HETEROCYCLES, Vol. 97, No. 2, 2018, pp. 1165 - 1174. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 14th February,2018, Accepted, 28th March, 2018, Published online, 6th April, 2018
DOI: 10.3987/COM-18-S(T)59

SYNTHESIS OF OROXYLIN A STARTING FROM NATURALLY ABUNDANT BAICALIN

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Abstract – A new approach to oroxylin A, a monomethylated trihydroxyflavone, is described. The starting material was baicalin, a representative naturally abundant flavonoid glucuronide. First, conditions for the cleavage of the glycosidic bond were established, using a mixture of water and conc. sulfuric acid (5:2) at 121 °C for 40 min. The hydrolysis was performed in a high-pressure steam sterilizer so that the temperature and reaction time were precisely controlled. Subsequent acetylation of the crude material furnished baicalein 6,7-diacetate on a preparative scale and in a reproducible manner. Next, the C-7 position was protected site-selectively with a methoxymethyl (MOM) group, taking advantage of an unexpected sequential migration of the two acetyl groups among the C-5, C-6, and C-7 positions under basic conditions. The removal of the two remaining acetyl groups followed by site-selective methylation of the C-6 position furnished 5-hydroxy-6-methoxy-7-methoxymethoxyflavone (oroxylin A C-7 MOM ether). Finally, by the deprotection of the MOM ether, oroxylin A was obtained in 6 total steps and 62% overall yield from baicalin.

Oroxylin A (**1a**) was first isolated from the bark of *Oroxylum indicum* as a yellow pigment.[1,2] While its physiological activity has garnered interest from many researchers,[3-10] a synergistic anti-inflammatory effect in conjunction with baicalein (**1b**) and wogonin (**2**) has recently been disclosed.[11-13] These three polyoxygenated flavonoids are the component in the extract from Scutellariae radix,[14] the dried root of *Scutellaria baicalensis* Georgi, a herbal medicine (Huang Qin in Chinese and Ogon or Ougon in Japanese). However, the content of three compounds in Scutellariae radix are considerably low, compared with the glucuronide form of **1b**, baicalin (**1c**) with a concentration of over 10 wt% in the dried root. Among these three aglycones (**1a**, **1b** and **2**), oroxylin A is the most scarce component.[15]
So far, some efforts have been devoted to its synthesis.[16] First-generation syntheses[17-19] started from a

substituted resorcinol (A).[20] Wessely-Moser rearrangement which was used in the syntheses suffered from the formation of wogonin-type regioisomer with methoxy group at C-8. Second-generation syntheses[6,7,21] used trimethylated starting materials (B)[22,23] and (C)[24] to avoid such inconvenience. The resulted regiochemically single precursor **1d** required site-selective demethylation at the final stage to form **1a**.

The synthesis based on naturally occurring materials is important, from the standpoint of green chemistry. *Scutellaria baicalensis* is an appropriate sustainable resource, as it is a cultivated plant for the commercial production of Chinese medicines.[14] Starting from baicalein (**1b**), chemical synthesis involving stepwise protection and methylation[25] as well as direct biocatalytic methylation[26] have been reported. However, baicalein is quite expensive, as it is one of three minor components in Scutellariae radix as mentioned before. Herein we report the short-step synthesis of **1a** from baicalin (**1c**), the most abundant ingredient in Scutellariae radix.

