HETEROCYCLES, Vol. 76, No. 2, 2008, pp. 1607 - 1615. © The Japan Institute of Heterocyclic Chemistry
Received, 31st March, 2008, Accepted, 12th June, 2008, Published online, 16th June, 2008. COM-08-S(N)79

# SYNTHESIS OF ORIENTED ANTI-VIRUS 7-*O*-SUBSTITUTED APIGENINS†

**Kin-ichi Oyama,[a] Tadao Kondo, and Kumi Yoshida[b,*]**

[a] Chemical Instrument Room, Research Center for Materials Science, [b]Graduate School of Inforamtion Science, Nagoya University, Chikusa, Nagoya 464-8601, Japan; *E-mail address: yoshidak@is.nagoya-u.ac.jp

**Abstract** – 7-*O*-Substituted apigenins were synthesized for searching anti-virus active compound. Using a commercially available naringenin as a starting material, 7-*O*-methylapigenin (**1**) and seven unnatural 7-*O*-substituted apigenin derivatives (**13**-**19**) were prepared via 4'-*O*-methoxymethylapigenin (**5**) as an intermediate.

## INTRODUCTION

Flavonoids are plant second metabolites possessing various biological functions and have a long history as Chinese medicine, herbal medicines and folk medicines. Among them flavone is one of important class of compounds that displays a broad range of medicinal properties.[1-3] Recently anti-virus activity of flavones attracts interests and some natural products such as 7-*O*-methylapigenin (**1**) was reported to posess a anti-influenza activity.[3] Therefore, we studied on anti-virus oriented synthesis of flavone derivatives. For this purpose divergent synthesis of 7-*O*-substituted flavones is necessary, but synthetic study of alkylated flavones by direct alkylation reaction is rare,[4] because regioselective reaction for polyphenolic OHs in flavone skelton is difficult. We have been studied on synthesis of flavonoids and reported the difference in reactivity of phenolic hydroxyl groups.[5-7] In the case of naringenin 7-OH showed the highest reactivity in nucleophilic alkylation and 4'-OH showed the next and 5-OH exhibited the lowest reactivity.[5,6] In benzylation of (+)-catechin 7-OH was less reactive than 5 and 4'-OH.[7] Furthermore, we have reported that DDQ oxidation of naringenin to apigenin proceed easily.[5] Therefore,

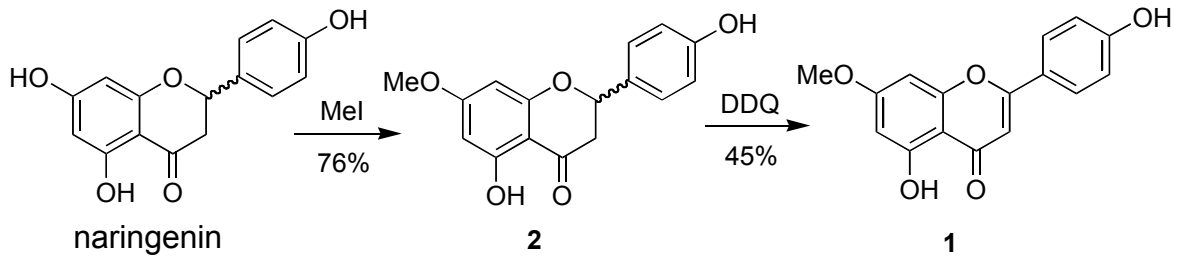
---

† Dedicated to Prof. Ryoji Noyori on the occasion of his 70th birthday.

