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Total Synthesis of Icaritin *via* Microwave-assistance Claisen Rearrangement

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Abstract: The novel total synthesis of icaritin (**1**), naturally occurring with important bioactive 8-prenylflavonoid, was performed *via* a reaction sequence of 8 steps including Baker-Venkataraman reaction, chemoselective benzyl or methoxymethyl protection, dimethyldioxirane (DMDO) oxidation, *O*-prenylation, Claisen rearrangement and deprotection, starting from 2,4,6-trihydroxyacetophenone and 4-hydroxybenzoic acid in overall yields of 23%. The key step was Claisen rearrangement under microwave irradiation. MS, ^{1}H and ^{13}C NMR techniques have been used to confirm the structures of all synthetic compounds.

Keywords: Icaritin, flavonoid, total synthesis, claisen rearrangement, microwave-assistance.

1. INTRODUCTION

Icaritin (**1**), the aglycone of icariin, is a natural prenylated flavonoid isolated from *Epimedium* Genus [1, 2]. It has shown to exhibit an interesting spectrum of pharmacological effects, such as antio steoporosis activity [3] and estrogen regulation [4]. Recently, icaritin was recognized as a novel anticancer agent that strongly inhibited growth of breast cancer MDA-MB-453 and MCF-7 cells at the concentrations of 2-3 μM [5]. Icaritin also "induces cell death in activated hepatic stellate cells through mitochondrial activated apoptosis and ameliorates the development of liver fibrosis in rats" [6]. Additionally, icaritin and its 3,7-bis-2-hydroxyethyl derivative can act as good phosphodiasterase-5 (PDE-5) inhibitor, which were claimed to be useful for improving the sexual performance and treatment of sexual problems [7].

On the other hand, natural resources of icaritin (**1**) are limited due to the low contents in *Epimedium* plants, which negatively influenced its further bioactivity evaluation. Therefore, chemical synthesis of **1** will be a very important alternative approach for addressing the problem of its availability. So far, **1** has been synthesized *via* an eight-step strategy including Houben-Hoesch acylation, Algar-Flynn-Oyamade reaction and Europium-promoted prenylation *etc*., starting from anhydrous phloroglucin but only 4.2% overall yield was obtained [8]. This method is considered time consuming, less efficient and inappropriate for larger scale synthesis of **1**.

As the continuation of our study on the chemistry and biology of flavonoids [9-11], we herein report the novel total synthesis of **1** through Baker-Venkataraman reaction, chemoselective benzyl or methoxymethyl protection, dimethyldioxirane (DMDO) oxidation, *O*-prenylation, Claisen rearrangement and deprotection, starting from 2,4,6-trihydroxyacetophenone and 4-hydroxybenzoic acid with a reaction sequence of 8 steps in overall yields of 23%. The key step of the synthetic route was *para*-Claisen rearrangement under microwave assistance.

2. RESULT AND DISCUSSION

The novel synthesis route of icaritin (**1**) was shown in (Scheme **1**). The 2,4,6-trihydroxyacetophenone and 4-methoxybenzoyl chloride were prepared from anhydrous phloroglucin with Houben-Hoesch acylation [12], and 4-hydroxybenzoic acid *via O*-methylation and acid chloration respectively. Acylation of **2** with **3** gave rise to aryl ester intermediate, which underwent the Baker-Venkataraman rearrangement and dehydrative closure of the flavone C ring to afford **4** in good yield.

Oxidation of **4** to the 3-hydroxyflavone **5** proved to be challenging. According to our previously published procedures [13], the oxidation of flavone **4** in one-step with dimethyldioxirone (DMDO) generated in situ from oxone and acetone at low temperature, followed by acid-induced rearrangement which gave the hydroxyflavone **5**. The oxidation reaction was completed in excellent regioselective and high yield within a short time period, it was easily conducted on a large scale and product could be purified by recrystallization. Subsequently, Pd/C catalyzed hydrogenolysis of benzyl ether **5** gave kaempferide **6**, for which the spectroscopic data was identical to that reported previously [14].

