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Practical Synthesis of Polymethylated Flavones: Nobiletin and Its Desmethyl Derivatives

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Supporting Information

ABSTRACT: We present a practical synthesis of the polymethoxylated citrus flavone nobiletin that is suitable for use on a hundred gram scale. Ready availability of this compound and its derivatives will aid detailed chemical-biological investigations of their biological activities, including activation of signaling via the cAMP-dependent protein kinase A/extracellular signal-related protein kinase/cAMP response element-binding protein pathway.

KEYWORDS: *nobiletin, sudatichin, flavonoid, practical synthesis*

INTRODUCTION

Nobiletin (**1**) (Figure 1), isolated from citrus fruits,[1] has various biological activities, such as activation of signaling via the cAMP-dependent protein kinase A (PKA)/extracellular signal-related protein kinase (ERK)/cAMP response element-binding protein (CREB) pathway in cell culture systems, including cultured rat hippocampal neurons, and may be a lead compound for novel antidementia agents.[2,3] However, commercially available natural **1** is expensive (47,300 yen/5 mg; ChromaDex, Inc.),[4] although synthetic **1** is currently available at a lower price (55,000 yen/500 mg; Wako Chemicals).[5] During the course of our work on flavone synthesis, we have developed an efficient synthesis of the flavone skeleton via a β-diketone intermediate, and we anticipated that this method might be suitable for the practical large-scale synthesis of **1** and its demethyl derivatives. which we report herein.

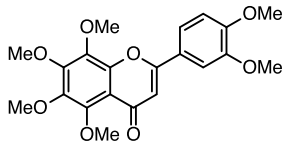


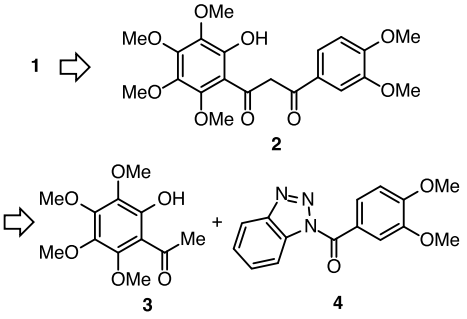
Figure 1. Structure of nobiletin (**1**).

RESULTS AND DISCUSSION

Our synthetic strategy is illustrated in Scheme 1. We anticipated that the synthesis of tetramethoxyacetophenone derivative **3** would be the key to this synthesis.

As shown in Scheme 2, the preparation of **3** began with 1,3,4,5-tetramethoxybenzene (**5**).[6] Upon treatment with acetyl chloride and aluminum trichloride, Friedel−Crafts acylation of **5** and concomitant demethylation proceeded to give acetophenone **6**. Subsequent O-methylation of **6** afforded tetramethoxyacetophenone **7**. After the Baeyer−Villiger oxidation reaction of **7** with *m*CPBA, hydrolysis of the generated acetate **8** gave phenol **9**. Since **9** was expected be sensitive to oxygen, all handling was carried out under an argon atmosphere. Next, methylation of labile phenol **9** by treatment with methyl iodide under basic conditions under an argon atmosphere to avoid oxidation gave **10**. Friedel−Crafts reaction of **10** and concomitant demethylation gave acetophenone **3**. Although the desired polymethoxyacetophenone unit had been obtained, it was difficult to ensure a stable supply by the first synthetic route. Thus, we modified the synthetic route of **3**.

Scheme 1. Synthetic Strategy for Nobiletin (1)



The modified synthesis of pentamethoxybenzene (**10**) started from inexpensive 1,2,3-trimethoxybenzene (**11**) (Scheme 3). The introduction of the hydroxyl group was achieved by formylation followed by Baeyer−Villiger oxidation. Upon treatment of **11** with dichloromethoxymethane in the presence of titanium tetrachloride, the formylation reaction proceeded to afford **12**. Previously, silica gel column chromatography (SiO_2 C.C.) had been required to remove

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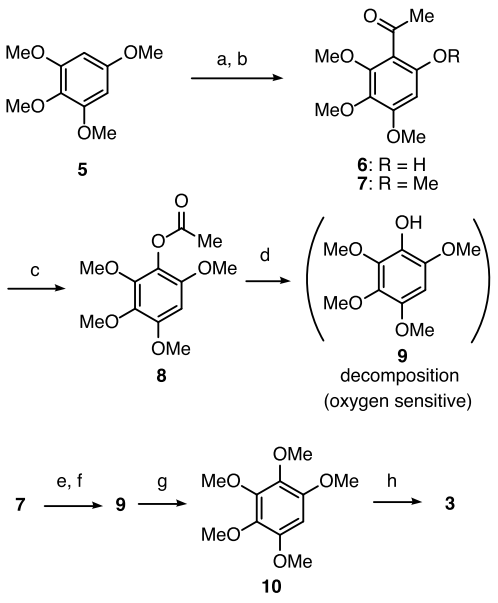
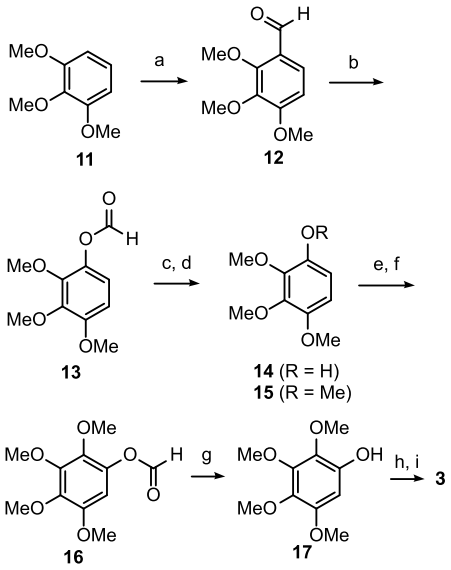
Scheme 2. Synthesis of the Key Unit 3 from 1,3,4,5-Tetramethoxybenzene (5)[a]