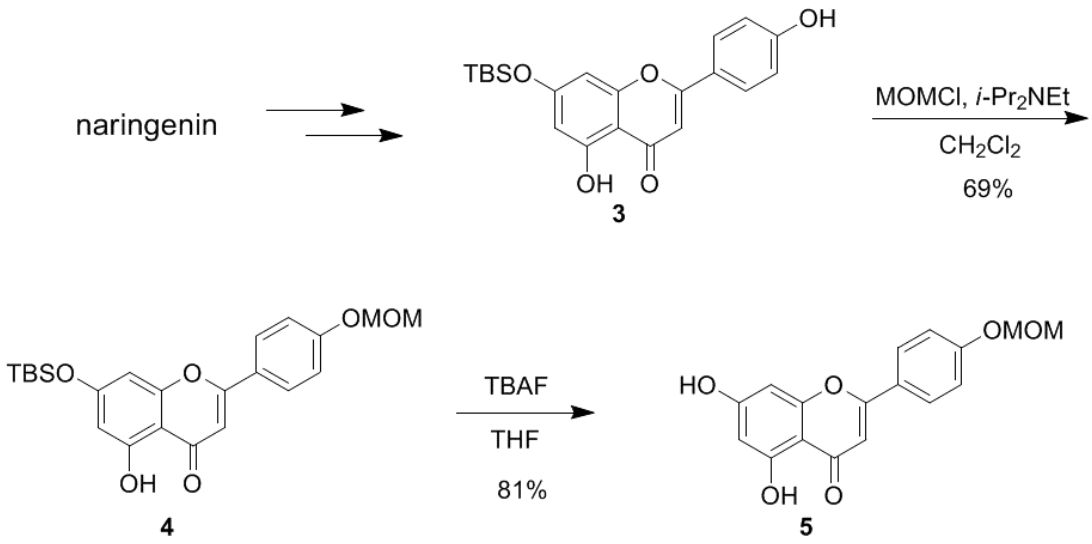
we planed to the synthesis of 7-*O*-subustituted apigenin derivatives from corresponding naringenin derivatives. Here, we report synthesis of a natural occurring 7-*O*-methylapigenin (**1**)[8] and seven unnatural 7-*O*-substituted apigenin analogues by a systematical synthesis via 4'-*O*-methoxymethylapigenin (**5**) as a key intermediate.

## RESULTS AND DISCUSSION

At first 7-*O*-methylapigenin (**1**) was synthesized. Commercially available naringenin was methylated with MeI to give 7-*O*-methyl compound **2** as a major compound (76%).[6] **2** was, then, oxidized with DDQ to give flavone **1** in 45% yield.




**Scheme 1**. Synthesis of 7-*O*-methylapigenin (**1**).

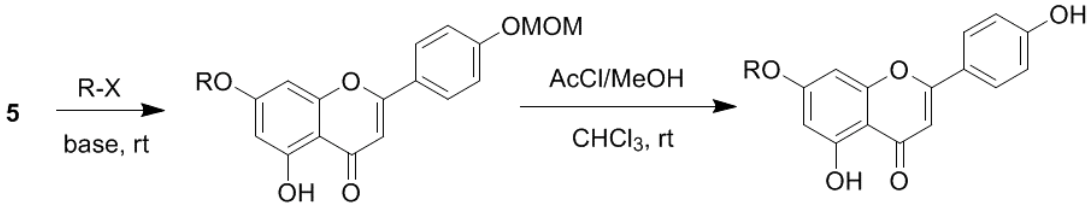



**Scheme 2**. Synthesis of 4'-*O*-methoxymethylapigenin (**5**).

Since the separation of **1** from DDQ was difficult because of the high polarity of **1**, this reaction sequence seemed to be improper for a large scale preparation and structural diversity oriented synthesis. Therefore,

we change the strategy; naringenin having bulky protecting group was oxidaized with DDQ, then replacing of protecting group and 7-*O*-alkylation reaction was carried out. We designed a precursor **5** for a key intermediate. 7-OH of naringenin was protected with TBS group, then the 2,3-bond was oxidized with DDQ to give **3**.[5] Then, 4'-OH was eterified by MOMCl (69%) followed by desilylation by TBAF to give **5** in 81%. Fortunately, **5** was purified by recrystallization.

**Table 1**. Synthesis of 7-*O*-substituted apigenin anlogues (**13-19**).




| entry | R-X | base | solvent | yield (%) | yield (%) |
|---|---|---|---|---|---|
| 1 | EtI | NaH | DMF | **6** (24) | **13** (87) |
| 2 | *n*-PrBr | NaH | DMF | **7** (61) | **14** (84) |
| 3 | *i*-PrBr | NaH | DMF | **8** (49) | **15** (84) |
| 4 | *n*-BuI | NaH | DMF | **9** (51) | **16** (96) |
| 5 | BnBr | NaH | DMF | **10** (66) | **17** (87) |
| 6 | MsCl | $Et_3N$ | $CH_2Cl_2$ | **11** (87) | **18** (97) |
| 7 | TsCl | $Et_3N$ | $CH_2Cl_2$ | **12** (81) | **19** (88) |