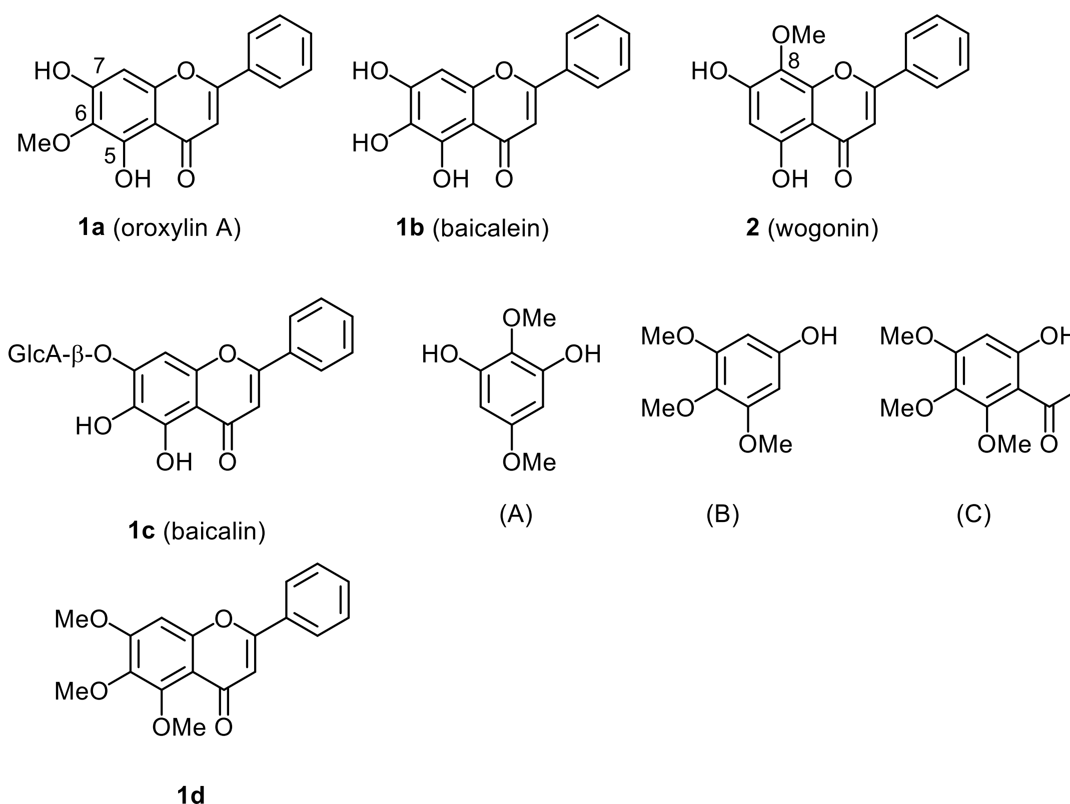
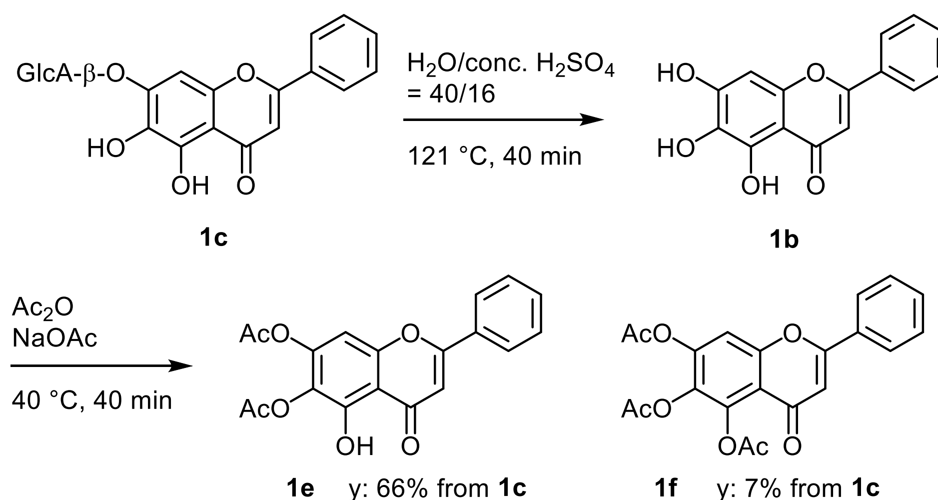


Figure 1. Polyoxygenated flavonoids (**1a**-**c** and **2**) found in Scutellariae radix extract and related compounds

The first task was the efficient preparation of the aglycone form **1b** (baicalein) from **1c** (baicalin). While hydrolysis of the glycosidic bond in **1c** by enzymes involved in the raw material of Scutellariae radix has been reported,[27,28] preparation of **1b** from isolated **1c** under acid catalysis has only been

examined by two groups.[29,30] Since the glycosidic bond in the glucuronide withstands acidic hydrolysis due to its terminal carboxylic acid moiety, the hydrolysis of **1c** required harsh conditions. For example, one group applied a hot mixture of water (abbreviated as W) and conc. sulfuric acid (abbreviated as S) in the ratio of 40:27 by adding the acid as a stream to a mixture of **1c** and water.[30] It was reported that the mixing was exothermic, and the temperature was automatically elevated to 110 °C. We attempted the same procedure; however, almost no hydrolysis was observed. The inner temperature did not exceed 90 °C.



