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SITE-SELECTIVE SYNTHESIS OF ACACETIN AND GENKWANIN THROUGH LIPASE-CATALYZED DEACETYLATION OF APIGENIN 5,7-DIACETATE AND SUBSEQUENT METHYLATION

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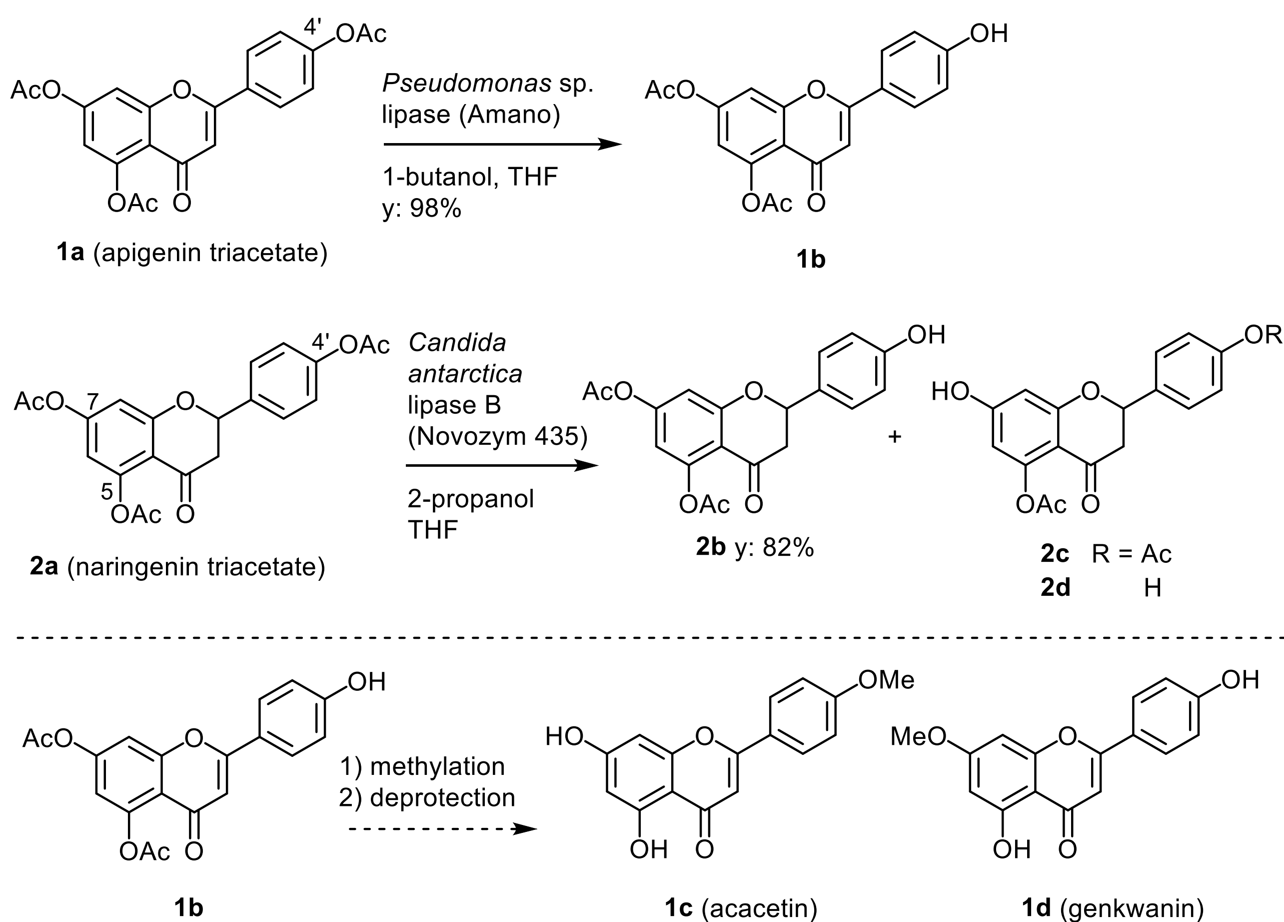
Abstract – *Candida antarctica* lipase B-catalyzed deacetylation proceeded with high site-selectivity on the C-4' acetyl group in apigenin triacetate to give apigenin 5,7-diacetate. Methylation of the liberated hydroxy group with the combination of trimethyloxonium tetrafluoroborate (Meerwein reagent) and 1,8-bis(dimethylamino)naphthalene (proton sponge) in CH_2Cl_2 proceeded in a quantitative manner to give the product methylated at the C-4' hydroxy group (acacetin 5,7-diacetate). Even with the same precursor, a different methylation product at the C-7 hydroxy group (genkwanin 4',5-diacetate) was obtained in 86% yield by applying iodomethane and Cs_2CO_3 in dimethyl sulfoxide (DMSO). The methylated products were deprotected to form acacetin and genkwanin. We inferred that the latter unexpected methylation was ascribable to the intermolecular migration of an acetyl group from C-7 to C-4'. DFT calculations indicated that the C-7 phenoxide ion was 12.6 kJ/mol more stable than the initially formed C-4' phenoxide ion.