7-OH of **5** was substituted with various alkyl- and sulfonyl-reagents (Table 1). The alkylation reaction of **5** was carried out with NaH and each alkylhalide in DMF to give 7-*O*-ethyl-, *n*-propyl-, *i*-propyl-, *n*-butyl- and benzyl-apigenin **6-10** (entries 1-5). Mesylation and tosylation of **5** were carried out with corresponding sulfonyl chloride with $Et_3N$ in $CH_2Cl_2$ to give **11** and **12** (Table 1, entries 6 and 7). Deprotection of 4'-*O*-MOM residue of **6-12** was carried out in AcCl/MeOH to be obtained 7-*O*-substituted apigenin derivatives **13-19** in high yield, repectively.

A naturally occurring 7-*O*-methylapigenin (**1**) with seven unnatural 7-*O*-substituted apigenins were synthesized from naringenin. The studies on anti-virus activities are in progress. Furthermore, 7-*O*-TBS-apigenin (**3**) and 4'-*O*-methoxymethylapigenin (**5**) should be a usuful and powerful intermediate for synthesis of a variety of apigenin derivatives, therefore, further synthesis of substituted apigenins are going on.

## EXPERIMENTAL

### General

Melting points were recorded on a Yanagimoto MP-S3 apparatus and uncorrected. IR spectra were obtained with a JASCO FT/IR-6100 spectrometer. NMR spectra were obtained with a JEOL A-600 ($^{13}$C: 150 MHz ), ECA-500 ($^{1}$H: 500 MHz, $^{13}$C: 125 MHz), and a JNM-A400 ($^{1}$H: 400 MHz, $^{13}$C: 100 MHz) instrument in a 5-mm ϕ tube at variable temperature using $CDCl_3$ and DMSO-$d_6$ as a solvent. Chemical shifts were reported as $\delta$ (ppm) with the $CD_2HCl$ resonance as a standard and the coupling constant was expressed in Hz. FABMS (*m*-nitrobenzyl alcohol as a matrix) were recorded on a JEOL JMS-700 spectrometer. Elemental analyses were perpormed on YANACO MT-6 elemental analyser. Silica gel column chromatography was performed with Fuji Silysia FL60D. Thin layer chromatography was performed on Merck Kieselgel 60 $F_{254}$.

### 7-*O*-Methylapigenin (1)

A solution of **2** (543 mg, 1.9 mmol) and DDQ (863 mg, 1.9 mmol) in 1,4-dioxane (15 mL) was refluxed for 15 h at 110 ˚C. The reaction mixture was purified by flash column chromatography (hexane-AcOEt 1:1) to afford **1** (241 mg, 45%) as a pale yellow powder: mp 293-294 ºC; IR (KBr) 3277, 1668, 1605, 1500, 1294 cm$^{-1}$; (DMSO-$d_6$, 500 MHz) $\delta$ 3.83 (3H, s), 6.34 (1H, d, $J$ = 2.0 Hz), 6.73 (1H, d, $J$ = 2.0 Hz), 6.81 (1H, s), 6.89 (2H, d, $J$ = 8.5 Hz), 7.92 (2H, d, $J$ = 8.5), 10.39 (1H, s), 12.92 (1H, s); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 56.6, 93.2, 98.5, 103.5, 105.2, 116.5, 121.6, 129.1, 157.7, 161.7, 161.8, 164.6, 165.7, 182.5; HRMS (FAB) Calcd. for $C_{16}H_{13}O_5$ (M+H$^+$) 285.0763, found 285.0775; Anal. Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25. Found: C, 67.24; H, 4.25

