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Concise total synthesis of flavone *C*-glycoside having potent anti-inflammatory activity

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Abstract—The total synthesis of anti-inflammatory active flavone *C*-glycoside isolated from oolong tea extract is achieved. Introducing a *C*-glucosyl moiety to an aryl system and constructing a fused tetracyclic ring characteristic to this natural product were conducted based on the *O*-to-*C* rearrangement of sugar moiety and the successive intramolecular Mitsunobu reaction, respectively. This concise and efficient synthetic pathway is applicable to the large-scale synthesis of target flavone and for constructing a large library of related compounds.

1. Introduction

Naturally-occurring aryl *C*-glycosides[1] exhibit interesting biological activities. Especially, *C*-glycosyl flavonoids show a variety of bioactivities such as antiviral,[2] cytotoxic,[3] and DNA binding[4] activities. Recently, a novel, anti-inflammatory active flavone *C*-glycoside **1**, which connects a mannose sugar moiety at the 6-position of a flavone skeleton, has been isolated as minor constituent of oolong tea extract.[5] The activity of **1** is exceptionally significant and evaluation based on the suppression of contact hypersensitivity in mice induced by the treatment of 2,4-dinitrofluorobenzene indicates that **1** is ~1000 times stronger than the conventionally used anti-inflammatory drug, dexamethasone. On the other hand, this flavone is structurally characterized by the fused tetracyclic ring system composed of a mannosyl moiety, A, and C rings of flavone framework. The intriguing biological activity, unique structural features, and limited natural sources promoted us to undertake a synthetic study of this flavone. The first total synthesis of **1** was accomplished recently by Nakatsuka and co-workers.[6] Herein, concise and efficient total synthesis of **1** based on *O*-to-*C* rearrangement[7] and intramolecular Mitsunobu reaction[8] for the *C*-glycoside formation and the construction of its tetracyclic ring system, respectively, is described (Fig. 1).

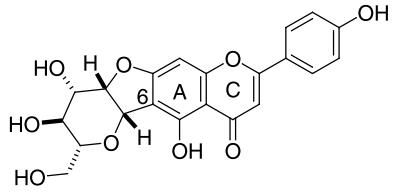

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Figure 1. Anti-inflammatory active flavone *C*-glycoside.

2. Results and discussion

Scheme 1 depicts the retrosynthetic pathway for compound **1**, where the fused tetracyclic ring system may be feasibly constructed by the regioselective intramolecular Mitsunobu reaction between the 2-position of the glucosyl moiety and the phenolic hydroxyl group of isovitexin derivative **2**. Mono-acylated aryl *C*-glycoside **3**, which can be prepared from **4**, was selected as a precursor for forming the flavone ring. The *C*-glycosidic linkage of **4** can be formed by an *O*-to-*C* rearrangement using acetophenone derivative **5** and the glycosyl donor **6** in the presence of Lewis acid catalyst.

According to the retrosynthetic pathway, the benzyl protected *C*-glucoside **9** was selected as a key intermediate (Scheme 2). Schmidt and co-workers prepared compound **9** via a four-step synthetic manipulation, including the *O*-to-*C* rearrangement of the corresponding α-*O*-glucoside, which was prepared by *O*-glucosidation using a TBS-protected acetophenone derivative followed by deprotection–protection sequence.[9]

