrogenation with DDQ to give another natural product, citrusinol (**3**). The spectra and melting point of synthetic **3** were identical to those of **3** obtained from *Citrus nobilis*.[14] The overall yield for the entire 10-step sequence from 2,4,6-trihydroxyacetophenone was 16%. The NMR spectroscopic data of the natural and synthetic flavonoids **1**, **2**, and **3** are shown in Tables 1, 2, and 3.

Table 1. Comparison of the NMR spectroscopic data of natural and synthetic flavonoid **1**.

Position	Synthesized compound	Natural compound	Synthesized compound	Natural compound
	δ_H [ppm]	δ_H [ppm]	δ_C [ppm]	δ_C [ppm]
2	–	–	145.4	141.6
3	9.52 (s)	8.57 (s)	136.3	136.8
4	–	–	175.6	171.2
4a	–	–	104.4	105.2
5	–	–	159.5	157.9
5-OMe	3.87 (s)	3.80	56.8	55.7
6	6.46 (d)	6.45 (s)	96.2	95.4
7	10.23 (s)	10.53 (s)	160.5	159.5
8	–	–	106.0	106.8
8a	–	–	155.6	155.4
1′	–	–	122.0	122.3
2′	8.05 (d)	7.99 (d)	129.5	128.6
3′	7.06 (d)	6.92 (d)	114.5	115.4
4′	–	–	158.7	158.5
4′-OH	10.69 (s)	9.94 (s)	–	–
5′	7.06 (d)	6.92 (d)	114.5	115.4
6′	8.05 (d)	7.99 (d)	129.5	128.6
1′′	3.46 (d)	3.46 (d)	21.6	21.4
2′′	5.18 (t)	5.18 (t)	123.0	122.7
3′′	–	–	131.4	130.9
4′′	1.63 (s)	1.63 (s)	25.8	25.4
5′′	1.75 (s)	1.76 (s)	18.3	17.8

Table 2. Comparison of the NMR spectroscopic data of natural and synthetic flavonoid **2**.

Position	Synthesized compound	Natural compound	Synthesized compound	Natural compound
	δ_H [ppm]	δ_H [ppm]	δ_C [ppm]	δ_C [ppm]
2	–		145.9	141.8
3	–	8.70 (s, OH)	136.8	137.3
4	–	–	175.1	171.1
4a	–	–	105.2	105.7
5	–	–	159.3	158.1
5-OMe	3.83 (s)	3.81 (s)	56.6 (s)	55.9
6	6.28 (s)	6.33 (s)	98.8	96.2
7	–	–	159.9	157.8
8	–	–	102.5	100.9
8a	–	–	153.8	154.9
1′	–	–	122.6	122.2
2′	8.02 (d)	8.04 (d)	128.1	128.6
3′	6.96 (d)	6.94 (d)	115.3	115.5
4′	–	–	157.3	158.5
4′-OH	10.23 (s)	9.97 (s)	–	–
5′	6.96 (d)	6.94 (d)	115.3	115.5
6′	8.02 (d)	8.04 (d)	128.1	128.6
1′′	2.82 (t)	2.87 (t)	16.8	16.0
2′′	1.83 (t)	1.88 (t)	32.4	31.1
3′′	–	–	77.6	75.9
4′′	1.33 (s)	1.35 (s)	25.6	26.3
5′′	1.33 (s)	1.35 (s)	25.6	26.3

Table 3. Comparison of the NMR spectroscopic data of natural and synthetic flavonoid **3**.