### 7-*O*-*tert*-Butyldimethylsilyl-4'-*O*-methoxymethylapigenin (4)

To a solution of **3** (581 mg, 1.51 mmol) and *i*-PrNEt$_2$ (0.39 mL, 2.26 mmol) in $CH_2Cl_2$ (10 mL) was added MOMCl (0.18 mL, 2.26 mmol) at rt. After stirring for 2 h, the reaction mixture was quenched by addition of saturated aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was purified by flash column chromatography (hexane-AcOEt 3:1) to give **4** (450 mg, 69%) as a pale yellow powder: mp 113-114 ºC; IR (KBr) 2928, 1651, 1606, 1499, 1235, 847 cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.28 (6H, s), 1.00 (9H, s), 3.50 (3H, s), 5.25 (2H, s), 6.30 (1H, d, $J$ = 2.0 Hz), 6.43 (1H, d, $J$ = 2.0 Hz), 6.58 (1H, s), 7.15 (2H, d, $J$ = 9.0 Hz), 7.83 (2H, d, $J$ = 9.0 Hz); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ -4.4, 18.2, 25.5, 56.3, 94.2, 98.7, 103.8, 104.6, 106.1, 116.5, 124.7, 128.0, 157.6, 160.2, 162.1, 162.2, 163.9, 182.5; HRMS (FAB) Calcd. for $C_{23}H_{29}O_6Si$ (M+H$^+$) 429.1733, found 429.1726.

**4'-*O*-Methoxymethylapigenin (5)**

To a solution of **4** (118 mg, 0.275 mmol) in THF (2 mL) was added TBAF (1 M solutin in THF) (275 μL, 0.275 mmol) at rt. After 10 min, the reaction mixture was poured into saturated aqueous $NH_4Cl$ and extracted with AcOEt. The combined extracts were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was purified by recrystallization (AcOEt-$CHCl_3$-hexane) to afford **5** (70 mg, 81%) as a pale yellow solid: mp 209-210 ºC; IR (KBr) 3162, 1650, 1620, 1506, 1237, 830 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.39 (3H, s), 5.29 (2H, s), 6.19 (1H, d, $J$ = 2.0 Hz), 6.49 (1H, d, $J$ = 2.0 Hz), 6.87 (1H, s), 7.17 (2H, d, $J$ = 9.0 Hz), 8.02 (2H, d, $J$ = 9.0 Hz), 12.89 (1H, s); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta$ 55.9, 93.8, 94.1, 99.0, 103.8, 103.9, 116.5, 123.9, 128.3, 157.4, 159.8, 161.5, 163.3, 164.3, 181.8; HRMS (FAB) Calcd. for $C_{17}H_{15}O_6$ ($M+H^+$) 315.0869, found 315.0869.

**Typical procedure for alkylation**

To a solution of **5** (15.7 mg, 50 μmol), and NaH (6 mg, 150 μmol) in DMF (0.5 mL) was added *n*-PrBr (14 μL, 150 μmol) at rt. After stirring for 2 h, the reaction mixture was quenched by addition of saturated aqueous $NH_4Cl$ and extracted with AcOEt. The combined extracts were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was purified by thin layer chromatography (hexane-AcOEt 3:1) to give **7** (10.9 mg, 61%) as a pale yellow powder.

**7-*O*-Ethyl-4'-*O*-methoxymethyl apigenin (6)**

Pale yellow powder: mp 131-132 ºC; IR (KBr) 2928, 1666, 1603, 1503, 1243, 828 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.45 (3H, t, $J$ = 7.0 Hz), 3.50 (3H, s), 4.10 (2H, q, $J$ = 7.0 Hz), 5.23 (2H, s), 6.35 (1H, d, $J$ = 2.0 Hz), 6.47 (1H, d, $J$ = 2.0 Hz), 6.58 (1H, s), 7.18 (2H, d, $J$ = 9.0 Hz), 7.82 (2H, d, $J$ = 9.0 Hz), 12.75 (1H, s); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 14.6, 56.3, 64.2, 93.0, 94.2, 98.4, 104.6, 105.5, 116.5, 124.7, 128.0, 157.7, 160.1, 162.1, 163.8, 164.9, 182.4; HRMS (FAB) Calcd. for $C_{19}H_{19}O_6$ ($M+H^+$) 343.1182, found 343.1177.