[a]Conditions: (a) AcCl, $AlCl_3$, Et_2O, 76%; (b) MeI, K_2CO_3, DMF, 70 °C, 94%; (c) *m*CPBA, CH_2Cl_2 then SiO_2 C.C.; (d) K_2CO_3, MeOH then SiO_2 C.C. under air; (e) SeO_2 (cat.), 30% H_2O_2, *t*-BuOH, 50 °C; (f) K_2CO_3, MeOH then SiO_2 C.C. under argon, 51% (two steps); (g) MeI, K_2CO_3, acetone (under Ar), 95%; (h) AcCl, $AlCl_3$, CH_2Cl_2, 45% (brsm 94%).

Scheme 3. Improved Synthesis of Acetophenone 3[a]



[a]Conditions: (a) $TiCl_4$, Cl_2CHOMe, CH_2Cl_2; (b) SeO_2 (cat.), 30% H_2O_2, *t*-BuOH, 50 °C; (c) Et_3N, MeOH; (d) MeI, K_2CO_3, acetone, 84% (four steps); (e) PhN(Me)CHO, $POCl_3$, 60 °C; (f) SeO_2 (cat.), 30% H_2O_2, *t*-BuOH, 50 °C; (g) Et_3N, MeOH; (h) MeI, K_2CO_3, acetone, 94% (four steps); (i) AcCl, $AlCl_3$, CH_2Cl_2, 45% (brsm 94%).

remaining *m*CPBA and *m*CBA in the Baeyer–Villiger oxidation. Here we used only a catalytic amount of selenium dioxide[7] in the presence of hydrogen peroxide in the oxidation step, and the product could be purified by solvent extraction. After the Baeyer–Villiger oxidation with selenium dioxide, methanolysis and subsequent methylation afforded 1,2,3,4-tetramethoxybenzene (**15**). Different reaction conditions were required for the second formylation reaction of **15**. The formylation of the stronger electrophile **15**, which has four methoxy groups, would match the mild acidic conditions of the Vilsmeier–Haack reaction.[8] After the Baeyer–Villiger oxidation with selenium dioxide, solvolysis of the generated formyl group afforded phenol **17**. Fortunately, **17** was more stable than **9** toward oxygen, even though they are regioisomers. Finally, methylation and acylation of **17** gave **3** without the sensitive care for the prevention of oxidation. A stable supply of the important synthetic intermediate **3** was eventually achieved by the modified synthetic route, which contains no chromatographic purification.

Benzotriazole derivative **4**,[9] which is readily obtainable from 3,4-dimethoxybenzoic acid (**18**), is a suitable acyl donor (Scheme 4). Generally, the reactions of acetophenone with readily available acyl halides provide the esters generated by the reaction with the phenolic hydroxyl group. The use of acylbenzotriazole as a soft nucleophile, however, directly afforded the *C*-acyl adduct. Moreover, acylbenzotriazoles were extremely stable, in contrast to labile acyl halides, which required preparation at the time of use. It is more suitable for the practical-scale synthesis that acylbenzotriazole **4** has high long-term storage stability. The desired C-acylation reaction of **3** with **4** in the presence of LHMDS at 0 °C afforded *β*-diketone **2**. Upon treatment with trifluoroacetic acid in methanol, cyclization (**2** → **19**) and dehydration (**19** → **20**) afforded **1**. This total synthesis of **1** was accomplished in 35% total yield in 11 steps starting from **11**.[10]

Our synthetic route illustrated in Scheme 4 was applied to the hundred gram scale preparation of nobiletin by USHIOchemix Ltd., and we and our collaborators are currently using this material for detailed investigation of its biological activities[11] and toxicological testing.

There have been few pharmacodynamic studies of dietary flavonoids using labeled synthetic compounds, even though several flavonoids are known to have beneficial effects both in vitro and in vivo.[16] Thus, we investigated the conversion of modified acetophenones and acylbenzotriazoles into desmethyl derivatives of nobiletin (Scheme 5). After the coupling of **4** and **22**[12] afforded *β*-diketone **23**, acidic cyclization of **23** gave flavone **24**. The demethylation of **24** under Node's conditions[13] afforded 5,4′-desmethylnobiletin (**26**) accompanied by debenzylation. The key to the regioselectivity and enhancement of the reactivity was the chelation of the Lewis acid to the carbonyl group (intermediate **25**). Additionally, 5-desmethylnobiletin (**27**) was obtained from **1** under Node's conditions by selective demethylation at the 5-position.