Position	Synthesized compound	Natural compound	Synthesized compound	Natural compound
	δ_H [ppm]	δ_H [ppm]	δ_C [ppm]	δ_C [ppm]
2	–	–	146.6	146.3
3	–	–	136.3	136.0
4	–	–	175.4	175.6
4a	–	–	103.7	101.2
5	–	–	159.2	160.8
5-OH	12.96 (s)	12.30 (s)	–	–
6	6.13 (s)	6.25 (s)	98.6	98.8
7	–	–	161.8	159.5
8	–	–	101.1	103.8
8a	–	–	151.8	150.9
1′	–	–	121.5	122.5
2′	8.11 (d)	8.22 (d)	129.1	129.6
3′	6.95 (d)	7.06 (d)	115.5	115.6
4′-OH	10.53 (s)	9.14 (s)	–	–
4′	–	–	158.7	159.3
5′	6.95 (d)	7.06 (d)	115.5	115.6
6′	8.11 (d)	8.22 (d)	129.1	129.6
1′′	6.72 (d)	6.63 (d)	114.2	114.5
2′′	5.56 (d)	5.79 (d)	127.1	127.5
3′′	–	–	77.8	78.1
4′′	1.41 (s)	1.49 (s)	26.9	28.4
5′′	1.41 (s)	1.49 (s)	26.9	28.4

Conclusion

Sophoflavescenol (**1**), flavenochromane C (**2**), and citrusinol (**3**) are three structurally similar naturally occurring flavonoids. They have excellent biological activities such as antitumor, antibacterial, and antifungal properties, or are lead compounds for the treatment of erectile dysfunction. We report here the first total synthesis of these compounds in 10–11 linear steps and in 16–23% overall yield, starting from 2,4,6-trihydroxyacetophenone. The assembly of the 8-prenylated flavonoid carbon skeleton was achieved via a 5-*O*-prenylflavonoid intermediate using a regioselective microwave-assisted Claisen rearrangement.

Experimental Section

General Remarks: Melting points were determined with a XRC-1 apparatus. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AV400 instrument, using tetramethylsilane as internal standard. Chemical shifts (δ) are reported in ppm, and coupling constants (J) in Hertz (Hz). Mass spectra (MS) and high-resolution mass spectrometry (HRMS) were determined with VG Autospec-3000 and Mat 95 XP spectrometers using the EI method. For microwave-assisted synthesis, an XH-MC-1 instrument with power (50–900 W, 2450 MHz) was used. Column chromatography was carried out on silica gel (200–300 mesh). Commercially available AR grade or chemically pure reagents were used. Anhydrous solvents were dried and redistilled. 2-Hydroxy-4,6-bis(methoxymethoxy)acetophenone (**4**) was synthesized according to a literature procedure.[10,11]

2′-Hydroxy-4,4′,6′-trimethoxymethoxylchalcone (5): Potassium hydroxide (20% aq.; 20 mL) was added to a stirred solution of 2-hydroxy-4,6-bis(methoxymethoxy)acetophenone (4.0 g, 15.62 mmol) and 4-methoxymethoxybenzaldehyde (2.5 g, 15.62 mmol) in ethanol (30 mL), and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was cooled to 0 °C (ice-water bath) and acidified with HCl (10% aq.). A yellow precipitate formed, which was collected by filtration, and washed with HCl (10% aq.). The yellow solid was recrystallized from petroleum ether/EtOAc to give chalcone **5** (5.36 g, 85%), m.p. 83–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.85 (s, 1 H, 2′-OH), 7.83 (d, J = 15.2 Hz, 1 H, β-CH=), 7.71 (d, J = 15.2 Hz, 1 H, α-CH=), 7.46 (d, J = 8.5 Hz, 2 H, 2-H and 6-H), 6.96 (d, J = 8.5 Hz, 2 H, 3′-H and 6′-H), 6.31 (d, J = 2.1 Hz, 1 H, 3′-H), 6.26 (d, J = 2.1 Hz, 1 H, 5′-H), 5.28, 5.26, 5.18 (3 s, each 2 H, 3 OCH_2O), 3.52, 3.48, 3.42 (3 s, each 3 H, 3 OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.2, 165.2, 163.5, 161.2, 159.7, 142.2, 129.3, 125.5, 124.8, 115.4, 107.7, 97.2, 95.6, 94.7, 94.3, 94.2, 56.8, 56.5, 56.2 ppm. MS (EI): m/z = 405 $[M + 1]^+$.

