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Semisynthesis of prunetin, a bioactive O-methylated isoflavone from naringenin, by the sequential deacetylation of chalcone intermediates and oxidative rearrangement

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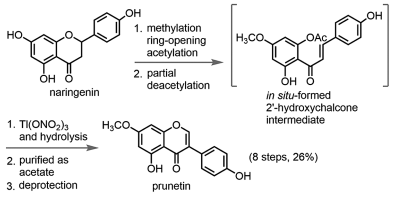
ABSTRACT

Prunetin (4′,5-dihydroxy-7-methoxyisoflavone) was semisynthesized in 8 steps from readily available naringenin in 26% total yield. The key reaction was chemoenzymatic sequential deacetylation to 6′-acetoxy-2′,4″-dihydroxy-4′-methoxychalcone, the *in situ*-formed precursor for thallium(III) nitrate-mediated oxidative rearrangement.

Graphical Abstract



Prunetin was semisynthesized from naringenin in 8 steps, based on stepwise deacetylation and subsequent thallium(III)-mediated oxidative rearrangement of a 2'-hydroxychalcone.

Keywords: O-methylated isoflavone, naringenin, chalcone, deacetylation, oxidative rearrangement

Prunetin (1a; Figure 1) is secreted from the roots of pea plants and attracts zoospores of the phytopathogenic fungus *Aphanomyces euteiches* (Yokosawa *et al.* 1986). Prunetin has been isolated from many plants, such as *Prunus emarginata* (Finnemore 1910), *Pterocarpus angolensis* (King and Jurd 1952), and *Crotalaria lachnophora* (Awouafack *et al.* 2011), and its structure was elucidated as a derivative of genistein (1b) methylated at the C-7 position (King and Jurd 1952). Prunetin exhibits several biological activities in the human body, including as a phytoestrogenic (Andres *et al.* 2015; Hillerns *et al.* 2005) and has bone-regeneration (Khan *et al.* 2015) anti-inflammatory (Yang *et al.* 2013), vasorelaxation, (Kim *et al.* 2018) and anti-osteoarthritis (Nam *et al.* 2016) properties.

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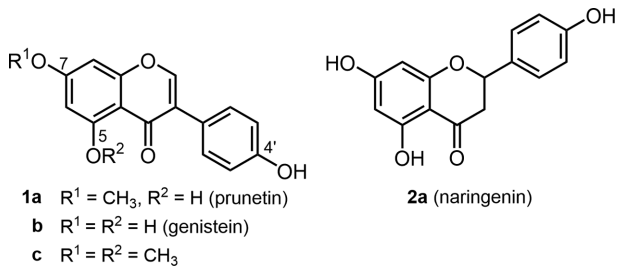


Figure. 1. Prunetin (1a), related isoflavones (1b, 1c), and naringenin (2a).

Prunetin (1a) can be prepared simply by methylating genistein (1b; Figure 1, Li *et al.* 2006), but genistein isolated from natural resources is expensive, prompting many researchers to develop general chemical synthetic routes for isoflavones (Lévai, 2004). For example, prunetin has been synthesized by site-selective demethylation at the C-5 position of the chemically synthesized 5,7-di-O-methylated precursor (1c) (Iyer *et al.* 1951; Sekizaki and Yokosawa, 1988). Our ongoing studies on the transformation of naturally occurring flavonoids (Kurahayashi *et al.* 2018; Kurahayashi *et al.* 2020; Tsunekawa *et al.* 2018) prompted us to synthesize 1a from readily available naringenin (2a; Figure 1), a hydrolysate of naturally abundant and inexpensive naringin (Kurahayashi *et al.* 2018), and retaining the carbon atoms in the original skeleton.

