

## Isolation and Identification of Two New Flavanones and a Chalcone from *Citrus kinokuni*<sup>1)</sup>

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**Two new flavanones and one chalcone were isolated from the peel of *Citrus kinokuni* HORT. ex TANAKA and identified as (2*S*)-5,6,7,8,4'-pentamethoxyflavanone (1), (2*S*)-5,6,7,3',4'-pentamethoxyflavanone (2) and 2'-hydroxy-3,4,3',4',6'-pentamethoxychalcone (3). The structures of new compounds were elucidated by spectroscopic analysis.**

**Key words** flavanone; chalcone; *Citrus kinokuni*; Rutaceae

Recently, we carried out primary screening of extracts of *Citrus* fruit to search for useful compounds for cancer chemoprevention.<sup>2)</sup> As a part of our studies on the constituents of these extracts, two new flavanones and one chalcone were isolated and identified as (2*S*)-5,6,7,8,4'-pentamethoxyflavanone (1), (2*S*)-5,6,7,3',4'-pentamethoxyflavanone (2) and 2'-hydroxy-3,4,3',4',6'-pentamethoxychalcone (3) from the peel of *Citrus kinokuni* HORT. ex TANAKA, along with 21 known compounds.

(2*S*)-5,6,7,8,4'-Pentamethoxyflavanone (1) was obtained as a yellow oil. The molecular formula C<sub>20</sub>H<sub>22</sub>O<sub>7</sub> was defined by a molecular ion peak at *m/z* 374.1366 in the high resolution (HR)-MS. The <sup>1</sup>H-NMR spectrum showed three characteristic signals for H-2, H-3<sub>ax</sub> and H-3<sub>eq</sub> at δ 5.38 (1H, dd, *J*=12.8, 3.1 Hz), 3.03 (1H, dd, *J*=16.5, 12.8 Hz) and 2.84 (1H, dd, *J*=16.5, 3.1 Hz), respectively, indicating that 1 had a flavanone skeleton. Five methoxy signals were observed at δ 4.05–3.83. In the aromatic proton region, A<sub>2</sub>B<sub>2</sub> signals at δ 7.39 (2H, d, *J*=8.5 Hz) and 6.94 (2H, d, *J*=8.5 Hz) indicated substitution at 4' on the B-ring. This was confirmed by the nuclear Overhauser effect (NOE) experiment, in which irradiation of the signal at δ 3.83 (4'-OMe) caused 5% enhancement of the signal at δ 6.94. Thus, the B-ring is 4'-methoxylated and the A<sub>2</sub>B<sub>2</sub> signals at δ 7.39 and 6.94 were assigned to H-2'/H-6' and H-3'/H-5' on the B-ring, respectively. In the <sup>13</sup>C-NMR spectrum, four methoxy signals were observed at lower magnetic field (δ 61.7–61.4). This suggests the presence of substituents at both *ortho* positions of the four methoxy groups,<sup>3)</sup> which were assigned to methoxyls on C-5, C-6, C-7 and C-8 of the A-ring. The circular dichroism (CD) spectrum showed a positive Cotton effect at 352 nm and a negative one at 315 nm, consistent with the *S*-configuration at C-2.<sup>4)</sup> On the basis of the above evidence, 1 was determined to be (2*S*)-5,6,7,8,4'-pentamethoxyflavanone.

(2*S*)-5,6,7,3',4'-Pentamethoxyflavanone (2) was obtained as a yellow oil. The molecular formula C<sub>20</sub>H<sub>22</sub>O<sub>7</sub> was defined by a molecular ion peak at *m/z* 374.1365 in the HR-MS. In the <sup>1</sup>H-NMR spectrum, characteristic flavanone proton signals for H-2 [δ 5.34 (1H, dd, *J*=13.3, 2.6 Hz)], H-3<sub>ax</sub> [δ 3.03 (1H, dd, *J*=16.7, 13.3 Hz)] and H-3<sub>eq</sub> [δ 2.77 (1H, dd, *J*=16.7, 2.6 Hz)] were recorded. Three ABC type aromatic proton signals at δ 7.00 (1H, dd, *J*=1.7, 8.5 Hz), 6.99 (1H, d, *J*=1.7 Hz) and 6.90 (1H, d, *J*=8.5 Hz) were characteristic of