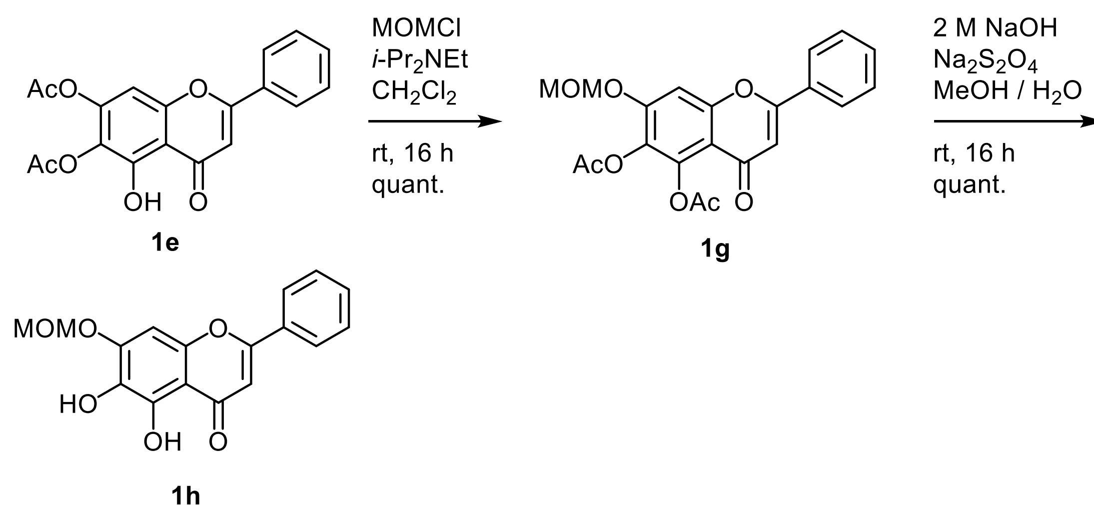
Scheme 1. Acidic hydrolysis of glucuronide in **1c** and isolation of 6,7-diacetate **1e**

To control the temperature and reaction time, we applied a high-pressure steam sterilizer. First, according to the previous report,[30] we heated **1c** in a mixture of W/S (40:27) at 121 °C, which is the standard sterilization temperature, for 30 min. When the vessel was opened, we observed that in the flask black tar precipitated, which indicated the progress of hydrolysis and side reactions owing to the harsh condition. Then we weakened the acidity by decreasing the proportion of sulfuric acid. Using a mixture of W/S (40:9) at 121 °C for 30 min, the resulting light yellow-green precipitates were revealed to be a mixture of **1c** and **1b** in a 100:16 ratio judged by the ^{1}H NMR spectrum (see Experimental). Increasing the proportion of sulfuric acid (W/S = 40:16) under the same temperature and time furnished grey-brown precipitates, and the conversion was improved to 86%. With a slightly longer reaction time (40 min), most of the starting material was consumed and the conversion reached 94%. A lower temperature (110 °C) and a longer reaction time (60 min) were unsatisfactory, achieving only 50% conversion.

The direct purification of **1b** from the resulting mixture was troublesome due to the contamination with tar-like byproducts. Therefore, the crude material obtained by the established conditions (W/S = 40:16,

121 °C, 40 min) was acetylated under mild conditions. Chromatographic separation furnished 6,7-diacetate **1e** (66%) together with a small amount of triacetate **1f**[29,31] (7%) (Scheme 1).

With **1e** in hand, we planned the synthesis of **1a**, by differentiation of the two acetates at C-6 and C-7 positions.[32] Prior to such an event, introduction of a methoxymethyl (MOM) protective group was attempted on the free C-5 hydroxy group (Scheme 2). The reaction seemed to proceed without any difficulty, and a new product was obtained in a quantitative manner. Its ^{1}H NMR spectrum clearly indicated the presence of one MOM and two acetyl groups in the molecule. However, after alkaline hydrolysis of the two acetyl groups, the product showed a phenolic proton with a very downfield chemical shift [δ: 12.57 (1H, s)] in the ^{1}H NMR spectrum, which was very similar to the chemical shift of the proton for C-5 hydroxy group [δ: 12.94 (1H, s)] in 6,7-diacetate **1e**.