Partially protected forms of polyols including flavonoids and polyphenols are important starting materials for physiologically active substances. Commercially available and inexpensive polyols originating from natural resources can be derivatized to target molecules by way of site-selective chemo-enzymatic transformations of fully acetylated intermediates. In the key deacetylation reactions, chemical and enzymatic methods are sometimes complementary in terms of selectivity. Deacetylation by chemical reactions depends upon the electrophilicity of each acetyl group. For example, acyl groups at C-7 in flavonoid acetates are preferentially deacetylated due to the susceptibility of that carbonyl group toward

various nucleophiles,[1,2] compared to those at other positions. In contrast, enzymatic transformation often occurs at the least sterically hindered position of the substrate molecules,[3] and this tendency enables uncommon reactions in well-established chemical transformations. Indeed, *Pseudomonas* sp. lipase (Amano)-catalyzed deacetylation of apigenin triacetate (**1a**) with 1-butanol as a nucleophile in tetrahydrofuran (THF) has been reported. The reaction predominantly occurred at the C-4' acetyl group and the product **1b** was obtained in 98% yield.[4] With a similar flavanone as the substrate, we independently observed that naringenin triacetate (**2a**) treated with 2-propanol in THF under the catalysis of *C. antarctica* lipase B gave **2b** in 82% yield. The transesterification also predominantly occurred at the C-4' position over the formation of regioisomer **2c** and further deacylated product **2d**.[5,6]