H-6', H-2' and H-5', respectively, which means the B-ring is 3',4'-methoxylated. The NOE experiment verified the B-ring substitution. Irradiation of the signal at δ 3.92 (3'-OMe) caused 11% enhancement of the signal at δ 6.99 (H-2') and irradiation of the signal at δ 3.90 (4'-OMe) caused 12% enhancement of the signal at δ 6.90 (H-5'). Among five methoxy signals observed at δ 3.95–3.83, it remained to assign the position of the three methoxy groups on the A-ring. In the NOE experiment, irradiation of the signal at δ 3.88 (7-OMe) caused 15% enhancement of the signal at δ 6.35 and irradiation of the signals at δ 3.95 and 3.83 showed no enhancement of any aromatic proton signals. The <sup>13</sup>C-NMR spectrum showed that the signals of two methoxy carbons were observed at lower magnetic field (δ 61.6, 61.3), and suggested that these two methoxy groups had substituents at both *ortho* positions, respectively.<sup>3)</sup> The H-5 and H-8 signals of flavonoids resonate at δ 7.5–7.6 and δ 6.5–6.9,<sup>5,6)</sup> respectively. Thus, the A-ring aromatic proton signal at δ 6.35 (1H, s) was assigned to H-8. Though 2 had no optical activity in a polarimeter at 589 nm,<sup>7)</sup> the CD spectrum showed a positive Cotton effect at 345 nm and a negative one at 313 nm, consistent with the *S*-configuration at C-2.<sup>4)</sup> The structure of 2 was deduced as (2*S*)-5,6,7,3',4'-pentamethoxyflavanone.

2'-Hydroxy-3,4,3',4',6'-pentamethoxychalcone (3) was obtained as pale yellow needles, mp 134–136 °C. The molecular formula C<sub>20</sub>H<sub>22</sub>O<sub>7</sub> was defined by a molecular ion peak at *m/z* 374.1368 in the HR-MS. The UV absorption (373 nm), the <sup>1</sup>H-NMR signals [δ 7.74 (1H, d, *J*=15.6 Hz, H-β), 7.87 (1H, d, *J*=15.6 Hz, H-α)] and the <sup>13</sup>C-NMR signals [δ<sub>C</sub> 144.2 (C-β), 126.6 (C-α)] strongly suggested the presence of a chalcone skeleton. The <sup>1</sup>H-NMR spectrum showed five methoxy signals (δ 4.03–3.70) and a hydrogen

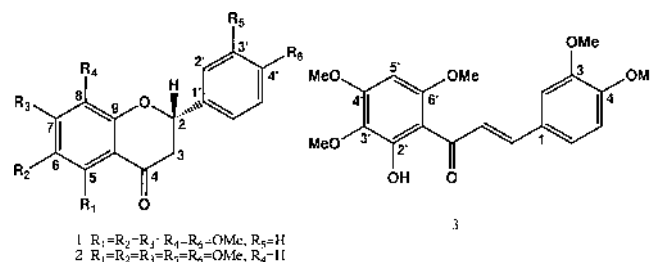


Fig. 1. Structures of 1–3

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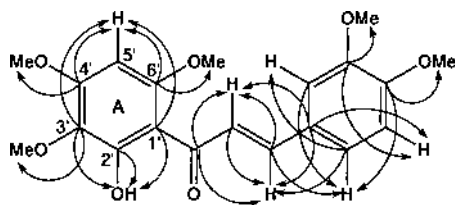