5,4′,7-Trimethoxymethylflavone (6): A solution of **5** (5.0 g, 12.37 mmol) and I_2 (1.9 g) in DMSO (60 mL) was stirred at reflux for 24 h. The reaction mixture was cooled to room temperature, then poured into cold water. Saturated aqueous $Na_2S_2O_3$ was added, and the mixture was extracted with dichloromethane. The organic layer was dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The solid residue was re crystallized from dichloromethane/petroleum ether to give **6** (3.48 g, 70%) as yellow crystals, m.p. 124–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.8 Hz, 2 H, 2′-H and 6′-H), 7.05 (d, J = 8.8 Hz, 2 H, 3′-H and 5′-H), 6.78 (d, J = 2.1 Hz, 1 H, 8-H), 6.67 (d, J = 2.1 Hz, 1 H, 3-H), 6.50 (s, 1 H, 6-H), 5.26, 5.18, 5.16 (3 s, each 2 H, 3 OCH_2O), 3.49, 3.44, 3.42 (3 s, each 3 H, 3 OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4, 161.2, 160.8, 159.7, 159.3, 158.1, 127.6, 124.8, 116.4, 110.6, 107.7, 101.1, 97.2, 95.6, 94.2, 56.6, 56.5, 56.3 ppm. HRMS (EI): calcd. for $C_{21}H_{22}O_8$ $[M]^+$ 402.1309; found 402.1322.

3-Hydroxy-5,4′,7-trimethoxymethylflavone (7): A solution of **6** (3.5 g, 8.70 mmol) in acetone/ CH_2Cl_2 (3:4; 210 mL) was mixed with a solution of Na_2CO_3 (14 g) and $NaHCO_3$ (7 g) in water (100 mL), and the mixture was vigorously stirred at 0 °C. Then a solution of Oxone (60 g) in water (200 mL) was added dropwise over 5 h, and after the addition was complete, the pH of the reaction mixture was adjusted to pH 9. Then the reaction mixture was stirred for a further 24 h, after which the mixture was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with saturated NaCl (aq.) and saturated $Na_2S_2O_3$ (aq.), and dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure.

A solution of *p*-toluensulfonic acid (15 mg) in dry acetone (30 mL) was added to solid residue, and the resulting mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, and the solid residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 3:1) to give **7** (2.76 g, 76%) as a yellow solid, m.p. 143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.6 Hz, 2 H, 2′-H and 6′-H), 7.02 (d, J = 8.6 Hz, 2 H, 3′-H and 5′-H), 6.81 (d, J = 1.7 Hz, 1 H, 8-H), 6.73 (d, J = 1.7 Hz, 1 H, 6-H), 5.35, 5.25, 5.20 (3 s, each 2 H, 3 OCH_2O), 3.56, 3.51, 3.19 (3 s, each 3 H, 3 OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 162.4, 161.2, 158.4, 158.2, 146.1, 137.5, 130.5, 123.7, 114.4, 103.5, 97.6, 96.8, 95.5, 94.4, 92.7, 57.6, 56.5, 55.4 ppm. MS (EI): m/z = 419 $[M + 1]^+$.

3,5-Hydroxy-4′,7-dimethoxymethylflavone (8): A solution of **7** (2.5 g, 5.98 mmol) and HCl (3 N aq.; 3 mL) in EtOH (20 mL) was stirred at room temperature for 30 min. The mixture was poured into ice-water, and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was

recrystallized from EtOAc/petroleum ether to give **8** (2.0 g, 89%) as a yellow solid, m.p. 154–155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.85 (s, 1 H, 5-OH), 8.07 (d, J = 8.6 Hz, 2 H, 2′-H and 6′-H), 7.12 (d, J = 8.6 Hz, 2 H, 3′-H and 5′-H), 6.68 (d, J = 1.7 Hz, 1 H, 8-H), 6.48 (s, 1 H, 6-H), 5.26, 5.18 (3 s, each 2 H, 3 OCH_2O), 3.51, 3.21 (2 s, 9 H, 3 OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6, 163.3, 161.1, 160.4, 156.7, 146.2, 136.7, 129.8, 123.5, 114.4, 105.1, 98.8, 94.7, 94.4, 93.3, 56.3, 55.6 ppm. MS (EI): m/z = 375 $[M + 1]^+$.