In addition, 7-desmethylnobiletin (**32**) was also obtained from **3** (Scheme 6). The regioselective demethylation reaction proceeded at the 4-position of **3** to afford **29** through intermediate **28** activated by lithium chloride. After the benzylation of **29**, condensation of the resulting compound **30** with **4** in the same manner afforded **31** with concomitant Bn deprotection. Compound **32** was readily converted to 5,7-didemethylnobiletin (**35**). In order to decrease the reactivity of the electron-rich aromatic A ring of **29**, acetate was selected for the protecting group of phenol **29**. Acetylation of **32** by treatment with acetic anhydride and DMAP afforded **33**. After the demethylation of **33** under Node's conditions to afford **34**, the following deacetylation provided **35**. 5-Desmethylnobiletin (**27**) has already been converted into chemical probes labeled with ^{11}C for positron emission tomography[10] or conjugated

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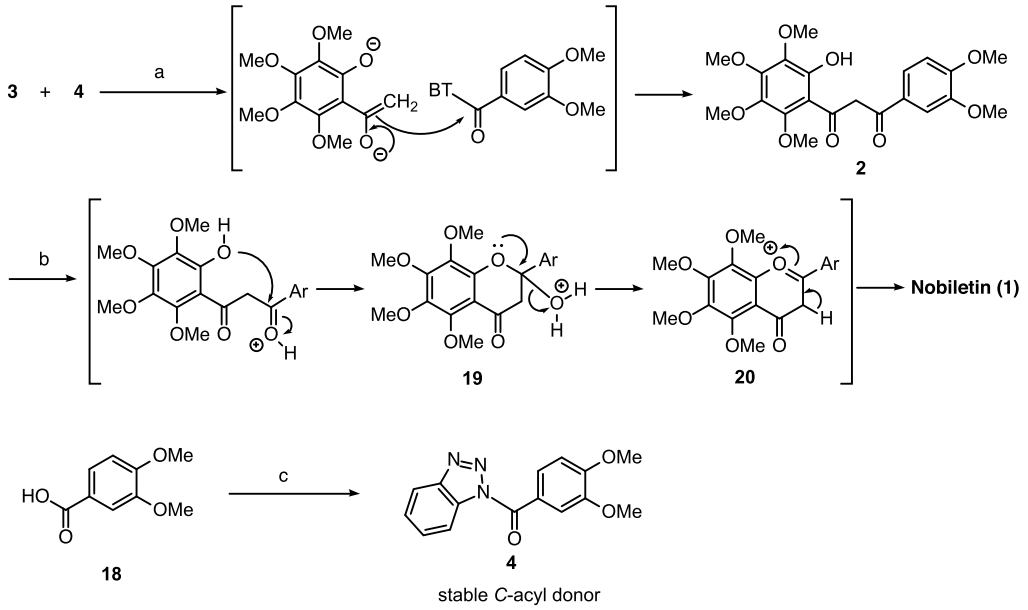
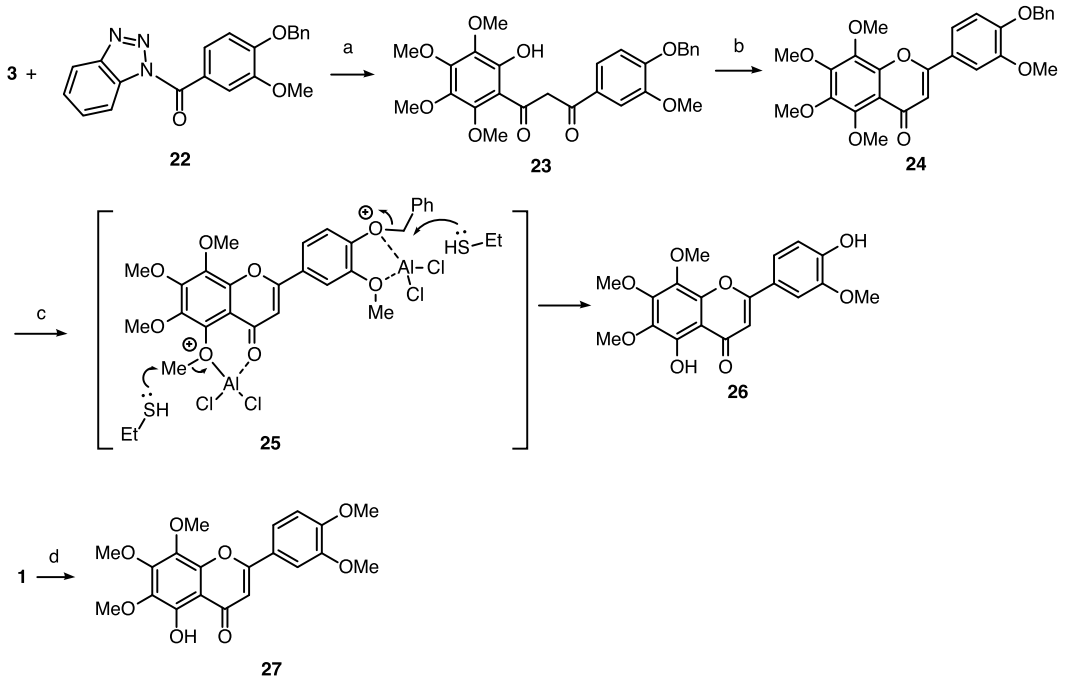
Scheme 4. Completion of the Synthesis of Nobiletin (1)[a]



[a]Conditions: (a) LHMDS, THF, 0 °C, 91%; (b) TFA, MeOH, 50 °C, 98%; (c) $SOCl_2$, DMF, CH_2Cl_2 then benzotriazole.