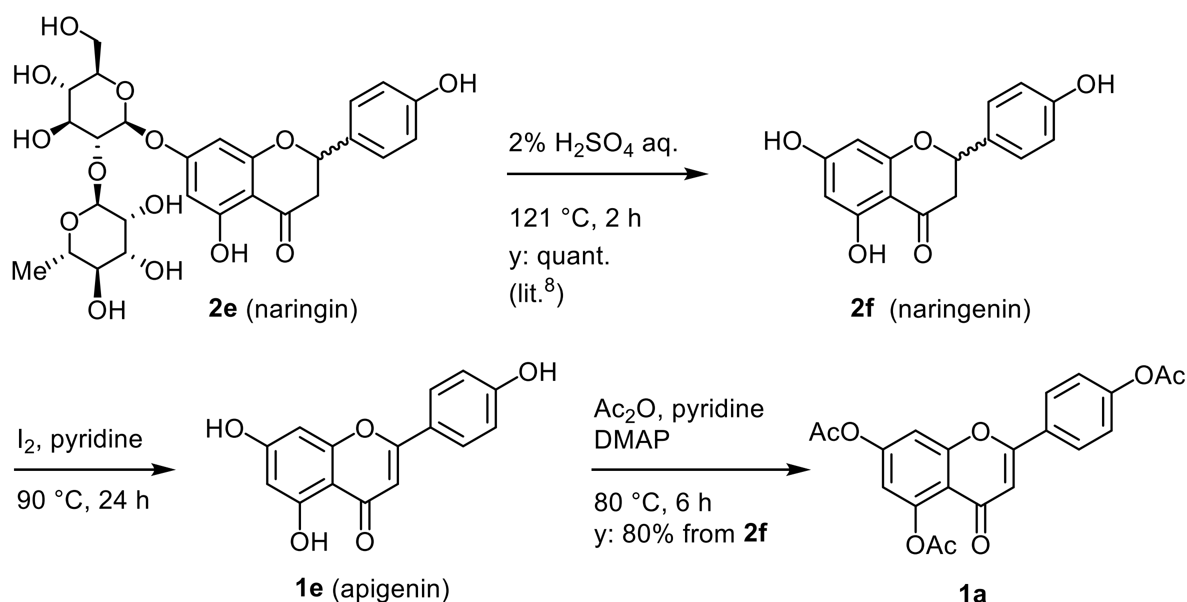


Scheme 1. Lipase-catalyzed C-4' selective deacetylation of **1a** and **2a**, and the derivation to **1c** and **1d** from **1b**

Toward the synthesis of acacetin (**1c**), we preliminary communicated the lipase-catalyzed transesterification of **1a** and some attempts in the methylation of the product **1b**.[3] Herein, we describe the experimental details of the lipase-catalyzed deacetylation of **1a**. Furthermore, we discovered that

two regioisomeric methylation products were accessible from the sole intermediate **1b** simply by changing the methylation conditions. Deprotection of the resulting methylated compounds furnished acacetin (**1c**) and genkwanin (**1d**).

Triacetate **1a**, the substrate of the lipase-catalyzed deacetylation, was prepared from naringin (**2e**) as a commercially available and inexpensive starting material as shown in Scheme 2. We have currently been studying the acidic hydrolysis of glycosidic side chain in flavonoids at elevated temperature, by applying a high-pressure steam sterilizer.[7,8] Exhaustive hydrolysis of neohesperidose in **2e** was accomplished in 2% sulfuric acid for 2 h at 121 °C to give naringenin (**2f**) quantitatively.[8] Dehydrogenation[9] of **2f** and the subsequent acetylation of resulting apigenin (**1e**) furnished apigenin triacetate (**1a**).