Scheme 2. Introduction of MOM group on the hydroxy group at C-7 accompanied by sequential migration of two acetyl groups

To confirm the position of MOM ether in the products, the nuclear Overhauser effect was measured as shown in Figure 2. Upon irradiation of the methylene protons in the MOM group, an nOe was observed to the C-8 proton (2.4%) in **1g**. Similarly, irradiation of the C-8 proton enhanced the intensity of protons in the MOM group (4.0%) of **1h**. We concluded that the MOM group was located on the hydroxy group at C-7 position, in contrast to previous studies. So far, methylation and benzylation occurred predominantly at C-5 and/or C-6 positions, from the same diacetate **1e**.[31]

We explain unexpected formation of **1g** as follows. During the reaction, a phenoxide at C-5 formed first (Figure 2, D). The two acetyl groups migrated in a sequential manner under basic conditions to form the more thermodynamically stable phenoxide ion at the C-7 position (Figure 2, E and its resonance structure F). Finally, this phenoxide attacked MOMCl to form **1g**. It has been reported that upon treatment of

triacetate **1f** with benzyl bromide under basic conditions, benzylation occurred site-selectively at C-7 position *via* the same intermediate E.[33,34] Generally, acetyl group at C-7 in flavones was easily deacetylated to give stable phenoxide.[32] We have also observed a similar migration of acetyl group to form a thermodynamically stable phenoxide at the C-7 position.[35]

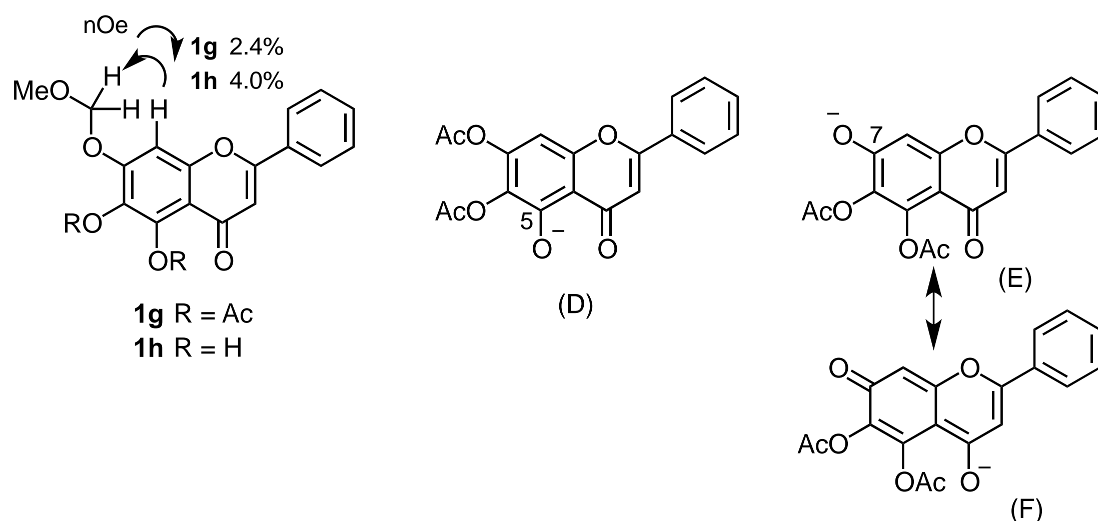
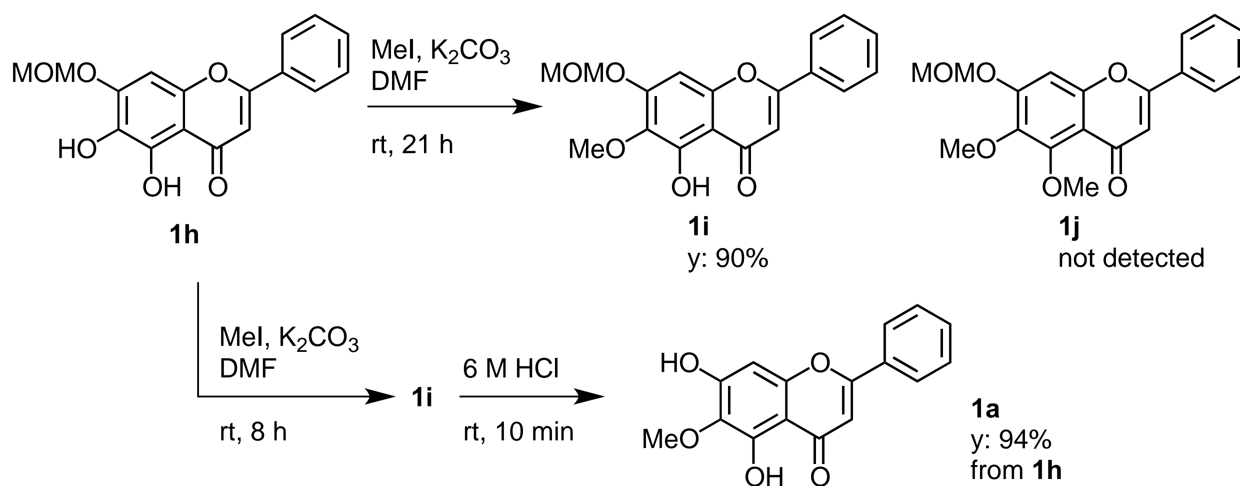