Scheme 5. Synthesis of Nobiletin Derivatives[a]



[a]Conditions: (a) LHMDS, THF; (b) $TsOH{\cdot}H_2O$, toluene; (c) EtSH, $AlCl_3$, CH_2Cl_2, 75%; (d) EtSH, $AlCl_3$, CH_2Cl_2, 75%.

with fluorescein (TokyoGreen) for visualizing the biodistribution or with biotin for identification of binding proteins.[14]

By means of a similar strategy for the desmethylation and flavone synthesis, efficient syntheses of sudatichin (**36**) and desmethylnobiletin derivatives **37**–**39**[15] were accomplished,[16] as shown in Figure 2.

SUMMARY

We have developed a practical synthesis of nobiletin (**1**) suitable for use on a large (100 g) scale. The methodology was also developed for efficient and flexible synthesis of a variety of methylated flavone derivatives. The desmethyl analogues should be applicable as tools for chemical biology studies by conversion into various probe molecules. Detailed studies of the biological activities of these compounds and metabolism of **1** are in progress.

EXPERIMENTAL SECTION

Materials and Instrumentation. ^1H NMR (270 MHz) and ^{13}C NMR (68 MHz) spectra were determined on a JEOL EX-270 instrument, ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were determined on JEOL ECA-500 and JEOL

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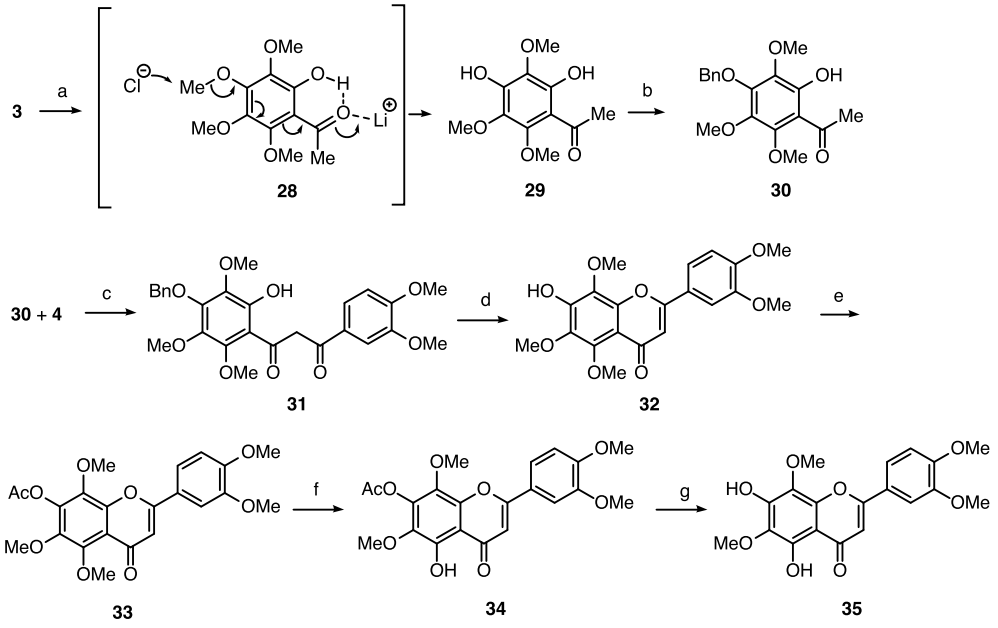
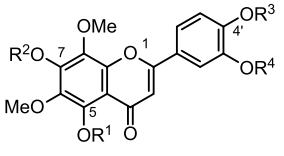
Scheme 6. Synthesis of 7-Desmethylnobiletin Derivatives[a]



[a]Conditions: (a) LiCl, DMF, 120 °C, 59% (brsm 70%); (b) BnBr, K_2CO_3, DMF, 79%; (c) LHMDS, THF, −78 to 0 °C, 70%; (d) TsOH, toluene, 80 °C, 63%; (e) Ac_2O, DMAP, pyridine; (f) EtSH, $AlCl_3$, CH_2Cl_2, 0 °C to rt, 80% (two steps); (g) K_2CO_3, MeOH, 99%.



	R^1	R^2	R^3	R^4
Sudachitin (**36**)	H	H	H	Me
37	Me	Me	Me	H
38	Me	H	H	Me
39	Me	Me	H	Me

Figure 2. Structures of desmethyl derivatives **36**−**39** of nobiletin (**1**).