3,4′,7-Tris-*O*-methoxymethylkaempferol (9): A solution of **8** (1.5 g, 4.0 mmol) and anhydrous K_2CO_3 (5 g, 36.2 mmol) in dry acetone (50 mL) was stirred for 30 min at room temperature. Chloromethyl methyl ether (0.6 mL, 4.5 mmol) was then added dropwise, and the reaction mixture was stirred at room temperature for 2 h. The organic phase was filtered, and the K_2CO_3 solid residue was washed with acetone. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 7:1) to give **9** (1.38 g, 83%) as a white powder, m.p. 112–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.55 (s, 1 H, 5-OH), 8.02 (d, J = 8.8 Hz, 2 H, 2′-H and 6′-H), 7.15 (d, J = 8.8 Hz, 2 H, 3′-H and 5′-H), 6.62 (d, J = 2.0 Hz, 1 H, 8-H), 6.46 (d, J = 2.0 Hz, 1 H, 6-H), 5.25, 5.23, 5.18 (3 s, each 2 H, 3 OCH_2O), 3.51, 3.49, 3.21 (3 s, each 3 H, 3 OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 164.2, 161.8, 158.6, 158.4, 146.7, 136.5, 131.4, 124.2, 116.2, 105.5, 101.6, 98.8, 95.8, 94.3, 94.2, 56.8, 56.5, 54.5 ppm. MS (EI): m/z = 419 $[M + 1]^+$.

5-*O*-Prenyl-3,4′,7-tris-*O*-methoxymethylkaempferol (10): A solution of **9** (1.2 g, 2.87 mmol) and anhydrous K_2CO_3 (5 g, 36.2 mmol) in dry acetone (50 mL) was stirred at room temperature for 1 h, then prenyl bromide (0.5 mL, 6.99 mmol) was added dropwise. The mixture was stirred at 50 °C for 5 h. After this time, the mixture was cooled to room temperature, and filtered. The filter residue was washed with acetone, and the solvent was evaporated from the combined filtrates. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc, 3:1) to give **10** (1.33 g, 95%) as a white solid, m.p. 67–69 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.5 Hz, 2 H, 2′-H and 6′-H), 7.63 (d, J = 8.5 Hz, 2 H, 3′-H and 5′-H), 6.56 (d, J = 1.9 Hz, 1 H, 8-H), 6.36 (d, J = 1.9 Hz, 1 H, 6-H), 5.48 (t, J = 6.1 Hz, 1 H, 2′′-H), 5.17, 5.15, 5.11 (3 s, each 2 H, 3 OCH_2O), 4.63 (d, J = 6.1 Hz, 2 H, 1′′-H), 3.46, 3.44, 3.15 (3 s, each 3 H, 3 OCH_3), 1.71 (s, 3 H, 4′′-CH_3), 1.65 (s, 3 H, 5′-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2, 163.5, 162.3, 160.4, 156.0, 145.4, 138.0, 136.3, 129.9, 127.8, 121.8, 116.7, 111.0, 98.9, 96.6, 94.6, 94.1, 93.3, 66.5, 56.5, 55.4, 55.3, 26.5, 19.9 ppm. MS (EI): m/z = 487 $[M + 1]^+$.