The selective *O*-methoxymethylation of **6** with chloromethylmethyl ether in dry acetone gave compound **7**. To our knowledge in flavonoid chemistry, the 5-hydroxy group in flavonoid easily form hydrogen bond with the adjacent carbonyl group, in fact, *O*-methoxymethylation of the 5-hydroxyl group is unavailable -chemoselective 3-*O*- and 7-*O*- methoxymethyation of **6** was therefore readily achieved using two equivalents of MOMCl to afford **7**. Further *O*-

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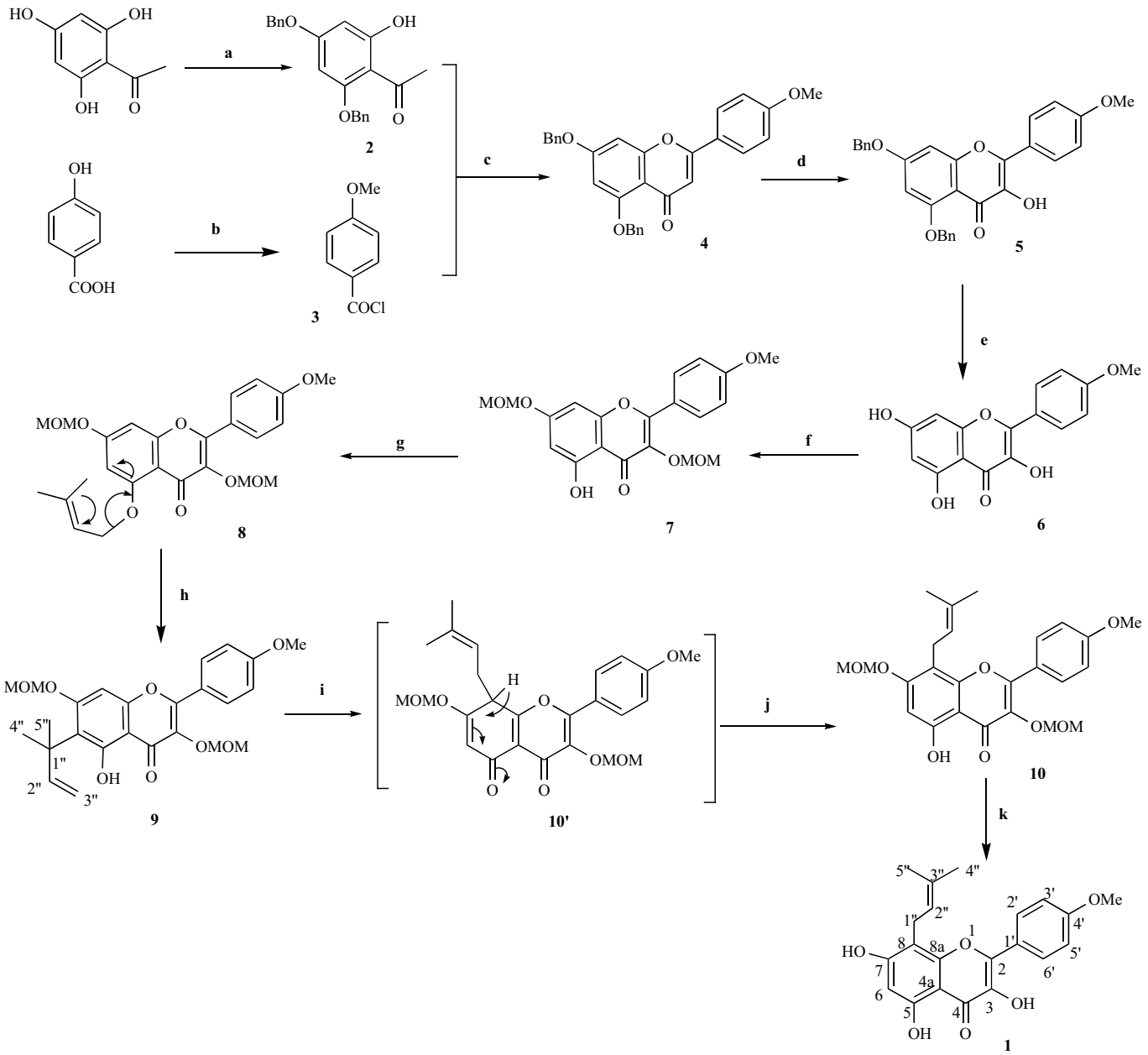