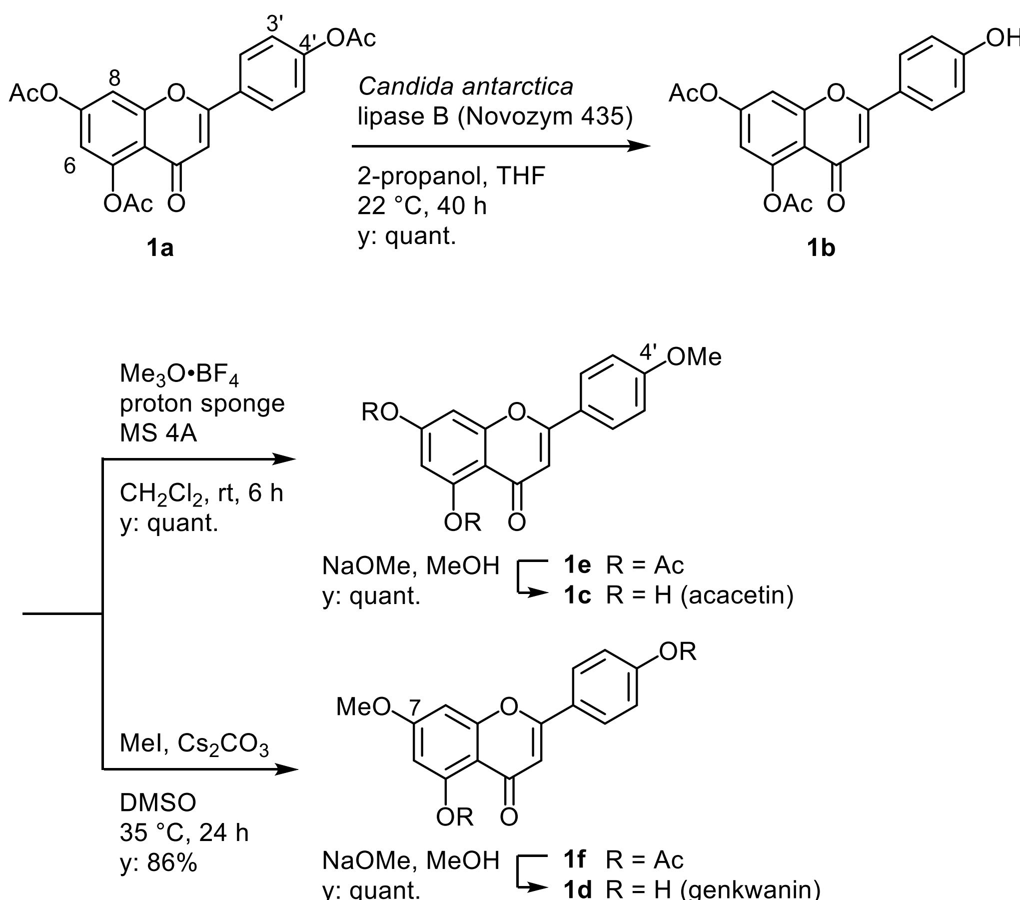


Scheme 2. Preparation of apigenin triacetate (**1a**) starting from naturally abundant naringin (**2e**)

For the site-selective deacetylation, we first attempted *Burkholderia cepacia* lipase (Amano PS-IM)-catalyzed transesterification with 1-butanol as a nucleophile in THF as the solvent at 42 °C, according to the conditions[4] shown in Scheme 1. Although the reaction proceeded in a site-selective manner, the formation of non-polar and polar byproducts other than major **1b** was detected by TLC analysis of the reaction mixture. We then modified the conditions to use 2-propanol in THF, which had been reported for the transformation of **2a**.[6] As reported in Miyazawa's pioneering works,[10,11] the use of secondary alcohols as nucleophiles was effective, and the reaction proceeded very quickly with either *B. cepacia* lipase (Amano PS-IM) or *C. antarctica* lipase B (Novozym 435). Byproduct formation was reduced with the use of *Candida* lipase, judging from the TLC analysis. We further examined the

preparative scale reaction with *C. antarctica* lipase B of **1a** with 2-propanol in THF. The combination of 2-propanol and THF was advantageous, as the desired product **1b** precipitated in the reaction mixture over the course of the desired reaction at 22 °C. In a >3-gram scale reaction, **1b** could be obtained in quantitative yield without any chromatographic separation (see Experimental). The position of the deacetylation was exclusively at C-4', which was supported by an upfield chemical shift of the C-3' signal in the ^{1}H NMR spectrum as shown in Table 1.

After screening of the methylation conditions, we discovered that a methylated product **1e** or **1f** was selectively formed by adopting two different methylation conditions (Scheme 3). The methylation of the liberated hydroxy group at C-4' in **1b** proceeded smoothly by applying trimethyloxonium tetrafluoroborate (Meerwein reagent) with 1,8-bis(dimethylamino)naphthalene (proton sponge)[12,13] in CH_2Cl_2 to give **1e** in a quantitative manner. Its ^{1}H NMR spectrum was in accordance with that reported previously.[14] The remaining two acetyl protective groups were deprotected by treatment with sodium methoxide in MeOH to furnish **1c** (acacetin) in quantitative yield. The physicochemical and spectral properties of synthetic **1c** were in accordance with those of reported acacetin[15,16] isolated from *Robinia pseudoacacia*[17] and other plants, and showed an inductive effect on melanogenesis.[18]



Scheme 3. Lipase-catalyzed site-selective deacetylation of **1a**, and the different methylation products at the liberated C-4' hydroxy group in **1b**

Next, methylation of **1b** at the same position (C-4') was attempted by the action of another methylating agent, iodomethane with Cs_2CO_3 as base in dimethyl sulfoxide (DMSO). To our surprise, the major product **1f** (86%) possessed a different R_f value on TLC analysis compared with that of **1e** (for details, see Experimental). Although both products (**1e** and **1f**) possessed the same molecular ion peak by mass spectrometry, the ^{1}H NMR spectrum of the newly methylated product was in accordance with that of previously reported **1f**.[19]