α-500 instruments, and ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were determined on a JEOL LA-400 instrument. Chemical shifts (δ) for ^{1}H NMR spectra are reported in parts per million downfield from tetramethylsilane as the internal standard, and coupling constants are given in hertz. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shifts for ^{13}C NMR are reported in parts per million relative to the center line of the triplet at 77.0 ppm for deuteriochloroform. High-resolution mass spectrometry (HRMS) was performed on a JEOL MStation 700. Fast atom bombardment (FAB) mass spectra were obtained with 3-nitrobenzyl alcohol as the matrix and a Bruker Daltonics micrOTOF (ESI). Analytical thin-layer chromatography (TLC) was performed on Merck precoated analytical plates (0.25 mm thick, silica gel 60 F_{254}). Preparative TLC separations were made on 7 cm × 20 cm plates prepared with a 0.25 mm or 0.50 mm layer of Merck silica gel 60 F_{254}. Compounds were eluted from the adsorbent with 10% methanol in chloroform. Column chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (spherical) 40−50 μm, Silica Gel 60 (spherical) 63−210 μm, or Silica Gel 60 N (spherical, neutral) 63−210 μm. Reagents and solvents were commercial grade and were used as supplied with the following exceptions: dichloromethane, diethyl ether, *n*-hexane, tetrahydrofuran, and toluene were dried over 4 Å molecular sieves, and methanol and acetonitrile were dried over 3 Å molecular sieves. All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

2,3,4-Trimethoxybenzaldehyde (12). To a stirred solution of **11** (44.7 g, 266 mmol) in CH_2Cl_2 (500 mL) were added $TiCl_4$ (58.3 mL, 532 mmol, 2.0 equiv) and Cl_2CHOMe (47 mL, 532 mmol, 2.0 equiv) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 3 h, poured into cold water, and extracted with CH_2Cl_2. The organic layer was washed with 6 M HCl followed by saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude residue **12** (52.7 g) was applied to the following reaction without further purification.

2,3,4-Trimethoxyphenol (14). To a solution of crude residue **12** (52.7 g) in *t*-BuOH (500 mL) were added SeO_2 (590 mg, 5.32 mmol, 0.02 equiv) and H_2O_2 (60 mL, 532 mmol, 2.0 equiv) at 50 °C. The reaction mixture was stirred at 50 °C for 1.5 h and then allowed to cool to room temperature. The resulting mixture was quenched with saturated aqueous Na_2SO_3 at 0 °C, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude residue **13** (53.6 g) was applied to the following reaction without further purification.

To a solution of crude residue **13** (53.6 g) in MeOH (500 mL) was added Et_3N (35 mL, 253 mmol, 1.0 equiv) at 0 °C. The mixture was stirred at room temperature for 0.5 h and then concentrated under reduced pressure. The crude residue was dissolved in CH_2Cl_2, and the solution was acidified with 2 M HCl. The organic layer was extracted with 2 M NaOH. The water layer was acidified with 6 M HCl and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue **14** (46.3 g) was applied to the following reaction without further purification.

1,2,3,4-Tetramethoxybenzene (15). To a stirred solution of crude residue **14** (46.3 g) in acetone (500 mL) were added K_2CO_3 (69.5 g, 503 mmol, 1.9 equiv) and MeI (31.3 mL, 503 mmol, 1.9 equiv) at 0 °C under an Ar atmosphere.

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The reaction mixture was stirred at room temperature for 40 h. The resulting mixture was poured into Et_2O and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The crude residue was washed with MeOH and filtered to afford **15** (44.3 g, 233 mmol, 84%, four steps from **11**) as a white solid (mp 86−89 °C, lit. 85−88 °C). Spectral data for **15** were in good agreement with the reported data.[17]

2,3,4,5-Tetramethoxyphenol (17). $POCl_3$ (0.73 mL, 8.07 mmol, 1.6 equiv) and *N*-methyl formanilide (0.18 g, 1.35 mmol) were stirred at room temperature for 20 min. To the reaction mixture was added **15** (1.0 g, 5.04 mmol), and the resulting mixture was stirred at 60 °C for 6 h. After cooling, the reaction mixture was quenched with water at 0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude residue (1.5 g) was applied to the following reaction without further purification.

To a solution of the crude residue (1.5 g) in *t*-BuOH (10 mL) were added SeO_2 (11 mg, 0.151 mmol, 0.03 equiv) and H_2O_2 (1.14 mL, 10.1 mmol, 2.0 equiv) at 50 °C. The reaction mixture was stirred at 50 °C for 2.5 h and allowed to cool to room temperature. The resulting mixture was quenched with saturated aqueous Na_2SO_3 at 0 °C, poured into water, and extracted with EtOAc. The organic layer was washed with water followed by brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude residue **16** (1.7 g) was applied to the following reaction without further purification.

To a solution of crude residue **16** (1.7 g) in MeOH (16 mL) was added Et_3N (0.7 mL, 5.04 mmol, 1.0 equiv) at 0 °C. The mixture was stirred at room temperature for 45 min and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and acidified with 2 M HCl. The organic layer was extracted with 2 M NaOH. The water layer was acidified with 6 M HCl and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue **17** (1.03 g) was applied to the following reaction without further purification.