Keywords: Flavone *C*-glycoside; *O*-to-*C* rearrangement; Mitsunobu reaction; Anti-inflammatory activity.
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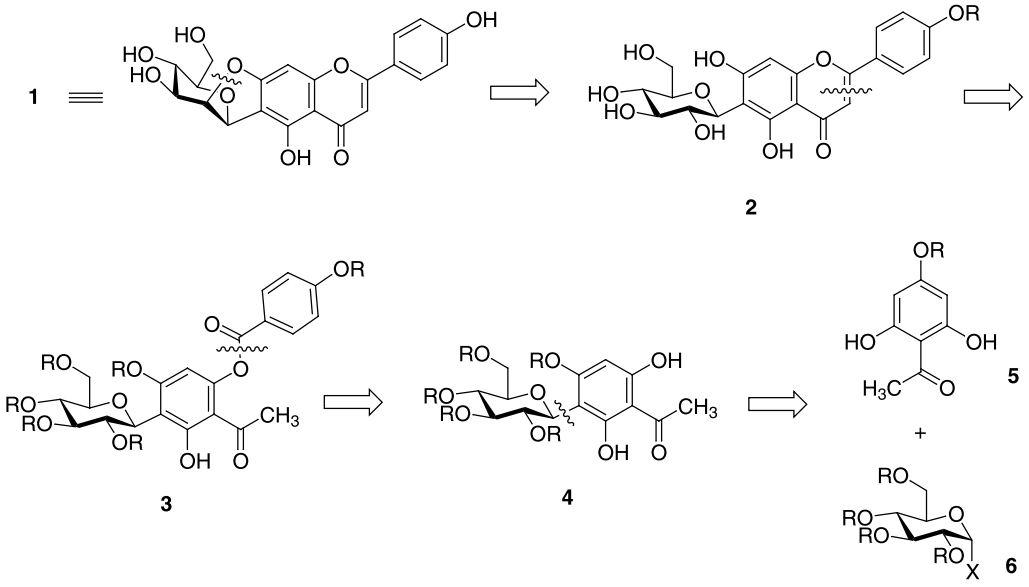
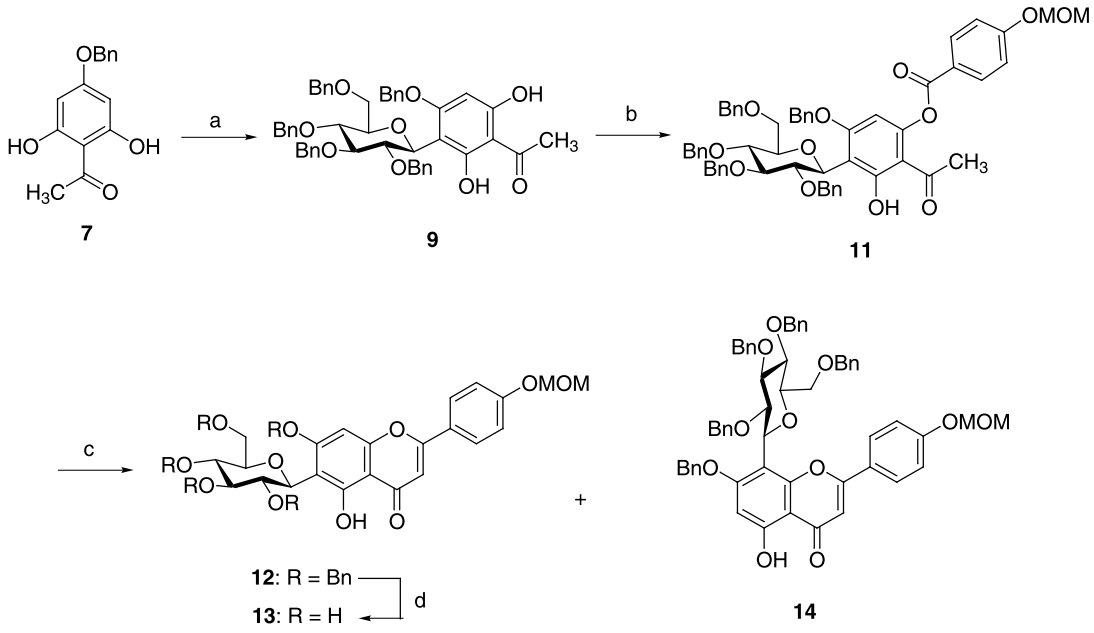


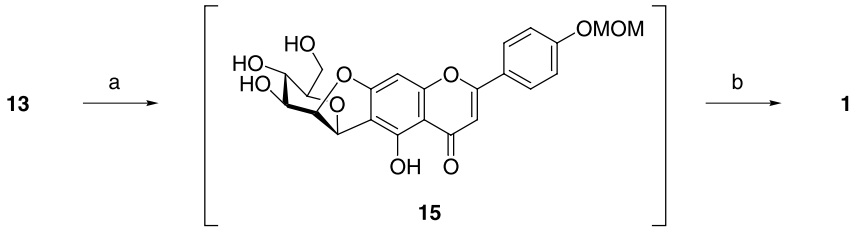
Scheme 1. Retrosynthetic analysis of **1**.