5-Hydroxy-8-prenyl-3,4′,7-tris-*O*-methoxymethylkaempferol (11): A solution of **10** (1.0 g, 2.05 mmol) in dry *N*,*N*-diethylaniline (15 mL) was stirred under microwave irradiation (700 W) under a nitrogen atmosphere at 190 °C for 45 min. After this time, the reaction mixture was cooled to room temperature and acidified with HCl (1 M aq.; 15 mL). The mixture was extracted with dichloromethane, the organic phase was dried with anhydrous Na_2SO_4, and the solvent was evaporated. The solid residue was purified by silica gel chromatography (petroleum ether/EtOAc, 7:1) to give **11** (0.82 g, 82%) as a white solid, m.p. 115–117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.96 (s, 1 H, 5-OH), 7.82 (d, J = 8.5 Hz, 2 H, 2′-H and 6′-H), 7.63 (d, J = 8.5 Hz, 1 H, 3′-H and 5′-H), 6.36 (s, 1 H, 6-H), 5.52 (t, J = 6.2 Hz, 1 H, 2′′-H), 5.24, 5.18, 5.15 (3 s, each 2 H, 3 OCH_2O), 3.52, 3.48, 3.44 (3 s, each 3 H, 3 OCH_3), 3.04 (d, J = 6.1 Hz, 2 H, 1′′-H), 1.73 (s, 3 H, 4′′-CH_3), 1.65 (s, 3 H, 5′′-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 164.2, 160.2, 159.7, 158.6, 146.9, 136.9, 131.6, 128.5, 123.6, 121.6, 114.5, 108.8, 103.5, 96.8, 94.6, 94.1, 93.6, 56.6, 55.3, 55.2, 25.4, 21.8, 19.4 ppm. MS (EI): m/z = 487 $[M + 1]^+$. HRMS (EI): calcd. for $C_{26}H_{30}O_9$ $[M]^+$ 486.1890; found 486.1892.

7,8-(2,2-Dimethyl-2*H*-pyran)-5,4′-dihydroxyflavonol (12): $(CH_3)_2SO_4$ (10.53 mmol, 1.0 mL) was added dropwise to a stirred solution of **11** (500 mg, 1.02 mmol) in NaOH (5% aq.; 15 mL). The reaction mixture was stirred at room temperature, and maintained at pH 9–10 for 5 h. After this time, the reaction mixture was adjusted to pH 6 using HCl (2% aq.), and then the mixture was extracted with ethyl acetate (3× 20 mL). The organic phase was dried with anhydrous sodium sulfate, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 5:1) to give **12** (400 mg, 80%) as a white solid, m.p. 107–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.7 Hz, 2 H, 2′-H and 6′-H), 7.01 (d, J = 8.7 Hz, 2 H, 3′-H and 5′-H), 6.35 (s, 1 H, 6-H), 5.41 (t, J = 5.5 Hz, 1 H, 2′′-H), 5.35, 5.25, 5.20 (3 s, each 2 H, 3 OCH_2O), 3.79 (s, 3 H, 5-OCH_3), 3.56, 3.51, 3.19 (3 s, each 3 H, 3 OCH_3), 3.11 (d, J = 5.3 Hz, 1 H, 1′′-H), 1.72 (s, 3 H, 4′′-CH_3), 1.63 (s, 3 H, 5′′-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.2, 163.4, 161.8, 159.6, 158.5, 146.1, 137.5, 130.5, 128.6, 123.2, 120.3, 113.7, 108.8, 104.6, 97.6, 96.9, 95.9, 94.4, 57.8, 56.7, 56.4, 55.8, 25.7, 22.4, 19.0 ppm. MS (EI): m/z = 501 $[M + 1]^+$. HRMS (EI): calcd. for $C_{27}H_{32}O_9$ $[M]^+$ 500.2042; found 500.2046.