We envisioned the oxidative rearrangement of 2′-hydroxychalcone (3a) mediated by thallium(III) nirate (TTN) (Farkas *et al.* 1974; Sekizaki and Yokosawa, 1988; Thakkar and Cushman, 1995) as the key reaction for the transformation (Scheme 1). In 3a, the electron-rich property is advantageous for the higher migrating property of aromatic ring (Thakkar and Cushman, 1995) from initial intermediate (X) to the following oxonium ion (Y), and thus the oxygen function at the C-4″ position should be a free hydroxy group rather than protected form with an electron-withdrawing group. The addition of methanol provides an acetal (Z), and the treatment under acidic conditions deprotects both of dimethyl acetal and phenolic acetate to furnish 1a. Through this transformation, only one phenolic hydroxy group should be temporarily protected, between the hydroxy groups at the C-2′ and C-6′ positions, for efficient oxidative rearrangement. If both of phenolic hydroxy groups are over-deprotected to 3b, it would spontaneously cyclize to undesired flavanone by-product 2b.

Results and discussion

The first step of the present synthesis involved the directed introduction of a methyl group at the most acidic C-7 hydroxy group of naringenin (2a) (Kim *et al.* 2007; Oyama and Kondo, 2004). The methylation at C-7 was driven to completion by treating 2a with a slight excess (1.1 equivalent) of dimethyl sulfate. However, the desired product 2b was contaminated with over-methylated byproducts such as 2c. Without isolating each component, direct acetylation of the mixture at high temperature (Fujise and Sasaki, 1938; Shimokoriyama, 1949) furnished a mixture of chalcone acetates 3c and 3d, which behaved similarly during chromatographic purification.

To synthesize the key intermediate 3a, the two acetyl protective groups at C-4″ and C-2′ were deprotected by the complementary use of lipase and a Lewis acid in a stepwise manner. First, the mixture of 3c and 3d was subjected to *Candida antarctica* lipase B (Novozym 435)-catalyzed deacetylation (Fujita *et al.* 2019; Hanamura *et al.* 2016; Kobayashi *et al.* 2013; Tsunekawa *et al.* 2018) to liberate the C-4″ position as a free hydroxy group, aiding the isolation of 3e by leaving over-methylated by-products such as 3d intact. Chromatographic purification and subsequent crystallization from diethyl ether furnished the desired 3e in 80% yield from 2a in 3 steps (Scheme 2).

Next, we attempted to deacetylate one of the two acetyl groups at C-2′ and C-6′ located adjacent to the aromatic carbonyl group by activating with a Lewis acid, boron trifluoride-diethyl ether complex [$BF_3{\cdot}OEt_2$] (Narender *et al.* 2008; Tsunekawa *et al.* 2018) and subsequently treating with water. The desired 2′-hydroxychalcone 3a was obtained only in 22% yield because the product was susceptible to over-deacetylation. Moreover, chromatographically purified 3a contained undesired flavanones due to 3b being prone to spontaneous cyclization as suggested in Scheme 1, even under neutral conditions. Similar behavior was observed with the closely related compound 6′-acetoxy-2′-hydroxychalcone (Shimokoriyama, 1949).

Then, the solution of *in situ*-formed 3a in 1,4-dioxane was submitted to TTN-mediated oxidative rearrangement in methanol. Contrary to a previous report (Taylor *et al.* 1976), oxidative rearrangement of the substrate in methanol was faster than in a mixture of methanol and trimethyl orthoformate. Hydrolytic cleavage of the dimethyl acetal moiety and the remaining acetyl group under acidic conditions, followed by neutralization, provided the desired 1a as a crude mixture. However, purification from the highly polar inorganic debris and by-products was difficult due to the low solubility of 1a in organic solvents. The crude material was thus site-selectively acetylated and isolated as the corresponding monoacetate 1d in 33% yield from 3e in 4 steps. Forcing the acidic cleavage using a prolonged reaction time and subsequent workup omitting the neutralization step resulted only in the undesired formation of a nitrated by-product. Its structure was determined to be 4 after acetylation (Scheme 2). An alternative approach using phenyliodine (III) bis(trifluoroacetate) (PIFA)-mediated oxidative rearrangement (Miki *et al.* 1994) provided only a trace amount of the desired isoflavone being detected in the crude product due to the predominant formation of flavanones through spontaneous cyclization of the chalcone intermediates.