Scheme 2. Synthesis of isovitexin and vitexin derivatives. Reagents and conditions: (a) *O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl) trichloroacetimidate (**8**), TMSOTf, CH_2Cl_2, 0 °C to rt, 69%; (b) 4-(methoxymethoxy)benzoic acid (**10**), DCC, DMAP, CH_2Cl_2, rt, 82%; (c) K_2CO_3, pyridine, reflux, 1 h, **12** (17%), **14** (15%); (d) $Pd(OH)_2$, H_2, EtOH, 35 °C, 95%.

We envisaged that **9** could be directly formed from monobenzyl protected acetophenone derivative **7**,[10] which is readily available from phloroglucinol on the gram scale, as a starting glycosyl acceptor. Using improvements from previous preparations, the direct synthesis of **9** from **7** was attempted. As expected, glycosylation of **7** with *O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)trichloroacetimidate (**8**)[11] in the presence of catalytic amounts of TMSOTf[12] gave the desired β-configured **9** via *O*-to-*C* rearrangement in 69% yield. Subsequent condensation of **9** with 4-(methoxymethoxy)benzoic acid (**10**)[13] selectively afforded monoacylated derivative **11**. The appearance of two sets of peaks in the ^1H and ^{13}C NMR spectra, which both agree with the structure of **11**, suggests that **11** exists as a rotational isomer at ambient temperature on the NMR time-scale.

Although the many synthetic flavonoid studies are reported, reliable and mild reaction conditions for C ring formation are not readily available. Both of the following synthetic methods, (i) Baker–Venkataraman rearrangement-successive acid catalyzed cyclization,[9] and (ii) chalcone formation-oxidative cyclization using I_2[14] or another oxidant,[15] have been widely used for this purpose. However, both cyclizations often require strongly acidic or basic conditions to obtain the desired flavones in satisfactory chemical yields. We decided to apply the cyclization conditions,[16]



Scheme 3. Completion of the synthesis of the target flavone. Reagents and conditions: (a) 1,1′-azobis(*N*,*N*-dimethylformamide), Bu_3P, THF, 50 °C; (b) 4 N HCl–dioxane, MeOH, rt, 32% (two steps).

which were previously employed for preparing flavonol derivatives. Thus, upon refluxing a pyridine solution of **11** in the presence of K_2CO_3, both the isovitexin-type flavone **12** and vitexin-type derivative **14** were obtained as separable mixture in 17 and 15% yields, respectively. The formation of both isomeric flavones indicated that the C ring construction occurred via Baker–Venkataraman rearrangement of the acyl group and successive cyclization under these reaction conditions.

Removing the benzyl protecting groups of **12** by hydrogenation with Pearlman's catalyst in EtOH provided **13** in excellent yield.

Next, we turned our attention to constructing the tetracyclic ring system that corresponds to the left part of the molecule. Intramolecular cyclization of **13** under modified Mitsunobu conditions[8b,c] in THF followed by the removal of the MOM protecting group by treating with 4 N HCl–dioxane in MeOH to yield target flavone **1** in 32% for two steps without generation of another flavone isomers (Scheme 3). It is noteworthy that flavone **15** was synthesized as a dominant product in the first step even in the presence of reactive primary and phenolic hydroxyl groups in substrate **13**.

3. Conclusion

In summary, the total synthesis of compound **1** was accomplished by combining *C*-glycoside formation, flavone ring construction, and intramolecular Mitsunobu reaction as key steps. This concise and efficient synthetic protocol, which consists of six steps from known acetophenone derivative **7** in 3% overall yield, could be employed not only for large-scale synthesis of target flavone, but also for preparing related derivatives that would be useful for studying structure–activity relationship. Synthetic efforts for preparing a series of flavone derivatives based on this synthetic pathway and evaluating their biological activities are currently under investigation in our laboratory.

4. Experimental

4.1. General

Melting points are uncorrected. Optical rotations were measured on a JASCO P-1030 polarimeter. ^1H and ^{13}C NMR spectra were obtained on JEOL ECA-500 at 500 and 125 MHz, respectively, with chemical shifts being reported as δ ppm from tetramethylsilane as an internal standard. IR spectra were recorded on a JASCO WS/IR-8000. The mass spectra were measured on a JEOL MStation JMS-700 spectrometer. THF was distilled from sodium benzophenone ketyl, CH_2Cl_2, MeOH and pyridine were from calcium hydride, magnesium and NaOH, respectively. Unless otherwise noted, all reactions were run under an argon atmosphere. All extractive organic solutions were dried over anhydrous $MgSO_4$, filtered and then concentrated under reduced pressure. Column chromatography was carried out with silica gel 60N spherical (63–210 mesh, KANTO CHEMICAL) or Sephadex LH-20 (Amersham Biosciences).