Sophoflavescenol (1): Compound **12** (250 mg, 0.51 mmol) was dissolved in EtOH (15 mL) and HCl (3 M aq.; 2.5 mL), and the reaction mixture was stirred for 2 h. Then the mixture was poured into ice-water, and extracted with EtOAc (3× 20 mL). The combined organic phases were dried with anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. The solid residue was recrystallized from EtOAc/petroleum ether to give **1** (181 mg, 96%) as yellow needles, m.p. 272–274 °C (ref.[15] 273–275 °C). ^{1}H NMR (400 MHz, [D_6]-DMSO): δ = 10.69 (s, 1 H, 4′-OH), 10.23 (s, 1 H, 7-OH), 9.52 (s, 1 H, 3-OH), 8.05 (d, J = 8.5 Hz, 2 H, 2′-H and 6′-H), 7.06 (d, J = 8.6 Hz, 2 H, 3′-H and 5′-H), 6.46 (d, J = 2.2 Hz, 1 H, 6-H), 5.18 (t, J = 6.2 Hz, 1 H, 2′′-H), 3.87 (s, 3 H, 5-OCH_3), 3.46 (d, J = 6.1 Hz, 2 H, 1′′-H), 1.75 (s, 3 H, 4′′-CH_3), 1.63 (s, 3 H, 5′′-CH_3) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 175.6, 160.5, 159.5, 158.7, 155.6, 145.4, 136.3, 131.4, 129.5, 123.0, 122.0, 114.5, 106.0, 104.4, 96.2, 56.8, 25.8, 21.6, 18.3 ppm. MS (EI): m/z = 369 $[M + 1]^+$. HRMS (EI): calcd. for $C_{21}H_{20}O_6$ $[M]^+$ 368.1262; found 368.1254.

8-Prenylkaempferol (13): A solution of **11** (300 mg, 0.6 mmol) and HCl (3 M aq.; 3 mL) in CH_3OH (20 mL) was stirred at reflux for 2 h. After this time, the mixture was cooled to room temperature, and poured into ice-water. A yellow precipitate was formed, which was collected by filtration. The yellow solid was recrystallized from petroleum ether/EtOAc to give **13** (203 mg, 96%) as a pale yellow solid, m.p. 224–225 °C (ref.[16] 226 °C). ^{1}H NMR (400 MHz, [D_6]-DMSO): δ = 12.48 (s, 1 H, 5-OH), 10.68 (s, 1 H, 4′-OH), 10.54 (s, 1 H, 7-OH), 9.59 (s, 1 H, 3-OH), 8.16 (d, J = 8.6 Hz, 2 H, 2′-H and 6′-H), 7.14 (d, J = 8.6 Hz, 2 H, 3′-H and 5′-H), 6.25 (s, 1 H, 6-H), 5.21 (t, J = 5.6 Hz, 1 H, 2′′-H), 3.45 (d, J = 5.5 Hz, 2 H, 1′′-H), 1.73 (s, 3 H, 4′′-CH_3), 1.63 (s, 3 H, 5′′-CH_3) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 176.5, 164.3, 161.8, 160.6, 157.7, 146.2, 136.1, 131.9, 128.9, 123.4, 121.6, 116.4, 108.9, 105.1, 99.3, 25.5, 21.7, 19.2 ppm. MS (EI): m/z = 355 $[M + 1]^+$.

Flavenochromane C (2): A solution of **1** (150 mg, 0.40 mmol) in H_2SO_4 (20% aq.; 10 mL) and CH_3OH (40 mL) was stirred at reflux for 2 h, then the mixture was poured into ice-water and extracted with EtOAc (3× 20 mL). The combined organic phases were dried with anhydrous Na_2SO_4, and the solvent was removed in vacuo.

The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 10:1) to give **2** (126 mg, 86%) as yellow needles, m.p. 266–268 °C (ref.[7] 268–270 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.23 (s, 1 H, 4′-OH), 8.02 (d, J = 8.9 Hz, 2 H, 2′-H and 6′-H), 6.96 (d, J = 8.9 Hz, 2 H, 3′-H and 5′-H), 6.28 (s, 1 H, 6-H), 3.83 (s, 3 H, 5-OCH_3), 2.82 (t, J = 6.2 Hz, 2 H, CH_2-1′′), 1.83 (t, J = 6.2 Hz, 2 H, CH_2-2′′), 1.33 (s, 6 H, 4′′-CH_3 and 5′′-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 159.9, 159.3, 157.3, 153.8, 145.9, 136.8, 128.1, 122.6, 115.3, 105.2, 102.5, 98.8, 77.6, 56.6, 32.4, 25.6, 16.8 ppm. MS (EI): m/z = 369 $[M + 1]^+$. HRMS (EI): calcd. for $C_{21}H_{20}O_6$ $[M]^+$ 368.1261; found 368.1254.