Table 1. Chemical shift change of selected signals in ^{1}H NMR spectra of apigenin derivatives **1a**, **1b**, **1e** and **1f** upon lipase-catalyzed deacetylation and subsequent methylation

	δ (ppm) in DMSO-d_6	
	H-3'	H-6 and H-8
1a	7.26	7.35, 6.85
1b	6.91	7.56, 7.03
1e	7.00	7.32, 6.81
1f	7.56	6.88, 6.63

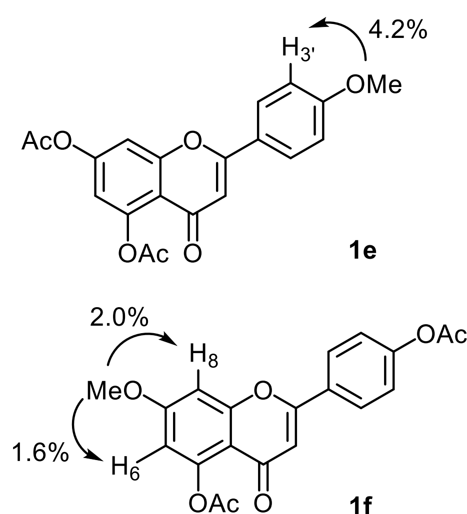


Figure 1. Elucidation of the regiochemistries of **1e** and **1f** using nOe measurements

The position of the methylation was confirmed by chemical shift changes of 3′-, 6- and 8-H in ^{1}H NMR and nuclear Overhauser effect (nOe) experiments. The proton chemical shifts of **1a**, **1b**, **1e** and **1f** are summarized in Table 1. After methylation with Meerwein reagent (**1b** to **1e**), the chemical shift for H-3' was almost unchanged and those for H-6 and 8 were shifted slightly upfield. In contrast, a significant downfield shift for 3′-H and upfield shifts for H-6 and 8 were observed upon methylation with iodomethane and Cs_2CO_3 (**1b** to **1f**). These changes suggested the introduction of a methyl group onto the chromone moiety (left part of **1f**) and an acetyl group into the benzene ring (right part of **1f**). Additionally, the nOe experiments indicated that the newly introduced methyl group was located at C-7 in **1f**, in contrast to that in **1e** (Figure 1). Finally, thus obtained **1f** was transformed to genkwanin (**1d**) by deprotection of the acetyl groups at C-4' and C-5. Genkwanin was first identified as a component[20] from the dried flower bud of *Daphne genkwa* Sieb. et Zucc., which is a herbal medicine known as

Yuanhua in Chinese and Genkwa in Japanese. Recently, its antibacterial,[21] anti-inflammatory,[22] and antitumor[23] activities have been reported.

We propose a mechanism of the unexpected migration of the acetyl group in the methylation step from **1b** to **1f** as follows.[7,24] After deprotonation of the C-4' hydroxy group, the phenoxide ion at C-4' intermolecularly attacks the most electrophilic acetyl group at C-7 of another molecule of **1b**, resulting in *in situ* formation of the thermodynamically more stable phenoxide ion at C-7. DFT calculations [PBE0/6-31+G(d), PCM (DMSO)] indicated that the C-7 phenoxide ion was 12.6 kJ/mol more stable than the initially formed C-4' phenoxide ion. Methylation with iodomethane at C-7 then occurs to give **1f**.

In the reaction using the proton sponge and Meerwein reagent in CH_2Cl_2, the proton sponge forms a chelation complex with **1b** by hydrogen bonding between the phenolic proton and two dimethylamino groups, but does not generate the phenoxide anion of **1b** with naked anion character. Accordingly, methylation immediately occurs at the C-4' position without migration of the acetyl group, although the difference in reactivity of the nucleophile toward the acetyl group or the methylating reagent is unclear.