**4'-*O*-Methoxymethyl-7-*O*-*n*-propylapigenin (7)**

Pale yellow powder: mp 115-116 ºC; IR (KBr) 2925, 1663, 1603, 1503, 1242, 829 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.05 (3H, t, $J$ = 7.0 Hz), 1.84 (2H, sec, $J$ = 7.0 Hz), 3.99 (2H, t, $J$ = 7.0 Hz), 5.25 (2H, s), 6.35 (1H, d, $J$ = 2.0 Hz), 6.47 (1H, d, $J$ = 2.0 Hz), 6.57 (1H, s), 7.15 (2H, d, $J$ = 9.0 Hz), 7.82 (2H, d, $J$ = 9.0 Hz), 12.75 (1H, s); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 10.4, 22.3, 56.3, 70.1, 93.0, 94.2, 98.5, 104.6, 105.4, 116.5, 124.7, 127.9, 157.7, 160.1, 162.1, 163.8, 165.1, 182.4; HRMS (FAB) Calcd. for $C_{20}H_{21}O_6$ ($M+H^+$) 357.1338, found 357.1338.

**4'-*O*-Methoxymethyl-7-*O*-*i*-Propylapigenin (8)**

Pale yellow powder: mp 144-145 ºC; IR (KBr) 2925, 1663, 1609, 1499 1237, 840 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.39 (6H, d, $J$ = 6.0 Hz), 3.50 (3H, s), 4.63 (1H, sep, $J$ = 6.0 Hz), 5.25 (2H, s), 6.33 (1H, d, $J$ = 2.0 Hz), 6.45 (1H, d, $J$ = 2.0 Hz), 6.57 (1H, s), 7.15 (2H, d, $J$ = 9.0 Hz), 7.82 (2H, d, $J$ = 9.0 Hz), 12.69 (1H, s); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 21.9, 56.3, 70.7, 93.9, 94.2, 99.1, 104.6, 105.3, 116.5, 124.7, 128.0, 157.8, 160.1, 162.2, 163.8, 164.0, 182.4; HRMS (FAB) Calcd. for $C_{20}H_{21}O_6$ ($M+H^+$) 357.1338, found 357.1338.

**7-*O*-*n*-Butyl-4'-*O*-methoxymethylapigenin (9)**

Pale yellow powder: mp 120-121 ºC; IR (KBr) 2956, 1662, 1606, 1504, 1240, 836 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.99 (3H, t, $J$ = 7.0 Hz), 1.51 (2H, sec, $J$ = 7.0 Hz), 1.80 (2H, quint, $J$ = 7.0 Hz), 3.50 (3H, s), 4.04 (2H, t, $J$ = 6.5 Hz), 5.25 (2H, s), 6.35 (1H, d, $J$ = 2.0 Hz), 6.47 (1H, d, $J$ = 2.0 Hz), 6.57 (1H, s), 7.15 (2H, d, $J$ = 9.0 Hz), 7.83 (2H, d, $J$ = 9.0 Hz), 12.64 (1H, s); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 13.8, 19.1, 31.0, 56.3, 68.3, 93.0, 94.2, 98.5, 104.6, 105.4, 116.5, 124.7, 127.9, 157.7, 160.1, 162.1, 163.8, 165.1, 182.4; HRMS (FAB) Calcd. for $C_{21}H_{23}O_6$ ($M+H^+$) 371.1495, found 371.1505.

**7-*O*-Benzyl-4'-*O*-methoxymethylapigenin (10)**

Pale yellow powder: mp 101-102 ºC; IR (KBr) 2903, 1663, 1605, 1502, 1243, 834 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.50 (3H, s), 5.14 (2H, s), 5.25 (2H, s), 6.45 (1H, d, $J$ = 2.0 Hz), 6.56 (1H, d, $J$ = 2.0 Hz), 6.58 (1H, s), 7.15 (2H, d, $J$ = 9.0 Hz), 7.4-7.3 (5H, m), 7.82 (2H, d, $J$ = 9.0 Hz), 12.79 (1H, s); $^{13}C$ NMR ($CDCl_3$, 150 MHz) $\delta$ 56.3, 70.4, 93.5, 94.2, 98.8, 104.7, 116.6, 124.6, 127.5, 128.0, 128.3, 128.7, 135.8, 157.7, 160.2, 162.2, 163.9, 164.5, 182.4; HRMS (FAB) Calcd. for $C_{24}H_{21}O_6$ ($M+H^+$) 405.1338, found 405.1331.

**Typical procedure for Mesylation and tosylation**

To a solution of **5** (15.7 mg, 50 μmol), and $NEt_3$ (21 μL, 150 μmol) in $CH_2Cl_2$ (1 mL) was added MsCl (5 μL, 60 μmol) at 0 ºC. After stirring for 40 min, the reaction mixture was quenched by addition of saturated aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$. The combined extracts were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was purified by recrystallization (AcOEt-$CHCl_3$-hexane) to give **11** (17.0 mg, 87%) as a colorless powder.