4.1.1. *O*-to-*C* Rearrangement to 4-benzyloxy-2,6-dihydroxy-3-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-acetophenone (9). To a mixture of 4-benzyloxy-2,6-dihydroxyacetophenone (**7**)[10] (1.4 g, 5.4 mmol) and *O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)trichloroacetimidate (**8**)[11] (3.7 g, 5.4 mmol) in CH_2Cl_2 (40 mL) was added TMSOTf (97 μL, 0.54 mmol) at 0 °C. After being stirred at room temperature for 18 h, the mixture was added H_2O at 0 °C and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layer was washed with brine, dried and evaporated to give a residue, which was purified by column chromatography (SiO_2, toluene–EtOAc=9/1) to afford **9**[9] (2.9 g, 69%) as a colorless oil.

4.1.2. 4-Benzyloxy-2-hydroxy-6-(4-methoxymethoxybenzoyloxy)-3-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-acetophenone (11). A mixture of **9** (509 mg, 0.65 mmol), 4-(methoxymethoxy)benzoic acid (**10**)[13](117 mg, 0.65 mmol), DCC (161 mg, 0.78 mmol) and DMAP (8.0 mg, 65 μmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 12 h. After the addition of H_2O, the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried and evaporated to give a residue. The residue was purified by column chromatography (SiO_2, toluene–EtOAc=10/1) to afford **11** (504 mg, 82%) as a colorless oil.

$[\alpha]_D^{20}=-12.1$ (*c* 1.3, $CHCl_3$); ^1H NMR (C_6D_6, rotamers): δ 14.48, 13.59 (s, 1H, OH), 8.03 (d, 2H, J=8.5 Hz, Ar), 7.40–7.00 (m, 25H, Bn), 6.91 (d, 2H, J=8.5 Hz, Ar), 6.20, 6.10 (s, 1H, Ar), 5.57, 5.31 (d, 1H, J=9.4 Hz, sugar H-1), 5.00–4.20 (m, 10H, Bn), 4.72, 4.65 (dd, 1H, J=9.4, 10 Hz, sugar H-2), 4.65 (s, 2H, MOM), 4.02, 3.98 (t, 1H, J=8.8 Hz, sugar H-4), 3.88, 3.80 (dd, 1H, J=8.8, 10 Hz, sugar H-3), 3.76, 3.64 (m, 1H, sugar H-6), 3.58, 3.49 (m, 1H, sugar H-5), 2.97 (s, 3H, MOM), 2.22, 2.18 (s, 3H, Ac); ^{13}C NMR (C_6D_6, rotamers): δ 201.8, 201.4 (Ac), 164.8, 164.4 (Ar), 163.7, 162.2 (Ar), 162.2 (Ar), 162.1 (Ar), 154.0, 153.3 (Ar),

139.7–139.1 (Bn), 132.4 (Ar), 130.0–125.0 (Bn), 116.2 (Ar), 112.9, 112.4 (Ar), 110.9, 109.3 (Ar), 100.3, 100.1 (Ar), 93.8 (MOM), 88.1, 87.9 (sugar C-3), 80.1, 79.8 (sugar C-5), 79.2, 78.9 (sugar C-2), 75.2, 75.1 (sugar C-4), 74.7, 74.6 (sugar C-1), 75.0–70.0 (Bn), 69.2, 69.4 (sugar C-6), 55.6 (MOM), 31.7, 31.5 (Ac); IR ($CHCl_3$): 3011, 1738, 1607, 1283, 1244; MS (FAB) *m/z* 945 $(M+H)^+$; HRMS calcd for $C_{58}H_{57}O_{12}$ $(M+H)^+$ 945.3850, found 945.3846.