Fig. 2. C-H Long-Range Correlation in the HMBC Spectrum of 2'-Hydroxy-3,4,3',4',6'-pentamethoxychalcone (3)

bonded 2'-OH resonating at  $\delta$  13.88. The ABC type protons at  $\delta$  7.29 (1H, dd,  $J=8.3, 1.8$  Hz), 7.32 (1H, d,  $J=1.8$  Hz) and 7.02 (1H, d,  $J=8.3$  Hz) could be assigned to H-6, H-2 and H-5 of a 3,4-methoxylated B-ring. In the NOE experiment, irradiation of the signal at  $\delta$  3.90 (3-OMe) caused 11% enhancement of the signal at  $\delta$  7.32 (H-2) and irradiation of the signal at  $\delta$  3.87 (4-OMe) caused 14% enhancement of the signal at  $\delta$  7.02 (H-5). These results indicated the presence of a 3,4-dimethoxylated B-ring. In the NOE experiment, irradiation of the methoxy signals at  $\delta$  4.03 and 3.96 caused 12% and 16% enhancement of the signal at  $\delta$  6.32, respectively. Two possibilities (3',4',6'- or 3',5',6'-methoxylated) remained for the A-ring substitution. The positions of the three methoxy groups on the A-ring were elucidated through the use of the heteronuclear multiple bond correlation (HMBC) experiment (Fig. 2). The key correlation for assignment of A-ring substitution were observed for H-5'/C-1', C-3'; 2'-OH/C-1'. Thus, the A-ring aromatic proton signal at  $\delta$  6.32 (1H, s) was assigned to H-5', and **3** must therefore be 2'-hydroxy-3,4,3',4',6'-pentamethoxychalcone.

The known compounds were fully characterized as scoparone (**4**), scopoletin (**5**), nobiletin (**6**),<sup>8)</sup> sinensetin (**7**),<sup>8)</sup> tangeretin (**8**),<sup>8)</sup> 5-hydroxy-6,7,8,4'-tetramethoxyflavone (**9**),<sup>9)</sup> 5-hydroxy-6,7,3',4'-tetramethoxyflavone (**10**),<sup>10,11)</sup> 5-demethylnobiletin (**11**),<sup>9,12)</sup> 6-demethoxynobiletin (**12**),<sup>8)</sup> 6-demethoxytangeretin (**13**),<sup>8)</sup> 5,6,7,4'-tetramethoxyflavone (**14**),<sup>13,14)</sup> 3,5,6,7,3',4'-hexamethoxyflavone (**15**),<sup>15,16)</sup> 3'-hydroxy-5,6,7,8,4'-pentamethoxyflavone (**16**),<sup>17)</sup> 3,5,6,7,8,3',4'-heptamethoxyflavone (**17**),<sup>8)</sup> 7-hydroxy-5,6,3',4'-tetramethoxyflavone (**18**),<sup>17)</sup> 7-hydroxy-5,6,8,3',4'-pentamethoxyflavone (**19**),<sup>18)</sup> 5,7,8,3',4'-pentamethoxyflavone (**20**),<sup>19)</sup> 5-O-demethylcitromitin (**21**),<sup>20)</sup> 3,4,3',4',5',6'-hexamethoxy-2'-hydroxychalcone (**22**),<sup>21)</sup> 2'-hydroxy-4,4',5',6'-tetramethoxychalcone (**23**)<sup>22,23)</sup> and  $\beta$ -sitosterol (**24**) by direct comparison with authentic samples and/or spectral data reported in the literature.

#### Experimental

All melting points were measured on a micro melting point apparatus (Yanaco). <sup>1</sup>H-, <sup>13</sup>C-NMR, NOE and HMBC spectra were recorded on A-500 or A-600 (JEOL) spectrometers in CDCl<sub>3</sub> or acetone-*d*<sub>6</sub>. Chemical shifts are shown in  $\delta$ -values (ppm) with tetramethylsilane (TMS) as an internal reference. Electron impact (EI)-MS and HR-MS were taken with a JMS DX-303 (JEOL) spectrometer having a direct inlet system. UV spectra were recorded on a Shimadzu UV-160 A in EtOH, IR spectra on a Shimadzu IR-435 in CHCl<sub>3</sub>, optical rotation on a DIP-370 (Jasco) in MeOH and CD spectra on a J-600 (Jasco) in MeOH.