Finally, the acetyl group in the thus-obtained 1d was removed by applying above-mentioned *C. antarctica* lipase B-mediated transesterification (Fujita *et al.* 2019; Hanamura *et al.* 2016; Kobayashi *et al.* 2013; Tsunekawa *et al.* 2018) to give prunetin 1a in quantitative yield (Scheme 2). The ^{1}H- and ^{13}C-NMR spectra of 1a were in accordance with those reported previously (Awouafack *et al.* 2011). In the present case, high reactivity in the lipase-catalyzed deacetylation at C-4′ was in good accordance with those observed in chalcone (Tsunekawa *et al.* 2018), flavanone (Kobayashi *et al.* 2013), and flavone (Fujita *et al.* 2019; Hanamura *et al.* 2016) derivatives.

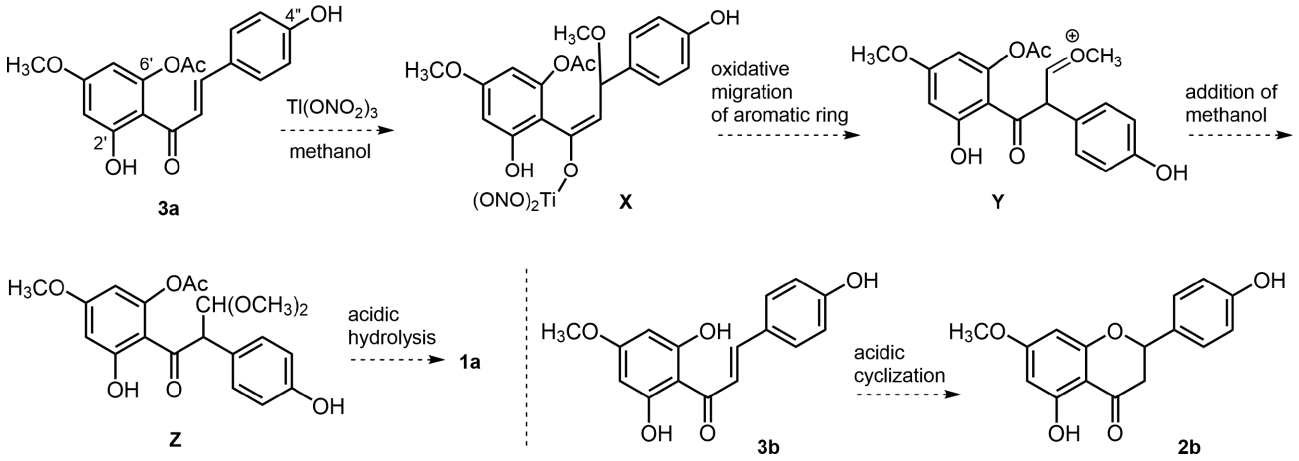
Conclusion

In this way, we achieved the semisynthesis of prunetin (1a) in 8 steps and a total yield of 26% from naringenin (2a), retaining all the original carbon atoms.