4.2. Flavone ring formation to isovitexin and vitexin derivatives

A mixture of **11** (693 mg, 0.74 mmol), K_2CO_3 (507 mg, 3.7 mmol) and MS 4 Å (70 mg) in pyridine (148 mL) was stirred under reflux for 1 h. After concentration of the reaction mixture, the residue was diluted with EtOAc and washed with saturated $CuSO_4$. The organic layer was washed with brine, dried and evaporated to give a residue. The residue was purified by column chromatography (SiO_2, toluene–EtOAc=20/1) to afford the less polar fraction containing vitexin derivative **14** and the pure isovitexin derivative **12** (115 mg, 17%) as a polar fraction. Further purification of the less polar fraction by preparative HPLC (YMC-pack ODS-A S-5 SH-343-5, CH_3CN, 6 mL/min, t_R=20.7 min) gave vitexin derivative **14** (100 mg, 15%).

4.2.1. 7-Benzyloxy-5-hydroxy-2-(4-methoxymethoxyphenyl)-6-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-4*H*-1-benzopyran-4-one (isovitexin derivative) (12). Pale yellow oil; $[\alpha]_D^{20}=-18.0$ (*c* 1.2, $CHCl_3$); ^1H NMR (C_6D_6, rotamers): δ 14.34, 14.27 (s, 1H, OH), 7.53–6.80 (m, 25H, Bn), 7.32 (m, 2H, Ar), 6.91 (m, 2H, Ar), 6.36, 6.34 (s, 1H, Ar), 6.14, 6.06 (s, 1H, Ar), 5.55, 5.38 (d, 1H, J=9.5 Hz, sugar H-1), 5.05, 4.63 (t, 1H, J=9.5 Hz, sugar H-2), 5.00–4.40 (m, 10H, Bn), 4.65 (s, 2H, MOM), 4.06, 4.04 (t, 1H, J=9.2 Hz, sugar H-4), 3.90, 3.87 (m, 1H, sugar H-3), 3.85, 3.76, 3.72, 3.64 (m, 2H, sugar H-6), 3.67, 3.57 (m, 1H, sugar H-5), 3.02 (s, 3H, MOM); ^{13}C NMR (C_6D_6, rotamers): δ 182.5 (C=O), 163.8, 162.2 (Ar), 163.0 (Ar), 161.7, 161.0 (Ar), 160.2 (Ar), 157.7, 157.6 (Ar), 130.0–127.0 (Bn), 128.5 (Ar), 125.5 (Ar), 116.4 (Ar), 110.9, 110.6 (Ar), 105.8 (Ar) 106.0, 105.5 (Ar), 93.5 (MOM), 91.7, 91.0 (Ar), 87.5 (sugar C-3), 80.5 (sugar C-5), 79.3, 78.9 (sugar C-2), 78.7 (sugar C-4), 75.2–73.5 (Bn), 73.2, 73.0 (sugar C-1), 69.2 (sugar C-6), 56.2 (MOM); IR ($CHCl_3$): 3011, 2930, 2866, 1655, 1609, 1454, 1348; MS (FAB) *m/z* 927 $(M+H)^+$; HRMS calcd for $C_{58}H_{55}O_{11}$ $(M+H)^+$ 927.3745, found 927.3782.

4.2.2. 7-Benzyloxy-5-hydroxy-2-(4-methoxymethoxyphenyl)-8-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-4*H*-1-benzopyran-4-one (vitexin derivative) (14). Pale yellow oil; $[\alpha]_D^{20}=-20.5$ (*c* 1.2, $CHCl_3$); ^1H NMR (C_6D_6): δ 14.02 (s, 1H, OH), 7.70–6.50 (m, 25H, Bn), 7.91 (d, 2H, J=9.2 Hz, Ar), 7.06 (m, 2H, Ar), 6.36 (s, 1H, Ar), 6.35 (s, 1H, Ar), 5.33 (d, 1H, J=9.9 Hz, sugar H-1), 5.00–4.00 (m, 10H, Bn), 4.68 (s, 2H, MOM), 4.34 (m, 1H, sugar H-2), 4.19 (m, 1H, sugar H-4), 3.83 (t, 1H, J=8.8 Hz, sugar H-3), 3.71 (dd, 1H, J=3.5, 10.7 Hz, sugar H-6a), 3.52 (dd, 1H, J=1.2, 10.7 Hz, sugar H-6b), 3.40 (d, 1H, J=9.9 Hz, sugar H-5), 2.99 (s, 3H, MOM); ^{13}C NMR (C_6D_6): δ 182.8 (C=O), 163.8 (Ar), 163.3 (Ar), 162.5 (Ar), 160.4 (Ar), 155.9 (Ar), 140.0–125.0 (Bn), 129.6 (Ar), 125.2 (Ar), 117.7 (Ar), 106.1 (Ar) 105.5 (Ar), 93.9 (MOM), 96.4 (Ar), 88.5 (sugar C-3), 79.9 (sugar C-5), 78.6 (sugar C-4), 78.5 (sugar C-2), 80.0–70.0 (Bn), 75.5 (sugar C-1), 68.8 (sugar C-6), 55.5 (MOM); IR ($CHCl_3$): 3011, 2934, 2870, 1653, 1607, 1589, 1431, 1360; MS (FAB) *m/z* 927 $(M+H)^+$; HRMS calcd for $C_{58}H_{55}O_{11}$ $(M+H)^+$ 927.3745, found 927.3740.