**7-*O*-Mesyl-4'-*O*-methoxymethylapigenin (11)**

Colorless solid: mp 170-171 ºC; IR (KBr) 1651, 1605, 1364, 1239, 1001, 838 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.24 (3H, s), 3.51 (3H, s), 5.26 (2H, s), 6.70 (1H, d, $J$ = 2.0 Hz), 7.02 (1H, d, $J$ = 2.0 Hz), 6.68

(1H, s), 7.18 (1H, d, *J* = 9.0 Hz), 7.85 (2H, d, *J* = 9.0 Hz), 12.93 (1H, s); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 38.1, 56.3, 94.2, 101.1, 105.0, 105.2, 109.6, 116.7, 123.9, 128.3, 153.6, 156.8, 160.7, 162.4, 165.0, 182.6; HRMS (FAB) Calcd. for $C_{18}H_{17}O_8S$ ($M+H^+$) 393.0644, found 393.0640.

**4'-*O*-Methoxymethyl-7-*O*-tosylapigenin (12)**

Colorless solid: mp 164-165 ºC; IR (KBr) 1650, 1605, 1352, 1242, 998, 826 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.47 (3H, s), 3.51 (3H, s), 5.26 (2H, s), 6.32 (1H, d, *J* = 2.0 Hz), 6.65 (1H, s), 6.91 (1H, d, *J* = 2.0 Hz), 7.17 (2H, d, *J* = 9.0 Hz), 7.36 (2H, d, *J* = 8.0 Hz), 7.79 (2H, d, *J* = 8.0 Hz), 7.84 (2H, d, *J* = 9.0 Hz), 12.82 (1H, s); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 21.8, 56.3, 94.2, 101.6, 104.9, 105.5, 109.5, 116.7, 124.0, 128.2, 128.5, 130.0, 146.0, 154.3, 156.6, 160.6, 161.9, 164.9, 182.7; HRMS (FAB) Calcd. for $C_{24}H_{21}O_8S$ ($M+H^+$) 469.0957, found 469.0952.

**Typical procedure for deprotection of 6-12**

To a solution of **8** (9.3 mg, 26 μmol) in a mixture of MeOH (1 mL) and $CH_3Cl$ (1 mL) was added AcCl (0.3 mL) at rt. After 10 min, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The combined extracts were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was purified by thin layer chromatography (hexane-AcOEt 2:1) to give **14** (6.8 mg, 84%) as a pale yellow powder.

**7-*O*-Ethylapigenin** (**13**)

Pale yellow powder: mp 247-248 ºC: IR (KBr) 3146, 2925, 1663, 1598, 1256, 836 cm$^{-1}$; (DMSO-$d_6$, 500 MHz) $\delta$ 1.31 (3H, t, *J* = 6.0 Hz), 4.11 (2H, q, *J* = 7.0 Hz), 6.31 (1H, d, *J* = 2.0 Hz), 6.72 (1H, d, *J* = 2.0 Hz), 6.80 (1H, s), 6.89 (2H, d, *J* = 8.5 Hz), 7.92 (2H, d, *J* = 8.5), 10.45 (1H, s), 12.90 (1H, s); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 14.9, 64.7, 93.5, 98.8, 103.5, 105.0, 116.5, 121.6, 129.1, 157.7, 161.7, 161.8, 164.6, 164.9, 182.4; HRMS (FAB) Calcd. for $C_{17}H_{15}O_5$ ($M+H^+$) 299.0919, found 299.0929; Anal. Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.22 ; H, 4.73.

**7-*O*-*n*-Propylapigenin (14)**

Pale yellow powder: mp 209-210 ºC: IR (KBr) 3157, 2963, 1664, 1612, 1240, 833 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.94 (3H, t, *J* = 7.5 Hz), 1.72 (2H, sec, *J* = 7.5 Hz), 4.01 (2H, t, *J* = 7.5 Hz), 6.31 (1H, d, *J* = 2.0 Hz), 6.73 (1H, d, *J* = 2.0 Hz), 6.80 (1H, s), 6.89 (2H, d, *J* = 8.5 Hz), 7.92 (2H, d, *J* = 8.5), 10.44 (1H, s), 12.90 (1H, s); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 10.8, 22.3, 70.4, 93.6, 98.8, 103.5, 105.1, 116.5, 121.6, 129.1, 157.8, 161.7, 161.8, 164.6, 165.1, 182.4; HRMS (FAB) Calcd. for $C_{18}H_{17}O_5$ ($M+H^+$) 313.1076, found 313.1061; Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.16; H, 5.39.