**Extraction and Isolation** *Citrus kinokuni* HORT. ex TANAKA was cultivated and collected at the National Institute of Fruit Tree Science, Okitsu, Shizuoka. The dried peels (2.3 kg) of *C. kinokuni* HORT. ex TANAKA were extracted with acetone (5450 ml) at room temperature (3 d, 4 d) and under reflux for 7.5 h. The acetone extract (219.75 g) dissolved in 1 l of water was first extracted with AcOEt (11 $\times$ 3) and then extracted with *n*-butanol (750 ml $\times$ 3). The AcOEt extract (13.47 g) was chromatographed over silica

gel with toluene, CH<sub>2</sub>Cl<sub>2</sub>, AcOEt, acetone, and MeOH, successively. Each eluate was further subjected to preparative TLC repeatedly and furnished the known compounds, scoparone (**4**) (2.8 mg), scopoletin (**5**) (4.5 mg), nobiletin (**6**) (2.563 g), sinensetin (**7**) (15.5 mg), tangeretin (**8**) (649.3 mg), 5-hydroxy-6,7,8,4'-tetramethoxyflavone (**9**) (2.5 mg), 5-hydroxy-6,7,3',4'-tetramethoxyflavone (**10**) (12.8 mg), 5-demethylnobiletin (**11**) (185.3 mg), 6-demethoxynobiletin (**12**) (1.3 mg), 6-demethoxytangeretin (**13**) (149.2 mg), 5,6,7,4'-tetramethoxyflavone (**14**) (3.3 mg), 3,5,6,7,3',4'-hexamethoxyflavone (**15**) (3.4 mg), 3'-hydroxy-5,6,7,8,4'-pentamethoxyflavone (**16**) (22.9 mg), 3,5,6,7,8,3',4'-heptamethoxyflavone (**17**) (7.6 mg), 7-hydroxy-5,6,3',4'-tetramethoxyflavone (**18**) (3.7 mg), 7-hydroxy-5,6,8,3',4'-pentamethoxyflavone (**19**) (5.3 mg), 5,7,8,3',4'-pentamethoxyflavone (**20**) (1.3 mg), 5-O-demethylcitromitin (**21**) (3.6 mg), 3,4,3',4',5',6'-hexamethoxy-2'-hydroxychalcone (**22**) (37.5 mg), 2'-hydroxy-4,4',5',6'-tetramethoxychalcone (**23**) (4.8 mg) and  $\beta$ -sitosterol (**24**) (42.8 mg), in addition to the new compounds, (2*S*)-5,6,7,8,4'-pentamethoxyflavanone (**1**) (4.8 mg), (2*S*)-5,6,7,3',4'-pentamethoxyflavanone (**2**) (25.7 mg) and 2'-hydroxy-3,4,3',4',6'-pentamethoxychalcone (**3**) (3.3 mg). The new compounds were obtained from the AcOEt eluate by repeated PTLC [solvent system: acetone-CHCl<sub>3</sub> (1 : 9, 1 : 19 or 1 : 29), acetone-benzene (2 : 8), acetone-hexane (3 : 7), AcOEt-benzene (1 : 1), AcOEt-hexane (1 : 1)].