4.2.3. 6-(β-D-Glucopyranosyl)-5,7-dihydroxy-2-(4-methoxymethoxyphenyl)-4*H*-1-benzopyran-4-one (13). A mixture of **12** (10 mg, 11 μmol) and $Pd(OH)_2$ (2.0 mg) in EtOH (3.0 mL) was stirred at 35 °C for 1 h under hydrogen. After concentration of the reaction mixture, the residue was purified by column chromatography (SiO_2, $CHCl_3$–MeOH=5/1) to afford **13** (5.0 mg, 95%).

Mp 175–177 °C; yellow needles (from acetone–H_2O); $[\alpha]_D^{20}=+28.0$ (*c* 0.25, MeOH); ^1H NMR (acetone-d_6+D_2O): δ 8.00 (d, J=8.6 Hz, 2H), 7.20 (d, J=8.6 Hz, 2H), 6.69 (s, 1H), 6.54 (s, 1H), 5.30 (s, 2H), 4.94 (d, J=9.8 Hz, 1H), 3.9–3.7 (m, 3H), 3.7–3.3 (m, 3H), 3.45 (s, 3H); ^{13}C NMR (acetone-d_6+D_2O): δ 183.0, 164.3, 163.8, 161.0, 160.7, 157.7, 128.7, 124.9, 117.1, 108.5, 104.8, 104.5, 95.3, 94.6, 81.6, 79.0, 75.0, 72.9, 70.4, 61.5, 56.1; IR (Nujol): 3380, 1653, 1634, 1609, 1574, 1244, 1154, 984; MS (FAB) *m/z* 477 $(M+H)^+$; HRMS calcd for $C_{23}H_{25}O_{11}$ $(M+H)^+$ 477.1397, found 477.1353.

4.2.4. Transformation to target flavone 1. To a mixture of **13** (16 mg, 34 μmol), 1,1′-azobis(*N*,*N*-dimethylformamide) (12 mg, 68 μmol) in THF (2.0 mL) was added *n*-Bu_3P (17 μL, 68 μmol) at 0 °C. After stirring at 50 °C for 24 h, the mixture was concentrated and the residue was subjected to column chromatography (SiO_2, $CHCl_3$–MeOH=50/1) to afford the mixture (14.6 mg) containing compound **15**. Part of the mixture (6.7 mg) was dissolved in MeOH (1.0 mL) and treated with 4 N HCl–dioxane (0.2 mL). After stirring at room temperature for 30 min, the reaction mixture was evaporated to give a residue containing the target flavone **1**. The chemical yield (32%) of **1** from **13** was obtained from the HPLC quantification (YMC-pack ODS R-ODS-5A, MeOH–H_2O=1/1, 0.3 mL/min, t_R=37.0 min).

Under the same Mitsunobu conditions started from **13** (19 mg, 40 μmol) and subsequent deprotection by 4 N HCl–dioxane gave **1** (3.3 mg, 20%) after purification by column chromatography (Sephadex LH-20, MeOH). The synthetic **1** was identical with the authentic sample in terms of the ^1H and ^{13}C NMR spectroscopic data[5] as well as the retention time in HPLC analysis.

Mp 229–232 °C; yellow needles (from MeOH); $[\alpha]_D^{20}=-174.5$ (*c* 0.17, MeOH); IR (Nujol): 3345, 1672, 1626, 1611, 1574, 1561, 1252, 1086; MS (FAB) *m/z* 415 $(M+H)^+$; HRMS calcd for $C_{21}H_{19}O_9$ $(M+H)^+$ 415.1029, found 415.1032.

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