Scheme 1. (**a**) BrBn, K_2CO_3, acetone, reflux, 12 h, 85%; (**b**) $(Me)_2SO_4$, NaOH then $SOCl_2$, CH_2Cl_2, reflux, 86%; (**c**) K_2CO_3, acetone, reflux, 24 h, 70%; (**d**) DMDO, 0 °C, 24 h, r.t then p-toluensulfonic acid, 2 h, r.t, 75%; (**e**) 5% Pd/C, 24 h, r.t, 76%; (**f**) K_2CO_3, acetone, MOMCl, 6 h, r.t, 78%; (**g**) K_2CO_3, acetone, 3,3-dimethylallylbromide, 50 °C, reflux, 12 h, 89%; (**h**) *N,N*-Dietyllaniline, 190 °C, 36 h, reflux, 83% of **9**; (**h-j**) *N,N*-Dietyllaniline, microwave assistance, 190 °C, reflux, 30 min, 85% of **10**; (**k**) 3N HCl, CH_3OH, reflux, 96%.

prenylation at free 5-hydroxyl group of **7** gave **8** using 3,3-dimethylallylbromide as the electrophile reagent.

The *O*-prenylated Claisen precursor **8** was subjected to double sigmatropic rearrangement in *N,N*-diethylaniline under microwave heating leading to the corresponding *C*-prenylated product **10** in 85% yield. The rearrangement was assumed to proceed *via* the intermediate **9** in domino Claisen rearrangement reaction [15]. The last step is careful deprotection of the MOM groups under mild acidic condition which afforded the expected natural product icaritin **1**.

The Claisen rearrangement of the phenyl ether **8** as a key step in our synthetic strategy was investigated under microwave-assistance and conventional heating respectively. The effects on the regioselective and reaction rates by microwave-assistance and conventional heating were compared. While conventional heating, the *ortho*-rearranged product **9** was found to be the preferred one, and was isolated in 83% yield in *N,N*-diethylaniline at 190 °C, However, in the case of microwave-assistance, the para-rearranged product **10** was selected gained in 85% yield in the same system. The two products showed difference of ^{1}H NMR signals for the -$C(CH_3)_2CH{=}CH_2$ in **9** at δ 5.01 and 5.06 (2H, 2dd) and -CH_2-CH=$C(CH_3)_2$ in **10** at δ 3.42 (2H, d) to allow an unambiguous identification of two isomers. The results also demonstrated that microwave-assistance could greatly accelerate the reaction rate of the Claisen rearrangement. The reaction rates under microwave-assistance (700 W) are 72 times

higher than those acted by conventional heating at 190 °C. Thus, we confirmed that the microwave-assistance procedure was suitable for synthesis of MOM protected icaritin **10**.

3. EXPERIMENTAL

3.1. General

The ^1H and ^{13}C NMR spectra were recorded on a Bruker-AV400 spectrometer with internal standards of the different solvents. Mass spectra (MS) and high-resolution mass spectrometry (HRMS) were determined with VG Autospec-3000 or Mat 95 XP spectrometer by the EI method. The chemical shifts (δ) were measured by ppm, and coupling constant (*J)* was calculated in hertz (Hz). While melting points were determined by an XRC-1 apparatus and were uncorrected. Microwave-assistance XH-MC-1 used in organic synthesis having power 50-900 W, 2450 MHz was employed in experimental processes. Column chromatography was carried out on silica gel 200-300 mesh (Qingdao Ocean Chemical Products of China). Commercially available AR or chemically pure reagents, and anhydrous solvent removed redistilled water were employed.