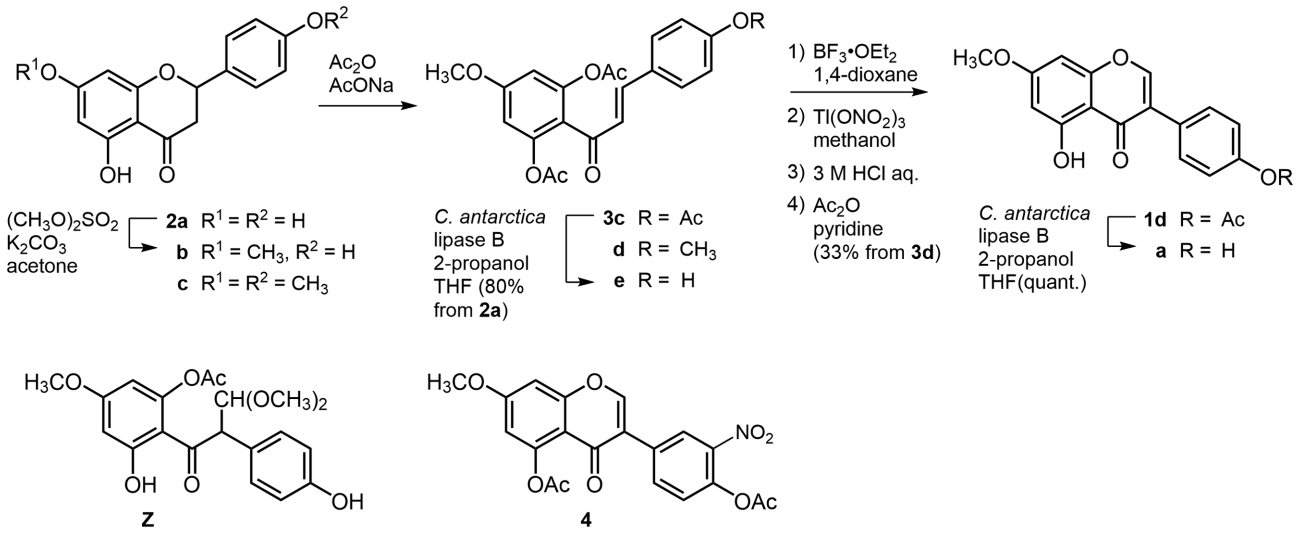
Experimental

General

Candida antarctica lipase B (Novozym 435) was purchased from Novozymes Japan. Naringenin was prepared from commercially available naringin (N0073 Tokyo Chemical Industry Co., Ltd.), according to the reported procedure (Kurahayashi *et al.* 2018). Column chromatography was performed with silica gel (Kanto



Scheme 1. Synthetic plan of prunetin (1a) from chalcone precursor (3a) by TTN-mediated oxidation, showing intermediates (X, Y, and Z).



Scheme 2. Chemoenzymatic semisynthesis of prunetin (1a) from naringenin (2a).

Chemical Co. Silica Gel 60 N 37 563-84, spherical and neutral, 40-50 μm). Melting points were measured on Mitamura Riken Kogyo MELTEMP and are uncorrected. ^{1}H-NMR spectra were measured at 400 MHz on a VARIAN 400-MR or at 500 MHz on a Bruker spectrometer (ascend TM) and ^{13}C-NMR spectra were measured at 100 MHz on a VARIAN 400-MR or at 125 MHz on a Bruker spectrometer (ascend TM). DMSO-d_6 and $CDCl_3$ were used as a solvent and the residual peaks were used as an internal standard (^{1}H-NMR: DMSO-d_6 2.48 ppm, $CDCl_3$ 7.26 ppm; ^{13}C-NMR: DMSO-d_6 39.9 ppm, $CDCl_3$ 77.0 ppm). IR spectra were measured as ATR on a Jasco FT/IR-4700 FT-IR spectrometer. High-resolution mass spectra (HRMS) were measured by a on Jeol JMS-T100LP AccuTOF.

2′,6′-Diacetoxy-4′-hydroxy-4′-methoxychalcone (3e)

To a suspension of 2a (naringenin, 2.72 g, 10.0 mmol), potassium carbonate (1.39 g), and anhydrous sodium sulfate (1.5 g) in acetone (100 mL) was added dimethyl sulfate (1.06 mL, 1.40 g, 1.1 eq.) and the mixture was stirred and heated under reflux for 3 h. After cooling, acetic anhydride (20 mL) was added a sodium acetate (8.60 g) and the mixture was stirred and the temperature was gradually raised. At between 90 and 100 °C, acetone was distilled off. Then the temperature was further raised to reflux and the mixture was stirred for 1 h, the formed acetic acid was distilled off. After acetic anhydride (5 mL) was added and the mixture was stirred and heated at 170 °C for 1 h, while distilling of acetic acid. Finally, acetic anhydride (5 mL) was further added and the heating was continued for 1 h with distilling off acetic acid. After cooling, the mixture was diluted with water and the organic materials were extracted with dichloromethane. The extract was washed with aqueous solution of sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give pale-yellow amorphous solid (4.15 g). Crude product contained 3c as the major product, judged by its ^{1}H-NMR spectrum. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.15 (6H, s), 2.31 (3H, s), 3.84 (3H, s), 6.62 (2H, s), 6.87 (1H, d, J = 16.0 Hz), 7.12 (2H, d, J = 8.4 Hz), 7.40 (1H, d, J = 16.0 Hz), 7.55 (2H, d, J = 8.4 Hz). The minor signals for other acetates (δ: 2.10 to 2.32) and other methyl ethers (δ: 3.82 to 2.86) were due to the presence of inseparable over-methylated contaminants. This crude product was employed for the next step without further purification.