4′-Desmethyl-β-anhydroicaritin (14): A solution of **13** (180 mg, 0.50 mmol) in H_2SO_4 (20% aq.; 15 mL) and MeOH (45 mL) was stirred at reflux for 2 h. Then the mixture was poured into ice-water, and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with water, and dried with anhydrous Na_2SO_4, and the solvent was removed. The solid residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 5:1) to give **14** (152 mg, 86%) as yellow needles, m.p. 207–209 °C (ref.[17] 209–210 °C). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.93 (s, 1 H, 5-OH), 10.35 (s, 1 H, 4-OH), 8.03 (d, J = 8.8 Hz, 2 H, 2′-H and 6′-H), 6.77 (d, J = 8.8 Hz, 2 H, 3′-H and 5′-H), 6.24 (s, 1 H, 6-H), 2.84 (t, J = 6.1 Hz, 2 H, 1′′-H), 1.84 (t, J = 6.1 Hz, 2 H, 2′′-H), 1.36 (s, 6 H, 4′′-CH_3 and 5′′-CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 174.1, 159.6, 158.3, 157.3, 152.8, 145.0, 136.2, 128.2, 122.6, 115.6, 104.9, 103.2, 96.8, 78.2, 30.7, 26.3, 16.7 ppm. MS (EI): m/z = 355 $[M + 1]^+$. HRMS (EI): calcd. for $C_{20}H_{18}O_6$ $[M]^+$ 354.1098; found 354.1096.

Citrusinol (3): A solution of **14** (120 mg, 0.33 mmol) and DDQ (110 mg) in dry 1,4-dioxane (15 mL) was heated at 110 °C and stirred under a nitrogen atmosphere for 24 h. Then the mixture was cooled to room temperature, and filtered, and the solvent was removed under reduced pressure. The resulting solid residue was purified by silica gel chromatography (petroleum ether/EtOAc, 6:1) to give **3** (88 mg, 76%) as a yellow solid, m.p. 251–253 °C (ref.[14] 253–254 °C). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.96 (s, 1 H, 5-OH), 10.53 (s, 1 H, 4′-OH), 8.11 (d, J = 8.6 Hz, 2 H, 2′-H and 6′-H), 6.95 (d, J = 8.6 Hz, 2 H, 3′-H and 5′-H), 6.72 (d, J = 10 Hz, 1 H, 1′′-H), 6.13 (s, 1 H, 6-H), 5.56 (d, J = 10 Hz, 1 H, 2′′-H), 1.41 (s, 6 H, 4′′-CH_3 and 5′′-CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 175.4, 161.8, 159.2, 158.7, 151.8, 146.6, 136.3, 129.1, 127.1, 121.5, 115.5, 114.2, 103.7, 101.1, 98.6, 77.8, 26.9 ppm. MS (EI): m/z = 353 $[M + 1]^+$. HRMS (EI): calcd. for $C_{20}H_{16}O_6$, $[M]^+$ 352.0947; found 352.0946.

Acknowledgments

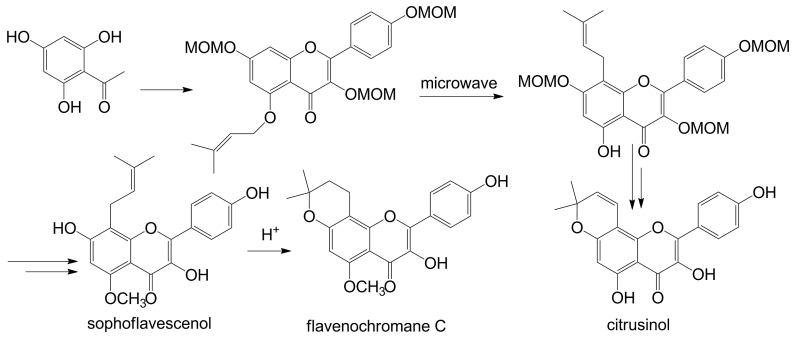
The authors thank the National Natural Science Foundation of China (NSFC) (grant numbers J1210040, 21342015) and the Hunan Provincial Natural Science Foundation of China (grant number 14JJ2048) for financial support.