3.1.1. Synthesis of 2-hydroxy-4,6-bis(benzyloxy) Acetophenone (2)

The solution of 2,4,6-trihydroxyacetophenone (5 g, 29.76 mmol) and anhydrous K_2CO_3 (15 g, 108.6 mmol) in 120 mL dry acetone was refluxed at 65 °C for 1 h. Then BnBr (7.5 mL, 63.05 mmol) was added dropwise. After stirring for 16 h, the organic phase was separated. The solvent was removed, and the residue was purified by column chromatography on silica gel (petroleum ether-EtOAc, *v/v*, 30:1) to give **2** (8.8 g, 85%) as white solids, mp 95-96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 14.04 (d, J = 2.0 Hz, 1H, 2-OH), 7.39-7.31 (m, 10H, ArH), 6.16 (s, 1H, 5-H), 6.07 (d, J = 13.5 Hz, 1H, 3-H), 5.05 (t, J = 6.0 Hz, 4H, $2OCH_2$), 2.54 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.2, 167.6, 165.1, 162.0, 135.9, 135.6, 128.8, 128.7, 128.5, 128.0, 127.7, 106.4, 94.8, 92.4, 71.1, 70.3, 33.7; EIMS: m/z 349 $(M+1)^+$.

3.1.2. Synthesis of 4-methoxybenzoyl Chloride (3)

The solution of 4-hydroxybenzoic acid (10 g, 74.07 mmol) in 100 mL 40% NaOH (aq) was strongly stirred at 40 °C and then $(CH_3)_2SO_4$ (17 mL, 63.05 mmol) was added dropwise. The mixture was stirred for 4 h, cooled at room temperature, acidated and filtered, The obtained residue was washed with H_2O and dried. The obtained white solid was poured into 30 mL of dichloromethane and refluxed. Then thionyl chloride ($SOCl_2$) (8.8 mL, 121 mmol) was put into the reaction system. The reaction mixture was stirred under reflux for 4 h. The solvent was removed under reduced pressure obtained **3 (**10.6 g, 86%) as white solid, mp 20-22 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.0 (d, J = 8.9 Hz, 2H, 2-H and 6-H), 6.88 (d, J = 8.9 Hz, 2H, 3-H and 5-H), 3.86 (s, 3H, OMe); EIMS: m/z 171 $(M+1)^+$.

3.1.3. Synthesis of 5,7-bis(benzyloxy)-2-(4-methoxyphenyl)-4H-chromen-4-one (4)

To a solution of compound **2** (5 g, 29.24 mmol) and anhydrous K_2CO_3 (15 g, 0.1 mol) 70 mL of dry acetone was stirred at room temperature for 30 min, then 4-methoxybenzoyl chloride (**3**) (7.5 mL, 63.07 mmol) was added dropwise. The temperature was increased up to 65 °C, after refluxing for 24 h, the organic phase was separated. The solvent was removed, and the residue was purified by column chromatography on silica gel (petroleum ether-EtOAc, *v/v*, 7:1) to afford **4** (5.42 g, 70%) as yellow powder, mp 150-152 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 8.6 Hz, 2H, 2'-H and 4'-H), 7.62 (d, J = 8.6 Hz, 2H, 3'-H, 5'-H), 7.02-7.44 (m, 10H, ArH), 6.65 (d, J = 8.6 Hz, 2H, 6-H), 6.59 (d, J = 8.6 Hz, 1H, 3-H), 6.50 (s, 1H, 8-H), 5.24 (d, J = 8.5 Hz, 2H, 5-OCH_2), 5.12 (s, 7-OCH_2), 3.88 (s, 3H, 4'-OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 163.6, 162.8, 162.0, 160.7, 159.7, 136.4, 135.8, 128.8, 128.6, 127.7, 126.6, 123.8, 114.4, 107.7, 104.6, 98.4, 94.4, 70.8, 70.5, 55.5; EIMS: m/z 465 $(M+1)^+$.