**7-*O*-*i*-Propylapigenin (15)**

Pale yellow powder: mp 255-256 ºC: IR (KBr) 3162, 2980, 1661, 1607, 1244, 834 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.26 (6H, d, $J$ = 6.0 Hz), 4.74 (1H, sep, $J$ = 6.0 Hz), 6.28 (1H, d, $J$ = 2.0 Hz), 6.72 (1H, d, $J$ = 2.0 Hz), 6.78 (1H, s), 6.89 (2H, d, $J$ = 8.5 Hz), 7.92 (2H, d, $J$ = 8.5), 10.45 (1H, s), 12.87 (1H, s); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz) $\delta$ 22.2, 71.0, 94.2, 99.5, 103.5, 104.9, 116.5, 121.6, 129.1, 157.9, 161.7, 161.8, 164.0, 164.6, 182.4; HRMS (FAB) Calcd. for $C_{18}H_{17}O_5$ ($M+H^+$) 313.1076, found 313.1061; Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 68.68 ; H, 5.26.

**7-*O*-*n*-Butylapigenin (16)**

Pale yellow powder: mp 183-184 ºC; IR (KBr) 3142, 2926, 1665, 1606, 1173, 819 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 500 MHz) $\delta$ 0.90 (3H, t, $J$ = 7.5 Hz), 1.41 (2H, sec, $J$ = 7.5 Hz), 1.68 (2H, sep, $J$ = 7.5 Hz), 4.06 (1H, t, $J$ = 7.5 Hz), 6.31 (1H, d, $J$ = 2.0 Hz), 6.74 (1H, d, $J$ = 2.0 Hz), 6.80 (1H, s), 6.89 (2H, d, $J$ = 8.5 Hz), 7.91 (2H, d, $J$ = 8.5), 10.42 (1H, s), 12.90 (1H, s); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz) $\delta$ 14.2, 19.2, 31.0, 68.7, 93.6, 98.8, 103.5, 105.1, 116.5, 121.6, 129.8, 157.7, 161.7, 161.8, 164.6, 165.1, 167.9, 182.4; HRMS (FAB) Calcd. for $C_{19}H_{19}O_5$ ($M+H^+$) 327.1232, found 327.1240; Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.37 ; H, 5.64.

**7-*O*-Benzylapigenin (17)**

Pale yellow powder: mp 217-218 ºC: IR (KBr) 3142, 2924, 1660, 1596, 1174, 834 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 500 MHz) $\delta$ 5.21 (2H, s), 6.43 (1H, d, $J$ = 2.0 Hz), 6.82 (1H, s), 6.83 (1H, d, $J$ = 2.0 Hz), 6.89 (2H, d, $J$ = 8.5 Hz), 7.32 (1H, m), 7.38 (2H, m), 7.44 (2H, m), 7.92 (2H, d, $J$ = 8.5), 10.41 (1H, s), 12.92 (1H, s); $^{13}C$ NMR (DMSO-$d_6$, 500 MHz) $\delta$ 70.5, 94.1, 99.1, 103.6, 105.3, 116.5, 121.6, 128.4, 128.7, 129.1, 136.7, 157.7, 161.7, 161.8, 164.7, 182.5; HRMS (FAB) Calcd. for $C_{22}H_{17}O_5$ ($M+H^+$) 361.1076, found 361.1069. ; Anal. Calcd for $C_{22}H_{16}O_5$: C, 73.33; H, 4.48. Found: C, 73.30 ; H, 4.79.