(2*S*)-5,6,7,8,4'-Pentamethoxyflavanone (**1**): Yellow oil,  $[\alpha]_D^{25} +8^\circ$  ( $c=0.074$ , MeOH); HR-MS  $m/z$ : 374.1366 ( $[M]^+$ , Found), 374.1364 (Calcd for C<sub>20</sub>H<sub>22</sub>O<sub>7</sub>); EI-MS  $m/z$ : 374 ( $[M]^+$ , base peak), 225, 210, 197, 195, 167; UV  $\lambda_{max}$  (EtOH, nm): 226, 277, 331; IR  $\nu_{max}$  (CHCl<sub>3</sub>, cm<sup>-1</sup>): 1680, 1600, 1580, 1510; <sup>1</sup>H-NMR (CDCl<sub>3</sub>,  $\delta$ ): 7.39 (2H, d,  $J=8.5$  Hz, H-2' and H-6'), 6.94 (2H, d,  $J=8.5$  Hz, H-3', H-5'), 5.38 (1H, dd,  $J=12.8, 3.1$  Hz, H-2), 4.05, 3.90, 3.85 (each 3H, s, OMe), 3.83 (6H, s, 2 $\times$ OMe), 3.03 (1H, dd,  $J=16.5, 12.8$  Hz, H-3<sub>ax</sub>), 2.84 (1H, dd,  $J=16.5, 3.1$  Hz, H-3<sub>eq</sub>); Differential NOE: irradiation of 4'-OMe ( $\delta$  3.83) gave 5% NOE at H-3' and H-5' ( $\delta$  6.94); <sup>13</sup>C-NMR (CDCl<sub>3</sub>,  $\delta$ ): 189.9 (s, C-4), 159.9 (s, C-4'), 153.4 (s, C-7), 152.6 (s, C-5), 150.2 (s, C-9), 141.1 (s, C-6), 137.9 (s, C-8), 130.9 (s, C-1'), 127.6 (d, C-2', C-6'), 114.2 (d, C-3', C-5'), 111.6 (s, C-10), 79.1 (d, C-2), 61.7, 61.6, 61.5, 61.4 (each q, OMe), 55.4 (q, 4'-OMe), 45.8 (t, C-3); CD ( $c=7.91 \times 10^{-5}$  mol/l, MeOH):  $[\theta]_{218} +14600$  (max),  $[\theta]_{238} +6800$ ,  $[\theta]_{273} 0$ ,  $[\theta]_{286} -3400$ ,  $[\theta]_{315} -7500$  (max),  $[\theta]_{333} 0$ ,  $[\theta]_{352} +9200$  (max).

(2*S*)-5,6,7,3',4'-Pentamethoxyflavanone (**2**): Yellow oil,  $[\alpha]_D^{25} \pm 0^\circ$  ( $c=0.1325$ , MeOH); HR-MS  $m/z$ : 374.1365 ( $[M]^+$ , Found), 374.1364 (Calcd for C<sub>20</sub>H<sub>22</sub>O<sub>7</sub>); EI-MS  $m/z$ : 374 ( $[M]^+$ , base peak), 210, 195, 164, 151; UV  $\lambda_{max}$  (EtOH, nm): 233, 278, 323; IR  $\nu_{max}$  (CHCl<sub>3</sub>, cm<sup>-1</sup>): 1680, 1600, 1520; <sup>1</sup>H-NMR (CDCl<sub>3</sub>,  $\delta$ ): 7.00 (1H, dd,  $J=8.5, 1.7$  Hz, H-6'), 6.99 (1H, d,  $J=1.7$  Hz, H-2'), 6.90 (1H, d,  $J=8.5$  Hz, H-5'), 6.35 (1H, s, H-8), 5.34 (1H, dd,  $J=13.3, 2.6$  Hz, H-2), 3.95 (3H, s, 6 or 5-OMe), 3.92 (3H, s, 3'-OMe), 3.90 (3H, s, 4'-OMe), 3.88 (3H, s, 7-OMe), 3.83 (3H, s, 5 or 6-OMe), 3.03 (1H, dd,  $J=16.7, 13.3$  Hz, H-3<sub>ax</sub>), 2.77 (1H, dd,  $J=16.7, 2.6$  Hz, H-3<sub>eq</sub>); Differential NOE: irradiation of 3'-OMe ( $\delta$  3.92) gave 11% NOE at H-2' ( $\delta$  6.99); irradiation of 4'-OMe ( $\delta$  3.90) gave 12% NOE at H-5' ( $\delta$  6.90); irradiation of 7-OMe ( $\delta$  3.88) gave 15% NOE at H-8 ( $\delta$  6.35); <sup>13</sup>C-NMR (CDCl<sub>3</sub>,  $\delta$ ): 189.4 (s, C-4), 159.8 (s, C-9 or C-7), 159.5 (s, C-7 or C-9), 154.3 (s, C-5), 149.6 (s, C-4' or C-3'), 149.4 (s, C-3' or C-4'), 137.7 (s, C-6), 131.2 (s, C-1'), 118.9 (d, C-6'), 111.4 (d, C-5'), 109.6 (d, C-2'), 109.3 (s, C-10), 96.5 (d, C-8), 79.5 (d, C-2), 61.6, 61.3 (each q, 5 or 6-OMe), 56.14, 56.05, 56.04 (q, 7, 3' or 4'-OMe), 45.6 (t, C-3); CD ( $c=7.11 \times 10^{-5}$  mol/l, MeOH):  $[\theta]_{215} +10100$  (max),  $[\theta]_{223} +4400$  (valley),  $[\theta]_{236} +13900$  (max),  $[\theta]_{256} +5300$ ,  $[\theta]_{271} +6000$ ,  $[\theta]_{281} 0$ ,  $[\theta]_{290} -7900$ ,  $[\theta]_{313} -20700$  (max),  $[\theta]_{330} 0$ ,  $[\theta]_{345} +17300$  (max).