1,2,3,4,5-Pentamethoxybenzene (10). To a mixture of crude **17** (1.03 g) and K_2CO_3 (1.33g, 9.62 mmol, 1.9 equiv) in acetone (16 mL) was added MeI (0.6 mL, 9.62 mmol, 1.9 equiv) under an Ar atmosphere. The reaction mixture was stirred at room temperature for 36 h. The resulting mixture was poured into Et_2O and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford **10** (1.08 g, 4.74 mmol, 94%, four steps from **15**) as a pale-yellow solid (mp 60−61 °C, lit. 59−61 °C). Spectral data for **10** were in good agreement with the reported data.[18]

1-(2-Hydroxy-3,4,5,6-tetramethoxyphenyl)ethanone (3). To a solution of **10** (1.0 g, 4.38 mmol) and AcCl (485 μL, 6.14 mmol, 1.4 equiv) in CH_2Cl_2 (10 mL) was added $AlCl_3$ (560 mg, 4.38 mmol, 1.0 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The resulting mixture was poured into 2 M NaOH at 0 °C and washed with Et_2O. The organic layer was washed with 2 M NaOH and concentrated under reduced pressure to recover the starting material **10** (513 mg, 51%). The water layers were combined, acidified with 6 M HCl at 0 °C, and extracted with Et_2O. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford **3** (508 mg, 1.98 mmol, 45%) as a yellow oil. ^1H NMR (270 MHz, $CDCl_3$): δ 13.2 (s, 1H, OH), 4.08 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.71(s, 3H, CH_3). Spectral data for **3** were in good agreement with the reported data.[19]

(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)(3,4-dimethoxyphenyl)methanone (4). To a solution of **18** (15.0 g, 82.3 mmol) in CH_2Cl_2 (200 mL) were added $SOCl_2$ (9.0 mL, 123 mmol, 1.5 equiv) and DMF (2.5 mL, 33 mol, 0.4 equiv) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at 0 °C for 1.5 h and then concentrated under reduced pressure to give a crude residue including acid chloride. To a solution of the crude acid chloride in CH_2Cl_2 (170 mL) were added Et_3N (11.4 mL, 82.3 mmol, 1.0 equiv) and benzotriazole (9.8 g, 82.3 mmol, 1.0 equiv) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at 0 °C for 30 min, quenched with 1 M NaOH at room temperature, and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a residue including **4**. The crude residue was purified by recrystallization from *n*-hexane/CH_2Cl_2 to afford **4** (19.1 g, 67.5 mmol, 82%, two steps from **18**) as a white solid (mp 131−132 °C). IR (film): 1691, 1271, 1047 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 8.37 (d, J = 8.5 Hz, 1H, Ar), 8.05 (d, J = 8.5 Hz, 1H, Ar), 7.82 (s, 1H, Ar), 7.70 (t, J = 7.5 Hz, 1H, Ar), 7.55 (t, J = 7.5 Hz, 1H, Ar), 7.04 (d, J = 7.5 Hz, 1H, Ar), 4.01 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 165.5, 153.9, 148.7, 145.5, 132.5, 130.2, 127.2, 126.1, 123.3, 120.0, 114.8, 113.9, 110.2, 56.1, 56.0. MS (FAB): m/z 283 $(M)^+$. HRMS (ESI): calcd for $C_{15}H_{13}N_3O_3Na^+$ $(M + Na)^+$, 306.0849; found, 306.0855.

Nobiletin (1). To a mixture of **3** (5.2 g, 0.69 mmol) and **4** (6.3 g, 0.76 mmol, 1.1 equiv) in THF (40 mL) was added LHMDS (81 mL, 81 mmol, 4.0 equiv, 1 M solution in THF) under an Ar atmosphere at −30 °C. The reaction mixture was stirred at 0 °C for 2 h, and the resulting mixture was quenched with saturated aqueous NH_4Cl at 0 °C and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue including **2**. The residue was purified by recrystallization from EtOAc/*n*-hexane to afford **2** (7.8 g, ca. 91%) as a yellow solid. The crude solid was applied to the following reaction without further purification.

To a solution of crude solid including **2** (3.1 g) in MeOH (30 mL) was added TFA (3 mL) at room temperature. The reaction mixture was stirred at 50 °C for 24 h. After stirring, the reaction mixture was concentrated under reduced pressure to give a residue including **1**. The residue was purified by recrystallization from hot MeOH to afford **1** (2.9 g, 98%) as a pale-yellow solid (mp 138 °C, lit. 137−138 °C). ^1H NMR (270 MHz, $CDCl_3$): δ 7.57 (d, J_1 = 8.6 Hz, J_2 = 2.1 Hz, 1H, Ar), 7.42 (d, J = 2.1 Hz, 1H, Ar), 7.00 (d, J = 8.6 Hz, 1H, Ar), 6.62 (d, 1H, CH), 4.11 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.00−3.95 (m, 12H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.1, 160.8, 151.7, 151.2, 149.1, 148.2, 147.5, 143.9, 137.8, 123.8, 119.4, 114.7, 111.1, 108.3, 106.7, 62.1, 61.8, 61.7, 61.5, 55.9, 55.8. Spectral data for **1** were in good agreement with the reported data.[20]

4′-Benzyloxyflavone 24. To a stirred solution of **3** (500 mg, 1.95 mmol) and **22** (842 mg, 2.34 mmol, 1.2 equiv) in THF (6.5 mL) was added LHMDS (7.8 mL, 7.8 mmol, 4.0 equiv, 1 M solution in THF) under an Ar atmosphere at −30 °C, and the reaction mixture was stirred for 1 h at 0 °C, quenched with saturated aqueous NH_4Cl at 0 °C, and

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extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 9/1 to 5/2) to afford a mixture of *β*-diketone **23** and slight amount of impurities (877 mg, ca. 91%) as a yellow solid. The crude solid was applied to the following reaction without further purification.