3.1.4. Synthesis of 5,7-bis(benzyloxy)-3-hydroxy-2-(4-methoxyphenyl)-4H- chromen-4-one (5)

A mixture of solution of compound **5** (1.5 g, 2.15 mmol) in 70 mL solvent acetone and CH_2Cl_2, *v/v*, 3:4 with 8 g Na_2CO_3 and 3.5 g $NaHCO_3$ in 70 mL of water, the mixture was strongly stirred at 0 °C. Then 13 g Oxone in 200 mL of water was slowly added dropwise for 5 hours. The solution was adjusted to pH 9. After stirring for 24 h, the organic phase was separated. The aqueous phase was extracted with dichloromethane (30 ml×3). The organic phase was combined and washed with NaCl (aq) and $Na_2S_2O_3$ (aq) three times and, dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, the residue was added 5 mg *p*-toluensulfonic acid in dry acetone. The solution was stirred at room temperature for 2 h. The crude solid was recrystallized from CH_3OH to afford **5** (1.16 g, 75%) as yellow powder, mp 254-256 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = *9.0* Hz, 2H, 2'-H and 6'-H), 7.61 (d, J = 7.3 Hz, 2H, ArH), 7.45-7.35 (m, 8H, ArH), 7.04 (d, J = 9.0 Hz, 2H, 3'-H and 5'-H), 6.66 (d, J = 2. 1 Hz, 1H, 8-H), 6.50 (d, J = 2.1 Hz, 1H, 6-H), 5.31 (s, 1H, 3-OH), 5.25 (s, 2H, 5-OCH_2), 5.16-5.12 (m, 2H, 7-OCH_2), 3.89 (s, 3H, 4'-OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 166.4, 160.6, 159.2, 158.5, 142.5, 137.6, 136.4, 135.7, 130.9, 128.9, 128.5, 127.8, 126.9, 126.7, 122.2, 114.0, 106.7, 97.5, 95.3, 71.3, 70.4, 58.0; E-SIMS: m/z 481 $(M+1)^+$.

3.1.5. Synthesis of Kaempferide (6)

A solution of compound **5** (1000 mg, 2.08 mmol) and 650 mg 5% Pd/C in 15 mL solvent (CH_3OH: EtOAc: 1:1) was stired under H_2 atmosphere (balloon) at room temperature. After stirring for 24 h, the organic phase was separated. The solvent was removed, and the residue was purified by column chromatography on silica gel (petroleum ether-EtOAc, *v/v*, 2:1) to obtain **6** (446 mg, 76%) as yellow powder, mp 224-226 °C; (lit. [16]: 225-227 °C); ^1H NMR (400 MHz, DMSO -d_6): δ 12.47 (s, 1H, 5-OH), 10.90 (s, 1H, 7-OH), 9.53 (s, 1H, 3-OH), 8.14 (s, 2H, 2'-H and 6'-H), 7.11 (s, 2H, 3'-H and 5'-H), 6.47 (s, 1H, 8-H), 6.21 (s, 1H, 6-H), 3.84 (s, 3H, 4'-OMe); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.5 (C4), 164.5 (C7), 161.2 (C5), 160.9 (C4'), 156.7 (C8a), 146.7 (C2), 136.5 (C3), 129.8 (C2' and C6'), 123.7 (C1'), 114.5 (C3' and C5'), 103.6 (C4a), 98.70 (C8), 93.9 (C6), 55.8 (4'-OMe); EIMS m/z 301 $(M+1)^+$; HR-EI-MS: m/z calcd for $C_{16}H_{12}O_6$, 300.0622 $[M]^+$, found 300.0628.