We attempted the methylation at C-4' in **1b** by diazomethane in a mixture of CH_2Cl_2 and diethyl ether as the solvent, since it is believed that the methylation proceeds through an ion pair between phenoxide and the protonated form of diazomethane. To our disappointment, the reaction furnished a complex mixture of products with methyl ethers and free phenols. Since both **1e** and **1f** were detected among the components, the initially formed C-4' phenoxide might escape from the solvent cage to a certain extent to form the C-7 phenoxide.

In conclusion, starting from naturally abundant naringin (**2e**), methylated flavonoids such as acacetin (**1c**) and genkwanin (**1d**) were synthesized. *C. antarctica* lipase B-catalyzed deacetylation of apigenin triacetate (**1a**) proceeded with high site-selectivity at the C-4' acetyl group to give apigenin 5,7-diacetate (**1b**) in quantitative yield. With the resulting key intermediate **1b**, the position of the methylation depended upon the reaction conditions. The combination of Meerwein reagent and proton sponge furnished the C-4' methylated product **1e** in a quantitative manner, as the precursor of acacetin (**1c**). In contrast, with the combination of iodomethane and Cs_2CO_3, the regioisomeric C-7 methylated product **1f** was obtained in 86% yield, which was transformed to genkwanin (**1d**).

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 500 MHz on a VARIAN 500-MR spectrometer, and ^{13}C NMR spectra were measured at 100 MHz on VARIAN 400-MR spectrometer or at 125 MHz on a VARIAN 500-MR spectrometer. DMSO-d_6 and $CDCl_3$ were used as solvents and the

residual peaks were used as internal standards (^{1}H NMR: 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. Thin layer chromatographic (TLC) analyses were performed using silica gel 60 F_{254} glass plates (Merck, 105715).

Starting Material. Naringin (N0073, **2e**) was purchased from Tokyo Chemical Industry Co., Ltd.

4',5,7-Triacetoxyflavone (apigenin 4',5,7-triacetate, 1a). Naringenin (**2f**) was prepared from **2e** according to the reported procedure.[8] To a solution of **2f** (1.36 g, 5.00 mmol) in pyridine (7.5 mL) was added iodine (1.40 g, 5.51 mmol), and the mixture was stirred for 24 h at 90 °C. To the mixture were added acetic anhydride (10 mL) and catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP), and further stirred for 6 h at 80 °C. After cooling, the mixture was concentrated *in vacuo* and the residue was diluted with water. The precipitates were collected by filtration and dissolved in $CHCl_3$. The resulting suspension was filtered to remove insoluble materials through a pad of Celite® and washed with $CHCl_3$. The filtrate and washings were combined and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (50 g). Elution with hexane/$CHCl_3$ (3:1 to 1:1) furnished **1a** as a colorless solid (1.67 g, 80%). Analytical sample of **1a** was obtained by the recrystallization from EtOH as colorless fine needles; mp 182.3-182.8 °C (lit., 185-186 °C[19]); IR 1754, 1641, 1611, 1505, 1478, 1416, 1373, 1180, 1135, 1084, 1012, 893, 840 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.35 (s, 3H), 2.36 (s, 3H), 2.44 (s, 3H), 6.62 (s, 1H), 6.85 (d, J = 2.2 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 2.2 Hz, 1H), 7.88 (d, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 21.2 (2C), 108.6, 109.0, 113.7, 114.9, 122.4 (2C), 127.6 (2C), 128.6, 150.2, 153.3, 154.0, 157.6, 161.7, 168.0, 168.9, 169.4, 176.3; HRMS (ESI) calcd for $C_{21}H_{16}NaO_8$ [M+Na^{+}] 419.0743, found 419.0739.