To a solution of crude *β*-diketone **23** (776 mg) in toluene (5.2 mL) was added TsOH monohydrate (297 mg, 2.34 mmol, 1.5 equiv) at room temperature, and the reaction mixture was stirred for 3 h at 80 °C, diluted with water, and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 10/3 to 10/7) to afford **24** (685 mg, 92%) as a colorless solid (mp 156−156.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (dd, J = 8.5, 2.3 Hz, 1H), 7.45 (t, J = 7.4 Hz, 2H), 7.39 (t, J = 7.4 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 6.61 (s, 1H), 5.25 (s, 2H), 4.10 (s, 3H), 4.02 (s, 3H), 3.99 (s, 3H), 3.95 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.3, 161.0, 151.4, 151.0, 149.7, 148.3, 147.7, 144.0, 138.0, 136.3, 128.7, 128.1, 127.2, 124.2, 119.4, 114.8, 113.4, 108.9, 106.9, 70.8, 62.2, 61.9, 61.8, 61.6, 56.0. HRMS (FAB): calcd for $C_{27}H_{26}O_8Na$ $[M + Na]^+$, 501.1525; found, 501.1520.

5,4′-Didemethylnobiletin (26). To a stirred solution of **24** (50.0 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) was added $AlCl_3$ (42.0 mg, 0.31 mmol, 1.5 equiv) in EtSH (1.0 mL) at 0 °C, and the reaction mixture was stirred for 2 h at room temperature, quenched with 2 M aqueous HCl at 0 °, and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1 to 5/2) to afford **26** (18.4 mg, 47%) as a yellow solid (mp 166−167 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.55 (s, 1H), 7.55 (dd, J = 8.5, 2.3 Hz, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.60 (s, 1H), 6.07 (s, 1H), 4.12 (s, 3H), 4.01 (s, 3H), 3.98 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.0, 164.0, 153.0, 149.5, 149.4, 146.9, 145.7, 136.5, 132.9, 123.2, 120.7, 115.1, 108.3, 106.9, 103.8, 62.1, 61.7, 61.1, 56.0. HRMS (FAB): calcd for $C_{19}H_{18}O_8Na$ $[M + Na]^+$, 397.0899; found, 397.0893.

5-Demethylnobiletin (27). To a stirred solution of **1** (50.0 mg, 0.12 mmol) in CH_2Cl_2 (1.2 mL) was added $AlCl_3$ (25.0 mg, 0.18 mmol, 1.5 equiv) in EtSH (1.2 mL) at 0 °C, and the reaction mixture was stirred for 2 h at room temperature, quenched with 2 M aqueous HCl at 0 °C, and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1 to 5/2) to afford **27** (36.5 mg, 76%) as yellow solid (mp 146 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.55 (s, 1H), 7.59 (dd, J = 8.5, 2.0 Hz, 1H), 7.43 (d, J = 2.0 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.62 (s, 1H), 4.12 (s, 3H), 3.99 (s, 3H), 3.984 (s, 3H), 3.978 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.9, 163.9, 152.9, 152.4, 149.5, 149.3, 145.7, 136.5, 132.9, 123.6, 120.1, 111.2, 108.6, 106.9, 103.9, 62.0, 61.7, 61.1, 56.1, 55.9. HRMS (FAB): calcd for $C_{20}H_{20}O_8Na$ $[M + Na]^+$, 411.1056; found, 411.1050.

Acetophenone 29. To a stirred solution of **3** (200 mg, 0.78 mmol) in DMF (2.6 mL) was added LiCl (331 mg, 7.80 mmol, 10 equiv) at room temperature, and the mixture was stirred for 18 h at 120 °C. After cooling to room temperature, the resulting mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 9/1 to 5/2) to afford **29** (112 mg, 59%) as a yellow solid and recovered starting material (22 mg). Mp: 93.5−94.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.50 (s, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.86 (s, 3H), 2.67 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.0, 153.9, 151.3, 149.7, 133.0, 131.0, 108.0, 61.0, 60.9, 60.8, 32.1. HRMS (FAB): calcd for $C_{11}H_{14}O_6Na$ $[M + Na]^+$, 265.0688; found, 265.0683.