3.1.6. Synthesis of 5-hydroxy-3,7-bis(methoxymethoxy)-2-(4-methoxyphenyl)-4H-chromen-4-one (7)

A solution of compound **6** (400 mg, 1.42 mmol) and dry K_2CO_3 (3.0 g, 21.72 mmol) in 20 mL dry acetone was stirred for 30 min at room temperature, then chloromethyl methoxy ether (0.5 mL, 3.69 mmol) was added dropwise. The mixture was then stirred for 6 h at room temperature and, the organic phase was separated. The solvent was removed in reduced pressure, the residue was poured into 7 mL of ethanolic and 0.5 mL of HCl (3% HCl in EtOH) and stirred at room temperature for 30 min. After diluting with H_2O, the solution was extracted by CH_2Cl_2, which was subsequently rinsed with H_2O. The combined extracts were then dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by column chromatography (petroleum ether-EtOAc, *v/v*, 7:1) to afford **7** (429 mg, 78%) as white powder, mp 158-159 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.57 (s, 1H, 5-OH), 8.04 (d, J = 8.7 Hz, 2H, 2'-H and 6'-H), 7.01 (d, J = 8.7 Hz, 2H, 3'-H and 5'-H), 6.81 (s, 1H, 8-H), 6.73 (d, J = 1.8 Hz, 1H, 6-H), 5.35 (s, 2H, 7-MOM), 5.20 (s, 2 H, 3-MOM), 3.89 (s, 3H, 4'-OMe), 3.56 (s, 3H, 7-MOM), 3.19 (s, 3H, 3-MOM); ^{13} C NMR (100 MHz, $CDCl_3$): δ 177.6 (C4), 164.6 (C7), 161.2 (C5), 159.6 (C4'), 158.4 (C8a), 158.2 (C1), 137.4 (C3), 130.4 (C2' and C6'), 123.2 (C1'), 113.7 (C3' and C5'), 104.6 (C4a), 97.6 (C6), 96.8 (C8), 95.5 (7-MOM), 94.4 (3-MOM), 57.6 (4'-OMe), 56.6 (7-MOM), 55.4 (3-MOM); EIMS: m/z 389 $(M+1)^+$.

3.1.7. Synthesis of 5-(3-methylbut-2-enyloxy)-3,7-bis(methoxymethoxy)-2-(4-methoxyphenyl)-4H-chromen-4-one (8)

The solution of compound **7** (200 mg, 0.52 mmol) and anhydrous K_2CO_3 (2 g, 14.49 mmol) in 10 mL dry acetone was stirred at room temperature for 1 h, then 3,3-dimethylallylbromide (300 µL, 1.62 mmol) was added dropwise, the temperature was increased in reflux at 50 °C for 12 h. The organic phase was separated. The solvent was removed, and the residue was purified by column chromatography on silica gel (petroleum ether-EtOAc, *v/v*, 5:1) to afford **8** (211 mg, 89%) as white solid, mp 76-77°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 8.7 Hz, 2H, 2'-H and 6'-H), 7.01 (d, J = 8.7 Hz, 2H, 3'-H and 5'-H), 6.82 (d, J = 7.5 Hz, 1H, 8-H), 6.70 (d, J = 7.5 Hz, 1H, 6-H), 5.57 (d, J = 8.1 Hz, 1H, 2''-H), 5.23 (s, 2H, 7-MOM), 5.20 (s, 2H, 3-MOM), 4.69 (d, J = 6.5 Hz, 2H, 5-OCH_2), 3.89 (s, 3H, 4'-OMe), 3.51 (s, 3H, 7-MOM), 3.19 (s, 3H, 3-MOM), 1.74 (s, 3H, 4''-Me), 1.70 (s, 3H, 5''-Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8 (C4), 161.7 (C7), 161.2 (C5), 160.3 (C4'), 158.4 (C8a), 153.3 (C2), 137.5 (C3), 130.5 (C2' and C6'), 123.1 (C1'), 119.8 (C2''), 113.9 (C3' and C5'), 109.9 (C4a), 99.9 (C8), 97.9 (C6), 95.6 (7-MOM), 94.5 (3-MOM), 66.9 (C1''), 57.5 (4'-OMe), 56.5 (7-MOM), 55.3 (3-MOM), 25.3 (C5''), 18.7 (C4''); EIMS: m/z 457 $(M+1)^+$.