Figure 2. Determination of structures of **1g** and **1h**, and initially formed phenoxide (D), stable phenoxide (E), and its resonance structure (F) in the sequential migration of the two acetates



Scheme 3. Methylation of **1h** and deprotection to oroxylin A (**1a**)

MOM ether **1h** seemed to be an ideal precursor for oroxylin A. Site-selective methylation furnished **1i** with a methyl ether at C-6 exclusively, in 90% yield. Neither the regioisomer of **1i** which has methyl ether at C-5 nor dimethylated form **1j** was not detected in the crude product. Hydroxy group at C-5 is less reactive than others due to the intramolecular hydrogen bonding with carbonyl group at C-4.

Finally, upon treatment with 6 M hydrochloric acid at the workup stage, the MOM ether was smoothly

deprotected to give **1a** in 94% yield from **1h** (Scheme 3). The spectral data were in good accordance with those reported previously.[36]

In conclusion, starting from naturally abundant baicalin (**1c**), an expeditious synthetic route to oroxylin A (**1a**) was achieved in 6 total steps and 62% overall yield. Establishment of the reaction conditions for the acid-catalyzed hydrolysis of **1c**, and the preparation of key intermediate **1g** by MOM ether formation at C-7 accompanied by sequential migration of the two acetyl groups among C-5, C-6 and C-7 positions were the key steps.

EXPERIMENTAL

Melting points were measured on a Mitamura Riken Kogyo MELTEMP or on a METTLER TOLEDO MP 70, and uncorrected. ^{1}H NMR spectra were measured at 400 MHz on a VARIAN 400-MR spectrometer or at 500 MHz on a VARIAN 500-MR spectrometer, and ^{13}C NMR spectra were measured at 125 MHz on a VARIAN 500-MR spectrometer. Acetone-d_6, DMSO-d_6, and $CDCl_3$ were used as solvents and the residual peaks were used as internal standards (^{1}H NMR: acetone-d_6 2.09, DMSO-d_6 2.48, $CDCl_3$ 7.26 ppm; ^{13}C NMR: DMSO-d_6 39.9, $CDCl_3$ 77.0 ppm). IR spectra were measured as ATR on a Jasco FT/IR-4700 spectrometer. High resolution mass spectra were recorded on JEOL JMS-T100LP AccuTOF. Silica gel 60 N (spherical and neutral; 40-50 μm, 37563-84) from Kanto Chemical Co. was used for column chromatography. TOMY LSX-500 high-pressure steam sterilizer was used for acidic hydrolysis over 100 °C. Preparative TLC was performed with Merck Silica Gel 60 F_{254} plates (0.5 mm thickness, No. 5744).

Starting Material. Baicalin (B2835, **1c**) was purchased from Tokyo Chemical Industry Co., Ltd.