Acetophenone 30. To a stirred solution of **29** (112 mg, 0.46 mmol) and K_2CO_3 (127 mg, 0.93 mmol, 2.0 equiv) in DMF (1.5 mL) was added benzyl bromide (0.06 mL, 0.51 mmol, 1.1 equiv) at room temperature, and the reaction mixture was stirred for 3 h, quenched with saturated aqueous NH_4Cl, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 9/1 to 5/2) to afford **30** (121 mg, 79%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, J = 7.4 Hz, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 5.28 (s, 2H), 3.95 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H), 2.68 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.3, 154.4, 152.6, 151.4, 138.4, 137.4, 137.1, 128.4, 128.2, 128.1, 110.8, 75.4, 61.2, 61.1, 61.0, 32.3. HRMS (FAB): calcd for $C_{18}H_{20}O_6Na$ $[M + Na]^+$, 355.1158; found, 355.1152.

7-Demethylnobiletin (32). To a stirred solution of **30** (730 mg, 2.20 mmol) and **4** (933 mg, 3.29 mmol, 1.5 equiv) in THF (7.3 mL) was added LHMDS (8.8 mL, 8.80 mmol, 4.0 equiv, 1 M solution in THF) under an Ar atmosphere at −30 °C, and the reaction mixture was stirred for 2.5 h at 0 °C, quenched with saturated aqueous NH_4Cl at 0 °C, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 9/1 to 5/2) to afford a mixture of *β*-diketone **31** and a slight amount of impurities (763 mg, ca. 70%) as a yellow solid. To a solution of crude *β*-diketone **31** (294 mg) in toluene (2.0 mL) was added TsOH monohydrate (168 mg, 0.89 mmol, 1.5 equiv) at room temperature, and the reaction mixture was stirred for 6 h at 80 °C, diluted with water, and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 10/3 to EtOAc only) to afford **32** (145 mg, 63%) as a colorless powder (mp 203−204 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (dd, J = 8.5, 2.3 Hz, 1H), 7.40 (d, J = 2.3 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.61 (s, 1H), 6.29 (s, 1H), 4.07 (s, 3H), 4.05 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.4, 160.8, 151.8, 149.2, 147.6, 147.4, 147.3, 138.5, 131.8, 123.9, 119.5, 111.9, 111.2, 108.5, 106.7, 62.1, 61.8, 61.6, 56.0, 55.9. HRMS (FAB): calcd for $C_{20}H_{20}O_8Na$ $[M + Na]^+$, 411.1056; found, 411.1050.

7-Acetoxyflavone 34. To a stirred solution of **32** (100 mg, 0.26 mmol) in pyridine (0.87 mL) were added acetic anhydride (0.10 mL, 1.29 mmol, 5.0 equiv) and DMAP (14 mg, 0.03 mmol, 0.1 equiv) at room temperature, and the reaction mixture was stirred for 30 min. The resulting mixture was evaporated under reduced pressure to afford a crude

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mixture of **33** (123 mg). To a stirred solution of crude **33** (50.0 mg) in CH_2Cl_2 (1.2 mL) was added $AlCl_3$ (23.0 mg, 0.17 mmol, 1.5 equiv) in EtSH (1.2 mL) at 0 °C, and the reaction mixture was stirred for 2 h at room temperature, quenched with 2 M aqueous HCl at 0 °C, and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1 to 2/1) to afford **34** (38.2 mg, 80%, two steps from **32**) as a yellow solid (mp 203−204 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.66 (s, 1H), 7.59 (dd, J = 8.5, 2.3 Hz, 1H), 7.41 (d, J = 2.3 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.66 (s, 1H), 3.98 (s, 6H), 3.97 (s, 3H), 3.95 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.1, 168.4, 164.2, 152.6, 149.4, 149.2, 145.2, 143.2, 136.0, 132.7, 123.4, 120.2, 111.3, 109.2, 108.7, 104.2, 62.0, 60.9, 56.1, 56.0, 20.5. HRMS (FAB): calcd for $C_{21}H_{20}O_9Na$ $[M + Na]^+$, 439.1005; found, 439.1000.

5,7-Didemethylnobiletin (35). To a stirred solution of **34** (18.0 mg, 0.04 mmol) in MeOH (0.5 mL) was added K_2CO_3 (12.0 mg, 0.09 mmol, 2.0 equiv) at room temperature, and the reaction mixture was stirred for 3 h, quenched with saturated aqueous NH_4Cl, and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1/1 to EtOAc only) to afford **35** (15.9 mg, 99%) as a yellow powder (mp 214−215 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.75 (s, 1H), 7.59 (dd, J = 8.5, 2.3 Hz, 1H), 7.41 (d, J = 2.3 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.60 (s, 1H), 6.42 (s, 1H), 4.05 (s, 3H), 4.03 (s, 3H), 3.99 (s, 3H), 3.98 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.9, 163.6, 152.3, 149.3, 148.8, 148.3, 145.7, 130.7, 127.3, 123.6, 120.0, 111.2, 108.6, 104.5, 103.9, 61.7, 61.0, 56.1, 56.0. HRMS (FAB): calcd for $C_{19}H_{18}O_8Na$ $[M + Na]^+$, 397.0899; found, 397.0894.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00091.

^{1}H and ^{13}C NMR spectra for compounds **1**, **3**, **4**, **10**, **15**, **24**, **26**, **27**, **29**, **30**, **32**, **34**, and **35** (PDF)

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Notes

The authors declare no competing financial interest.

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