[1] P. Basabe, M. de Román, S. I. Marcos, D. Diez, A. Blanco, O. Boder, F. Mollinedo, G. B. Sierra, G. J. Urones, *Eur. J. Med. Chem.* **2010**, *45*, 4258–4269.
[2] P. Tiziana, F. Silvia, G. Fravcesca, M. Alberto, G. Giovanni, L. Grazia, *Eur. J. Pharmacol.* **2009**, *620*, 120–130.
[3] X. Dong, Y. Fan, L. Yu, Y. Hu, *Arch. Pharmacol. Res.* **2007**, *340*, 372–376.
[4] T. H. Shin, J. K. Kim, H. J. Kwak, O. H. Chun, H. J. Kim, H. Park, H. D. Kim, S. Y. Lee, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2313–2316.
[5] A. H. Jung, E. S. Jin, J. R. Choi, T. H. Manh, S. Y. Kim, S. B. Min, K. Y. Son, R. B. Ahn, W. B. Kim, S. S. Sohn, S. J. Choi, *Arch. Pharmacol. Res.* **2011**, *34*, 2087–2099.
[6] X. Zhang, *Curr. Drug Targets: CNS Neurol. Disord.* **2004**, *3*, 137–152.
[7] P. Ding, F. D. Chen, F. K. Bastow, K. A. Nyarko, X. Wang, H. K. Lee, *Helv. Chim. Acta* **2004**, *87*, 2574–2580.
[8] H. Sasaki, H. Shibata, K. Imabay, Y. Takaishi, Y. Kashiwada, *J. Agric. Food Chem.* **2014**, *62*, 6345–6353.
[9] C. C. Shen, T. S. Wang, Y. S. Tsai, H. C. Yang, J. B. Shieh, C. C. Chen, *J. Nat. Prod.* **2005**, *68*, 791–793.
[10] S. R. Khupse, W. P. Erhardt, *J. Nat. Prod.* **2007**, *70*, 1507–1509.
[11] A. Detsi, M. Majdalani, A. K. Kontogiorgis, D. Hadjipavlou-Litina, P. Kefalas, *Bioorg. Med. Chem.* **2009**, *17*, 8073–8085.
[12] Z. Wu, L. S. Cai, J. W. Fan, Q. A. Wang, *Chin. J. Org. Chem.* **2012**, *32*, 1296–1302.
[13] J. Yu, J. Cui, C. Zhang, *Eur. J. Org. Chem.* **2010**, *36*, 7020–7026.
[14] S. T. Wu, *Phytochemistry* **1987**, *26*, 3094–3095.
[15] R. E. Woo, H. J. Kwak, J. H. Kim, H. Park, *J. Nat. Prod.* **1998**, *61*, 1552–1554.
[16] M. Komatsu, T. Tomimori, K. Hatayama, N. Mikuriya, *Yakugaku Zasshi* **1970**, *90*, 463–468.
[17] H. X. Zheng, Y. L. Kong, *Zhongcaoyao* **2002**, *33*, 964–967.

Received: December 27, 2014
Published Online: ■

EurJOC European Journal of Organic Chemistry

Flavonoids



The first total syntheses of sophoflavescenol, flavenochromane C, and citrusinol were achieved in 23, 17, and 16% yields, respectively, starting from 2,4,6-trihydroxyacetophenone and substituted benzaldehydes. The key step was a regioselective microwave-assisted Claisen rearrangement to form an 8-prenylated flavonoid from a 5-*O*-prenylflavonoid.

Keywords: Total synthesis / Natural products / Sigmatropic rearrangement / Cyclization / Fused-ring systems / Oxygen heterocycles