To a solution of the above-mentioned product in a mixture of 2-propanol (15 mL) and tetrahydrofuran (THF, 30 mL), which

was pre-dried over anhydrous sodium sulfate at room temperature overnight, was added an immobilized form of *C. antarctica* lipase B (Novozymes, Novozym 435, 500 mg) and anhydrous sodium sulfate (500 mg). The mixture was stirred for 30 h at 30 °C. The mixture was filtered to remove insoluble materials with a pad of Celite®. The precipitates were washed with ethyl acetate. The combined filtrate and washings were concentrated *in vacuo*. The residue was purified by silica gel column chromatography (45 g). Elution with dichloromethane-diethyl ether (20 : 1 to 2 : 1) gave amorphous solid. Recrystallization from diethyl ether furnished 3e (2.96 g, 80% from 2a) as pale-yellow hexagonal plates. Melting point was 158.5-159.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.14 (6H, s), 3.84 (3H, s), 5.58 (1H, broad s), 6.62 (2H, s), 6.78 (1H, d, J = 16.0 Hz), 6.81 (2H, d, J = 8.4 Hz), 7.37 (1H, d, J = 16.0 Hz), 7.40 (2H, d, J = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.9 (2C), 55.8, 106.9 (2C), 116.1 (2C), 119.4, 124.1, 126.4, 130.6 (2C), 146.7, 149.6 (2C), 159.1, 161.5, 169.2, 190.9 (2C). IR ν_{max} cm^{-1}: 3415, 1760, 1732, 1577, 1568, 1515, 1195, 1172, 1141, 1059, 894, 833. HR-MS [ESI+, (M + Na)$^+$]: calculated for $C_{20}H_{18}NaO_7$, 393.0950; found, 393.0963.

4′-Acetoxy-5-hydroxy-7-methoxyisoflavone (1d)

To a solution of 3e (741 mg, 2.0 mmol) in anhydrous 1,4-dioxane (12 mL) were added BF_3·OEt_2 (0.4 mL, 3.2 mmol) and the mixture was stirred for 2 h at 80 °C. After cooling, the mixture was diluted with methanol (133 mL) and TTN (1.96 g, 7.4 mmol) was added. The mixture was stirred for 1 h at room temperature. Then, hydrochloric acid (3 M, 6.8 mL) was added and the mixture was stirred and heated at reflux for 4.5 h. The mixture was neutralized by a portion-wise addition of sodium hydroxide (3.4 g), and evaporated to dryness *in vacuo* below 40 °C. The residue was suspended in a mixture of acetic anhydride (5 mL) and pyridine (5 mL) and the resulted mixture was stirred for 36 h at room temperature. The mixture was poured into ice, and the precipitates were collected by filtration and washed with water. The solid was extracted twice with hot acetone. The acetone solution was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was suspended with chloroform. The chloroform solution was filtered to remove insoluble materials with a pad of Celite®. The precipitates were washed with chloroform. The combined filtrate and washings were concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20 g). Elution with chloroform–ethyl acetate (10 : 1) gave yellow amorphous solid. Recrystallization from ethanol furnished 1d (215 mg, 33% from 3e) as pale-yellow fine needles. Melting point was 184.0-185.0 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.32 (3H, s), 3.88 (3H, s), 6.40 (1H, d, J = 2.0 Hz), 6.42 (1H, d, J = 2.0 Hz), 7.18 (2H, d, J = 9.0 Hz), 7.55 (2H, d, J = 9.0 Hz), 7.90 (1H, s), 12.77 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.3, 55.9, 92.6, 98.5, 106.1, 121.9 (2C), 123.3, 128.5, 130.1 (2C), 150.9, 153.4, 158.0, 162.9, 165.8, 169.5, 180.6. IR ν_{max} cm^{-1}: 3094, 1739, 1660, 1622, 1576, 1506, 1441, 1420, 1220, 1194, 828, 785. HR-MS [ESI+, (M + Na)$^+$]: calculated for $C_{18}H_{14}NaO_6$, 349.0688; found, 349.0683.