2'-Hydroxy-3,4,3',4',6'-pentamethoxychalcone (**3**): Pale yellow needles, mp 134–136 °C; HR-MS  $m/z$ : 374.1368 ( $[M]^+$ , Found), 374.1366 (Calcd for C<sub>20</sub>H<sub>22</sub>O<sub>7</sub>); EI-MS  $m/z$ : 374 ( $[M]^+$ , base peak), 195, 181, 167; UV  $\lambda_{max}$  (EtOH, nm): 373; IR  $\nu_{max}$  (CHCl<sub>3</sub>, cm<sup>-1</sup>): 1620, 1560, 1510; <sup>1</sup>H-NMR (acetone-*d*<sub>6</sub>,  $\delta$ ): 13.88 (1H, s, 2'-OH), 7.87 (1H, d,  $J=15.6$  Hz, H- $\alpha$ ), 7.74 (1H, d,  $J=15.6$  Hz, H- $\beta$ ), 7.32 (1H, d,  $J=1.8$  Hz, H-2), 7.29 (1H, dd,  $J=8.3, 1.8$  Hz, H-6), 7.02 (1H, d,  $J=8.3$  Hz, H-5), 6.32 (1H, s, H-5'), 4.03, 3.96 (each 3H, s, 4' or 6'-OMe), 3.90 (3H, s, 3-OMe), 3.87 (3H, s, 4-OMe), 3.70 (3H, s, 3'-OMe); Differential NOE: irradiation of 4' or 6'-OMe ( $\delta$  3.96) gave 15% NOE at H-5' ( $\delta$  6.32); irradiation of 6' or 4'-OMe ( $\delta$  4.03) gave 12% NOE at H-5' ( $\delta$  6.32); irradiation of 3-OMe ( $\delta$  3.90) gave 11% NOE at H-2 ( $\delta$  7.32); irradiation of 4-OMe ( $\delta$  3.87) gave 14% NOE at H-5 ( $\delta$  7.02); <sup>13</sup>C-NMR (acetone-*d*<sub>6</sub>,  $\delta$ ): 194.4 (s, C=O), 160.5 (s, C-2'), 160.2, 160.0 (each s, C-4' or 6'), 153.2 (s, C-4), 151.1 (s, C-3), 144.2 (d, C- $\beta$ ), 132.1 (s, C-3'), 129.7 (s, C-1), 126.6 (d, C- $\alpha$ ), 124.3 (d, C-6), 113.1 (d, C-5), 112.2 (d, C-2), 107.9 (s, C-1'), 89.2 (d, C-5'), 60.8, 57.1, 56.9, 56.65, 56.58 (each q, 5 $\times$ OMe).

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