**7-*O*-Mesylapigenin (18)**

Pale yellow solid: mp 228-229 ºC; IR (KBr) 3248, 1652, 1606, 1357, 1177, 836 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta$ 3.50 (3H, s), 6.81 (1H, d, $J$ = 2.0), 6.94 (2H, d, $J$ = 9.0 Hz), 7.00 (1H, s), 7.25 (1H, d, $J$ = 2.0 Hz), 8.01 (2H, d, $J$ = 9.0), 10.46 (1H, s), 13.12 (1H, s); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz) $\delta$ 38.3, 102.3, 104.1, 105.8, 109.5, 116.6, 121.2, 129.5, 154.1, 154.8, 161.7, 162.2, 165.6, 182.9; HRMS (FAB) Calcd. for $C_{16}H_{13}O_7S$ ($M+H^+$) 349.0382, found 349.0391; Anal. Calcd for $C_{16}H_{12}O_7S$: C, 55.17; H, 3.47. Found: C, 55.12 ; H, 3.54.

**7-*O*-Tosylapigenin (19)**

Pale yellow solid: mp 224-225 ºC; IR (KBr) 3220, 1651, 1604, 1338, 1180, 836 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 500 MHz) $\delta$ 2.39 (3H, s), 6.38 (1H, d, $J$ = 2.5 Hz), 6.91 (2H, d, $J$ = 8.5 Hz), 6.93 (1H, s), 7.02 (1H, d, $J$ = 2.5), 7.48 (2H, d, $J$ = 8.0 Hz), 7.81 (2H, d, $J$ = 8.0), 7.95 (2H, d, $J$ = 8.5), 10.51 (1H, s), 13.01 (1H, s); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz) $\delta$ 21.7, 102.1, 104.1, 105.3, 109.4, 116.6, 121.1, 128.9, 129.5, 131.0, 131.5, 146.9, 153.9, 156.6, 161.4, 162.2, 165.6, 182.7; HRMS (FAB) Calcd. for $C_{22}H_{17}O_7S$ ($M+H^+$) 425.695, found 425.0708; Anal. Calcd for $C_{22}H_{16}O_7S$: C, 62.26; H, 3.80. Found: C, 62.35 ; H, 3.95.

**ACKNOWLEDGEMENTS**

This work was financially supported by The Ministry of Education, Culture, Sports, Science and Technology, Japan (The 21st Century COE Program No. 14COEB01-00, Creative Scientific Research No.16GS0206, Global COE in Chemistry, Nagoya University and Research on Priority Area No. 18032037 and Young Scientist (B) No. 18780086).

**REFERENCES AND NOTES**

1. M. G. L. Hertog, E. J. M. Feskens, P. C. H. Hollman, M. B. Katan, and D. Kromhout, *Lancet,* 1993, **342**, 1007; J. Grassmann, S. Hippeli, and E. F. Elstner, *Plant Physiol. Biochem.,* 2002, **40**, 471.
2. H. Matsuda, K. Ninomiya, H. Shimoda, and M. Yoshikawa, *Bioorg. Med. Chem.,* 2002, **10**, 707; A. S. Awaad, D. J. Maitland, and G. A. Soliman, *Bioorg. Med. Chem.,* 2006, **16**, 4624.
3. T. Nagai, Y. Miyaichi, T. Tomimori, Y. Suzuki, and H. Yamada, *Chem. Pharm. Bull.,* 1990, **38**, 1329; K. Miki, T. Nagai, K. Suzuki, R. Tsujimura, K. Koyama, K. Kinoshita, K. Furuhata, H. Yamada, and K. Takahashi, *Bioorg. Med. Chem. Lett.,* 2007, **17**, 772.
4. M. Bouktaib, S. Lebrun, A. Atmani, and C. Rolando, *Tetrahedron,* 2002, **58**, 10001.
5. K.-i. Oyama and T. Kondo, *Tetrahedron,* 2004, **60**, 2025.
6. K.-i. Oyama and T. Kondo, *J. Org. Chem.,* 2004, **69**, 5240.
7. S. Nakamura, K.-i. Oyama, T. Kondo, and K. Yoshida, *Heterocycles,* 2007, **73**, 451.
8. B.-G. Kim, B.-. Jung, Y. Lee, H.-G. Hur, Y. Lim, and J.-H. Ahn, *J. Agric. Food Chem.,* 2006**, 54**, 823.
9. **3** was soluble in low polar solvent such as $CH_2Cl_2$, $CHCl_3$, AcOEt due to the TBS group and the separation from DDQ is easy.