Under forced reaction conditions as described in the text, an undesired derivative 4 was obtained after workup and acetylation. Melting point was 203.5-204.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.39 (3H, s), 2.41 (3H, s), 3.92 (3H, s), 6.66 (1H, d, J = 2.3 Hz), 6.81 (1H, d, J = 2.3 Hz), 7.28 (1H, d, J = 8.5 Hz), 7.82 (1H, dd, J = 2.2, 8.5 Hz), 7.92 (1H, s), 8.22 (1H, d, J = 2.2 Hz). IR ν_{max} cm^{-1}: 1756, 1638, 1530, 1355, 1287, 1257, 1196, 1136, 896, 831. ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.9, 21.2, 56.2, 99.1, 109.1, 111.7, 123.5, 125.3, 126.2, 130.7, 135.6, 141.6, 143.9, 151.1, 152.3, 159.0, 163.9, 168.7, 169.7, 173.7. HR-MS [ESI+, (M + Na)$^+$]: calculated for $C_{20}H_{15}NNaO_9$, 436.0645; found, 436.0625. Judged by these spectral data, its structure was supposed to be the diacetate of 3′-nitro (1530, 1355 ν_{max} cm^{-1}) derivative with a 1,3,4-trisubstituted aromatic ring.

4′,5-Dihydroxy-7-methoxyisoflavone (prunetin, 1a)

In a similar manner as described above, a suspension of 1d (32.6 mg, 0.10 mmol) in a pre-dried mixture of 2-propanol (0.66 mL) and THF (1.34 mL) was treated with *C. antarctica* lipase B (35 mg). The mixture was stirred for 18 h at 24 °C. Accompanied with the progress of the deacetylation, the suspension of the substrate turned to be homogeneous. The mixture was filtered to remove insoluble materials with a pad of Celite®. The precipitates were washed with THF. The combined filtrate and washings were concentrated *in vacuo* to give 1a (30.1 mg, quantitative yield) as pale-yellow solids. Melting point was 238.0-238.5°C [lit. (Awouafack et al. 2011) melting point 246-248°C]. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.85 (3H, s), 6.40 (1H, d, J = 2.4 Hz), 6.65 (1H, d, J = 2.4 Hz), 6.81 (2H, d, J = 8.8 Hz), 7.38 (2H, d, J = 8.8 Hz), 8.40 (1H, s), 9.58 (1H, s), 12.95 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 56.5, 92.8, 93.5, 105.8, 115.5 (2C), 121.5, 123.0, 130.6 (2C), 154.8, 157.9 (2C), 162.2, 165.7, 180.9. ^{1}H- and ^{13}C-NMR spectra were in good accordance with those reported previously. (Awouafack *et al.* 2011) IR ν_{max} cm^{-1}: 3365, 2957, 1660, 1611, 1568, 1505, 1534, 1190, 1153, 1051. HR-MS [ESI+, (M + Na)$^+$]: calculated for $C_{16}H_{12}NaO_5$, 307.0582; found, 307.0570.

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Author contribution

T.S designed this study and carried out the experiments; K.H. contributed to analytical works; T.S. wrote the manuscript with assistance from all authors; and S.H. supervised the research.

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Disclosure statement

The authors declare that they have no conflict of interest regarding this article.

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