5,7-Diacetoxy-4'-hydroxyflavone (apigenin 5,7-diacetate, 1b). To a suspension of **1a** (3.00 g, 7.57 mmol) in 2-propanol (20 mL) and THF (40 mL) was added an immobilized form of *C. antarctica* lipase B (Novozymes, Novozym 435, 300 mg). The mixture was stirred for 40 h at 22 °C. After diluted with diisopropyl ether (30 mL) and cooling with ice, the insoluble materials were collected by filtration. The residue was washed with cold diisopropyl ether, and extracted with hot 1,4-dioxane (60 mL) twice, to remove immobilized lipase. The filtrate and washings were combined and concentrated *in vacuo*. The residue was refluxed with EtOH. After cooling with ice, the residue was collected by filtration and washed with ice-cooled EtOH. A colorless solid **1b** was obtained as the first crop (2.59 g). Mother liquor, washings at the stage of the initial recovery of the product and washings by hot EtOH were further combined and concentrated *in vacuo*. The residue was suspended with EtOH, and ultrasonic vibration was applied to the mixture. Insoluble materials were collected by filtration and washed with EtOH.

Second crop of **1b** was obtained as a colorless solid in this way (402 mg). The combined yield was quantitative. Those samples showed only one spot on TLC. Analytical sample of **1b** was obtained by the recrystallization from EtOH as colorless needles; mp 197.5-197.8 °C; IR 1773, 1626, 1593, 1430, 1375, 1249, 1179, 1152, 1032, 854 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 2.30 (s, 3H), 2.31 (s, 3H), 6.72 (s, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 2.2 Hz, 1H), 7.56 (d, J = 2.2 Hz, 1H), 7.91 (d, J = 8.8 Hz, 2H), 10.33 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 21.3 (2C), 106.2, 110.1, 114.5, 114.8, 116.4 (2C), 121.3, 128.8 (2C), 149.8, 154.1, 157.4, 161.6, 162.7, 168.9, 169.3, 175.7; HRMS (ESI) calcd for $C_{19}H_{14}NaO_7$ [M+Na$^+$] 377.0637, found 377.0666.

5,7-Diacetoxy-4'-methoxyflavone (acacetin 5,7-diacetate, 1e). To a suspension of **1b** (250 mg, 0.706 mmol) in CH_2Cl_2 (14 mL) were added activated and powdered molecular sieves 4A (500 mg), 1,8-bis(dimethylamino)naphthalene (proton sponge, 756 mg, 3.53 mmol) and trimethyloxonium tetrafluoroborate (Meerwein reagent, 626 mg, 4.23 mmol). The mixture was stirred for 6 h at room temperature. The mixture was filtrated through a pad of Celite® to remove insoluble materials and the residue was washed with CH_2Cl_2. The filtrate and washings were combined and washed with 2 M HCl aq. solution (10 mL) three times and brine, and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (13 g). Elution with hexane/CH_2Cl_2 (1:9 to 1:20) furnished **1e** as a colorless solid (265 mg, quantitative yield). Analytical sample of **1e** was obtained by the recrystallization from EtOH as colorless fine needles; mp 198.7-199.2 °C (lit., 199 °C[15]); R_f 0.56 ($CHCl_3$/EtOAc = 1:2); IR 2938, 1761, 1628, 1605, 1514, 1424, 1368, 1258, 1179, 1136, 1033, 1015, 828, 648 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 2.43 (s, 3H), 3.87 (s, 3H), 6.56 (s, 1H), 6.81 (d, J = 2.2 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 2.2 Hz, 1H), 7.80 (d, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.7, 20.8, 55.1, 106.7, 108.6, 113.1, 114.1 (2C), 114.4, 122.8, 127.5 (2C), 149.7, 153.3, 157.2, 162.1, 162.2, 167.7, 169.1, 176.0; HRMS (ESI) calcd for $C_{20}H_{16}NaO_7$ [M+Na$^+$] 391.0805, found 391.0814.