6,7-Diacetoxy-5-hydroxyflavone (1e). High-pressure steam sterilizer was pre-heated to 80 °C. In a 500 mL-Erlenmeyer flask were placed **1c** (2.26 g, 5.00 mmol) and a magnetic stirrer bar. A mixture of water (40 mL) and conc. sulfuric acid (16 mL) was poured to the flask with stirring, while hot. The flask was loosely capped with polyurethane porous plug and placed in high-pressure steam sterilizer. The temperature and reaction time were set to 121 °C and 40 min. After cooling down to 75 °C, the flask was taken up and placed in an ice bath. The grey-brown precipitates were collected by filtration, and the residue was washed with water. The conversion of the reaction was estimated to be 94%, by the comparison of the integral of signals in ^{1}H NMR (DMSO-d_6) [δ: 6.61 (s) and 6.92 (s) ppm for **1b**, and 7.00 (s) and 7.04 (s) ppm for **1c**]. To the residue were added acetic anhydride (5 mL) and NaOAc (1.00 g), and the mixture was stirred at 40 °C for 40 min. After cooling, the mixture was poured into ice-water and the precipitates were collected by filtration. The precipitates were washed with water and then dissolved in CH_2Cl_2. The organic solution was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The black residue was purified by silica gel column chromatography

(60 g). First, elution with CH_2Cl_2 discharged black soot from the silica gel column. Further elution with CH_2Cl_2/THF (10/1 to 4/1) furnished **1e** as a yellow solid (1.18 g, 66%). Analytical sample of **1e** was obtained by the recrystallization from $CHCl_3$/*i*-Pr_2O (1/1) as pale yellow fine needles; mp 201.0-201.5 °C; IR 3086, 1789, 1619, 1448, 1354, 1287, 1182, 1081, 1009, 884, 773, 687, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.35 (s, 3H), 2.37 (s, 3H), 6.74 (s, 1H), 6.97 (s, 1H), 7.26-7.58 (m, 3H), 7.89 (d, J = 8.4 Hz, 2H), 12.94 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.2, 20.8, 101.6, 105.7, 109.5, 126.4 (3C), 129.2 (2C), 130.8, 132.3, 148.3, 153.4, 153.4, 165.1, 167.5, 167.7, 182.9; HRMS (ESI) calcd for $C_{19}H_{14}NaO_7$ [$M+Na^+$] 377.0637, found 377.0661.

From more polar fraction eluted on the occasion of chromatographic separation, triacetate **1f** (136 mg) was obtained. **1f:** ^1H NMR (500 MHz, acetone-d_6) δ: 2.34 (s, 3H), 2.35 (s, 3H), 2.37 (s, 3H), 6.78 (s, 1H), 7.56-7.62 (m, 3H), 7.66 (s, 1H) 8.07 (d, J = 8.4 Hz, 2H).

5,6-Diacetoxy-7-methoxymethoxyflavone (1g). To a solution of **1e** (1.00 g, 2.83 mmol) in CH_2Cl_2 were added *N*,*N*-diisopropylethylamine (940 μL, 5.69 mmol) and chloromethyl methy ether (430 μL, 5.66 mmol), and the mixture was stirred for 5 h at room temperature. The reaction mixture was quenched with satureted NH_4Cl aq. solution and extracted with EtOAc three times. The combined extract was washed with brine, and dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (30 g). Elution with hexane/$CHCl_3$ (1/10) furnished **1g** as a white solid (1.12 g, quantitative yield). Analytical sample was obtained by the recrystallization from $CHCl_3$/*i*-Pr_2O (1/3) as colorless prisms; mp 166.3-166.9 °C; IR 2935, 1766, 1628, 1464, 1356, 1159, 914, 884, 771, 687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 2.45 (s, 3H), 3.51 (s, 3H), 5.31 (s, 2H), 6.62 (s, 1H), 7.28 (s, 1H), 7.49-7.54 (m, 3H), 7.87 (dd, J = 8.5, 1.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.3, 20.9, 56.7, 94.9, 101.4, 108.1, 112.0, 126.2 (2C), 129.0 (2C), 130.9, 131.2, 131.6, 141.7, 153.7, 155.4, 162.3, 167.9, 168.7, 176.4; HRMS (ESI) calcd for $C_{21}H_{18}NaO_8$ $[M+Na]^+$ 421.0899, found 421.0885.