3.1.8. Synthesis of 5-hydroxy-3,7-bis (methoxymethoxy)-2-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)-4H-chromen-4-one (10) and 5-hydroxy-3,7-bis (methoxymethoxy)-2-(4-methoxyphenyl)-6-(1,1-dimethylallyl)-4H-chromen-4-one (9)

The solution of **8** (190 mg, 0.41 mmol) in 8 mL of dry *N,N*-diethylaniline was stirred in reflux under microwave-assistance (700 W) and nitrogen protection at 190 °C for 30 min. Cooled to room temperature, the reaction was diluted with dilute hydrochloric acid (1N HCl), the mixture was extracted with ethyl acetate (20 mL×3), and dried over anhydrous sodium sulfate. The organic phase was separated, the solvent was removed, and the residue was purified by column chromatography on silica gel (petroleum ether-EtOAc, *v/v*, 7:1) to give **10** (161 mg, 85%) as pale yellow powder, mp 179-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.47 (s, 1H, 5-OH), 8.03 (d, J = 8.6 Hz, 2H, 2'-H and 6'-H), 6.95 (d, J = 8.6 Hz, 1H, 3'-H and 5'-H), 6.16 (s, 1H, 6-H), 5.25 (t, J = 6.7 Hz, 2H, 1H, 2''-H), 5.19 (s, 2H, 7-MOM), 5.11 (s, 2H, 3-MOM), 3.83 (s, 3H, 4'-OMe), 3.42 (d, J = 2.4 Hz, 2H, 1''-H), 3.31 (s, 3H, 7-MOM), 3.13 (s, 3H, 3-MOM), 1.79 (s, 3H, 4''-Me), 1.70 (s, 3H, 5''-Me); ^{13}C NMR(100 MHz, $CDCl_3$): δ 178.5 (C4), 161.5 (C7), 160.5 (C4'), 159.5 (C8a), 156.2 (C5), 153.9 (C2), 135.3 (C3), 131.9 (C3''), 130.5 (C2' and C6'), 123.3 (C2''), 122.5 (C1'), 113.9 (C3' and C5'), 108.5 (C8), 105.7 (C4a), 100.1 (C6), 99.5 (7-MOM), 97.7 (3-MOM), 57.9 (4'-OMe), 56.3 (7-MOM), 55.4 (3-MOM), 31.7 (C1''), 26.6 (C4''), 16.3 (C5''); EIMS: m/z 457 $(M+1)^+$.