5,7-Dihydroxy-4'-methoxyflavone (acacetin 1c). To a suspension of **1e** (40.0 mg, 0.110 mmol) in anhydrous MeOH (1.6 mL) was added 28% NaOMe in MeOH (45.0 μL, 0.233 mmol), and the mixture was stirred for 1 h at room temperature. The reaction was quenched with saturated NH_4Cl aq. solution (1 mL) and extracted with EtOAc twice. The combined extract was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. A pale yellow solid **1c** was obtained (32.1 mg, quantitative yield). Analytical sample of **1c** was obtained by the recrystallization from MeOH as pale yellow fine needles; mp 254.8-255.2 °C (lit., 255-256 °C[15]); ^1H NMR (500 MHz, DMSO-d_6) δ: 3.84 (s, 3H), 6.19 (d, J = 2.2 Hz, 1H), 6.49 (d, J = 2.2 Hz, 1H), 6.86 (s, 1H), 6.98 (dd, J = 8.8, 2.0 Hz, 2H), 8.02 (dd, J = 8.8, 2.0 Hz, 2H), 10.84 (s, 1H), 12.91 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 56.0, 94.5, 99.3, 104.0, 104.2, 115.0 (2C), 123.3, 128.8 (2C), 157.8, 161.9, 162.7, 163.7, 164.7, 182.2.

4’,5-Diacetoxy-7-methoxyflavone (genkwanin 4’,5-diacetate, 1f). To a solution of **1b** (750 mg, 2.12 mmol) in dimethyl sulfoxide (DMSO, 5.0 mL) was added Cs_2CO_3 (1.38 g, 4.24 mmol), and the reaction mixture was stirred for 10 min at room temperature under nitrogen atmosphere. While a change of color of solution to orange was observed, iodomethane (530 μL, 8.51 mmol) was added dropwise, and the resulting mixture was stirred for 24 h at 35 °C. Then, the reaction was quenched with phosphate buffer solution (0.20 M, 10 mL) and ice-cooled water (30 mL). The precipitates were collected by filtration, and the resulting solid was washed water and then dried. The residue was suspended in $CHCl_3$, and dried over anhydrous Na_2SO_4, and the insoluble materials were filtered off. The resulting solution was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (15 g). Elution with $CHCl_3$/EtOAc (3:1) furnished **1f** as a colorless solid (670 mg, 86%). Analytical sample of **1f** was obtained by the recrystallization from EtOH as colorless fine needles; mp 195.8-196.0 °C (lit., 196 °C[19]); R_f 0.69 ($CHCl_3$/EtOAc = 1:2); IR 2934, 1747, 1635, 1603, 1504, 1436, 1415, 1375, 1349, 1193, 1154, 1086, 1012, 915, 898, 837, 666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.35 (s, 3H), 2.44 (s, 3H), 3.92 (s, 3H), 6.58 (s, 1H), 6.63 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.2 (2C), 56.0, 99.1, 108.4 (2C), 111.1, 122.3 (2C), 127.5 (2C), 129.0, 150.6, 153.1, 158.8, 161.2, 163.6, 169.0, 169.7, 176.4; HRMS (ESI) calcd for $C_{20}H_{16}NaO_7$ [M+Na$^+$] 391.0794, found 391.0814. Further elution in the column chromatography with $CHCl_3$/EtOAc (10:1) gave **1b** (8 mg, 5%) as the unreacted recovery.

4’,5-Dihydroxy-7-methoxyflavone (genkwanin, 1d). In a similar manner to synthesis of **1c**, **1f** (50.1 mg, 0.136 mmol) was treated with 28% NaOMe in MeOH (53.0 μL, 0.275 mmol) for 3 h at room temperature. The reaction was quenched with saturated NH_4Cl aq. solution (1.0 mL) and extracted with EtOAc twice. The combined extract was washed with brine, and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. A pale yellow solid **1d** was obtained (43.2 mg, quantitative yield). Analytical sample of **1d** was obtained by the recrystallization from MeOH as pale yellow fine needles; mp 284.0-284.7 °C (lit., 286 °C[19]); ^1H NMR (500 MHz, DMSO-d_6) δ: 3.85 (s, 3H), 6.36 (d, J = 2.2 Hz, 1H), 6.76 (d, J = 2.2 Hz, 1H), 6.84 (s, 1H), 6.91 (dd, J = 8.8, 2.0 Hz, 2H), 7.95 (dd, J = 8.8, 2.0 Hz, 2H), 10.37 (s, 1H), 12.95 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 56.4, 93.0, 98.3, 103.4, 105.1, 116.4 (2C), 121.5, 128.9 (2C), 157.6, 161.6, 161.7, 164.4, 165.4, 182.3.

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