5,6-Dihydroxy-7-methoxymethoxyflavone (1h). To a solution of **1g** (300 mg, 0.755 mmol) in MeOH (7.5 mL) and H_2O (7.5 mL) were added $Na_2S_2O_4$ (1.39 g, 7.99 mmol) and 2.0 M NaOH aq. solution (2.4 mL, 4.8 mmol), and the mixture was stirred for 16 h at room temperature. The reaction was quenched with saturated NH_4Cl aq. solution and the resulted mixture was extracted with CH_2Cl_2 three times. The combined extract was washed with brine and dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give **1h** (244 mg, quantitative yield). Analytical sample was obtained by the recrystallization from $CHCl_3$/*i*-Pr_2O (1/2) as intense yellow fine needles; mp 165.5-165.7 °C (lit, 160-162 °C[25]); IR 3026, 2939, 1602, 1462, 1347, 1284, 1152, 1114, 1062, 769, 684, 556 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 3.57 (s, 3H), 5.37 (s, 2H), 5.38-5.48 (br s, 1H), 6.70 (s, 1H), 6.92 (s, 1H), 7.26-7.56 (m, 3H), 7.91 (dd, J = 8.3, 2.0

Hz, 2H), 12.57 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 56.7, 94.0, 95.3, 105.2, 106.6, 126.3 (3C), 129.1 (2C), 130.2, 131.4, 131.8, 146.1, 150.3, 164.4, 182.8; HRMS (ESI) calcd for $C_{17}H_{14}NaO_6$ $[M+Na]^+$ 337.0688, found 337.0671.

5-Hydroxy-6-methoxy-7-methoxymethoxyflavone (1i). To a solution of **1h** (243 mg, 0.772 mmol) in DMF (15 mL) were added potassium carbonate (256 mg, 1.85 mmol) and iodomethane (96.0 μL, 1.54 mmol), and the mixture was stirred for 21 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl aq. solution and extracted with CH_2Cl_2 twice. The combined extract was washed with brine and dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (7 g). Elution with hexane/$CHCl_3$ (3/1 to 1/1) furnished **1i** (228 mg, 90%). Analytical sample was obtained by the recrystallization from $CHCl_3$/*i*-Pr_2O (1/2) as pale yellow leaflets; mp 144.0-144.2 °C (lit, 142-144 °C[25]); IR 2942, 1665, 1613, 1471, 1407, 1349, 1296, 1215, 1146, 1049, 954, 909 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 3.56 (s, 3H), 3.95 (s, 3H), 5.35 (s, 2H), 6.69 (s, 1H), 6.86 (s, 1H), 7.50-7.56 (m, 3H), 7.90 (dd, J = 8.3, 1.7 Hz, 2H), 12.74 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 56.6, 61.0, 94.0, 94.9, 105.4, 106.9, 126.3 (2C), 129.1 (2C), 131.2, 131.9, 133.3, 152.9, 153.4, 156.3, 164.2, 182.9; HRMS (ESI) calcd for $C_{18}H_{16}NaO_6$ $[M+Na]^+$ 351.0845, found 351.0861.

5,7-Dihydroxy-6-methoxyflavone (oroxylin A, 1a). In a similar manner to above-mentioned methylation, to a solution of **1h** (20.4 mg, 0.065 mmol) in DMF (2.0 mL) were added potassium carbonate (11.4 mg, 0.083 mmol) and iodomethane (6.0 μL, 0.097 mmol), and the mixture was stirred for 8 h at room temperature. To the mixture was added 6 M HCl aq. (1.0 mL) solution. After stirring for 10 min, the mixture was extracted with CH_2Cl_2 twice. The combined extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0.6 g). Elution with $CHCl_3$/EtOAc (400/1) furnished **1a** as a yellow solid (17.4 mg, 94%). Analytical sample was obtained by the recrystallization from EtOH as pale yellow fine needles; mp 198.0-198.5 °C (lit, 203-204 °C[21]); ^1H NMR (500 MHz, DMSO-d_6) δ: 3.74 (s, 3H), 6.63 (s, 1H), 6.97 (s, 1H), 7.55-7.62 (m, 3H), 8.06 (d, J = 8.6 Hz, 2H), 8.30 (s, 1H), 12.92 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 60.4, 94.9, 104.8, 105.1, 126.9 (2C), 129.6 (2C), 131.2, 131.9, 132.5, 153.0, 153.2, 158.1, 163.7, 182.8. Its ^1H NMR spectrum was identical with that of an authentic sample, and ^{13}C NMR spectrum was in good accordance with previously reported one.[36]

ACKNOWLEDGEMENTS

We thank Professor Fumiyuki Kiuchi and Dr. Tomofumi Shimizu for their valuable information on oroxylin A and related flavonoids.

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