The solution of **8** (190 mg, 0.41 mmol) in 8 mL of dry *N,N*-diethylaniline was stirred in reflux and nitrogen protection at 190 °C for 36 h. Cooled to room temperature, the reaction was diluted with dilute hydrochloric acid (1N HCl), the mixture was extracted with ethyl acetate (20 mL×3), and dried over anhydrous sodium sulfate. The organic phase was separated, the solvent was removed, and the residue was purified by column chromatography on silica gel (petroleum ether-EtOAc, *v/v*, 5:1) to give **9** (155 mg, 83%) as pale yellow powder, mp 142-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.42 (s, 1H, 5-OH), 7.84 (d, J = 8.7 Hz, 2H, 2'-H and 6'-H), 7.02 (d, J = 8.7 Hz, 2H, 3'-H and 5'-H), 6.35 (s, 1H, 8-H), 6.23 (dd, J = 9.3, 7.1 Hz, 1H, 2''-H), 5.35 (s, 2H, 7-MOM), 5.28 (s, 2H, 3-MOM, 5.06 (dd, J = 5.4, 3.6 Hz, 1H, 3''H), 5.01 (dd, J = 5.4, 3.3 Hz, 1H, 3''-H), 3.89 (s, 3H, 4-OCH_3), 3.57 (s, 3H, 7-OMOM), 3.47 (s, 3H, 3-OMOM), 1.65 (s, 3H, 4''-Me), 1.59 (s, 3H, 5''-Me); ^{13}C NMR(100 MHz, $CDCl_3$): δ 177.6 (C4), 162.6 (C7), 160.9 (C5), 159.8 (C4'), 158.5 (C2), 156.0 (C8a), 149.1 (C2''), 136.3 (C3), 128.8 (C2' and C6'), 123.0 (C1'), 114.4 (C6), 113.5 (C3' and C5'), 111.9 (C3''), 105.7 (C4a), 98.1 (7-MOM), 96.1 (3-MOM), 93.9 (C8), 55.9 (4'-OMe), 55.3 (7-MOM), 54.7 (3-MOM), 41.9 (C1''), 29.1 (C4'' and C5''); EIMS: m/z 457 $(M+1)^+$.

3.1.9. Synthesis of Icaritin (1)

The solution of **10** (120 mg, 0.26 mmol) in 15 mL CH_3OH and hydrochloric acid (3 N, 2.5 mL) was stirred and refluxed for 2 hour under the nitrogen protection. The solvent was removed under reduced pressure, the crude solid was recrystallized from CH_3OH to give **1** (92 mg, 96%) as light yellow powder: mp 231-232 °C (lit. [17]: 232-233 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.38 (s, 1H, 5-OH), 10.76 (s, 1H, 7-OH), 9.49 (s, 1H, 3-OH), 8.13 (d, J = 9.0 Hz, 2H, 2'-H and 6'-H), 7.13 (d, J = 9.1 Hz, 2H, 3'-H and 5'-H), 6.30 (s, 1H, 6-H), 5.18 (t, J = 6.8 Hz, 1H, 2''-H), 3.85 (s, 3H, 4'-OMe), 3.44 (d, J = 6.7 Hz, 2H, 1''-H), 1.75 (s, 3H, 4''-Me), 1.63 (s, 3H, 5''-Me); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.7 (C4), 161.7 (C7), 160.9 (C4'), 158.8 (C5), 153.9 (C8a), 146.6 (C2), 136.4 (C3), 131.5 (C3''), 129.6 (C2' and C6'), 124.1 (C1'), 122.9 (C2''), 114.6 (C3' and C5'), 106.1

(C4a), 103.5 (C8), 98.3 (C6), 55.9 (4'-OMe), 25.9 (C1''), 21.7 (C4''), 18.3 (C5''); EIMS m/z 369 $[M+1]^+$; HR-EI-MS: m/z calcd for $C_{21}H_{20}O_6$, 368.1262 $[M]^+$, found 368.1254.

4. CONCLUSION

Icaritin (**1**) was synthesized from 2,4,6-trihydroxy-acetophenone and 4-hydroxybenzoic acid *via* a reaction sequence of 8 steps including Baker-Venkataraman reaction, chemoselective benzyl or methoxymethyl protection, dimethyldioxirane (DMDO) oxidation, *O*-prenylation, Claisen rearrangement and deprotection in overall yields of 23%. The key step of the synthetic route was *para*-Claisen rearrangement under microwave-assistance.

CONFLICT OF INTEREST

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

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SUPPLEMENTARY MATERIALS

Supplementary material is available on the publisher's web site along with the published article.

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