New Secoiridoid Glucosides from *Swertia japonica*

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Four new secoiridoid glucosides, swertiajaposides C–F (**1**–**4**, resp.), were isolated from the whole plant of *Swertia japonica* MAKINO together with two known compounds, 8-hydroxy-10-hydrosweroside (**5**) and senburiside IV (**6**). The structures of **1**–**4** were elucidated on the basis of spectroscopic, chemical, and physicochemical evidence.

Introduction. – The whole plants of *Swertia japonica* MAKINO (Gentianaceae) are the crude drug Swertia Herb, used as a stomachic or stimulant of appetite in Japan [1]. The constituents of this crude drug have previously been investigated and shown to contain secoiridoid glucosides [2–6], xanthones [7–10], flavonoids [11], biphenyl glucosides [12], triterpenoids [9][13], and 2,8-dioxabicyclo[3.3.1]nonanes [14]. In previous works we reported the structure determination of ten new secoiridoid glucosides [15][16], a new unsaturated alcohol glucoside [16], and a new lignan glucoside [16] from the whole plant of *S. japonica*. Here, we report the isolation and structure elucidation of four new secoiridoid glucosides, swertiajaposides C–F (**1**–**4**, resp.), together with two known compounds, 8-hydroxy-10-hydrosweroside (**5**) and senburiside IV (**6**), from the whole plant of *S. japonica*.

Results and Discussion. – The dried whole plants of *S. japonica* were extracted with MeOH. The MeOH extract was partitioned between H_2O and $CHCl_3$, H_2O and Et_2O, H_2O and AcOEt, and H_2O and BuOH. The BuOH-soluble fraction was subjected to column chromatography (silica gel and *Sephadex LH-20*) and preparative HPLC to afford two new compounds, named swertiajaposide C (**1**) and swertiajaposide F (**4**), and two known compounds, 8-hydroxy-10-hydrosweroside (**5**) and senburiside IV (**6**). The H_2O-soluble fraction was subjected to column chromatography (*Diaion HP-20* and silica gel) and preparative HPLC to afford two new compounds, named swertiajaposide D (**2**) and swertiajaposide E (**3**).

Swertiajaposide C (**1**) was obtained as an amorphous powder. The molecular formula of **1** was determined as $C_{17}H_{24}O_{10}$ based on the positive HR-FAB-MS (*m/z* 389.1442 ($[M+H]^+$, calc. 389.1447)). Acid hydrolysis of **1** gave D-glucose, which was identified by its retention time and optical rotation using chiral detection by HPLC analysis. The ^{1}H-NMR spectrum of **1** (in CD_3OD; *Table 1*) exhibited signals due to one Me group (δ(H) 1.97 (*d*, $J=7.3$)), two CH_2 (one oxygenated), one MeO group (δ(H) 3.58 (*s*)), one oxygenated CH (δ(H) 5.38 (*d*, $J=1.2$)) and one C=C–H moiety.

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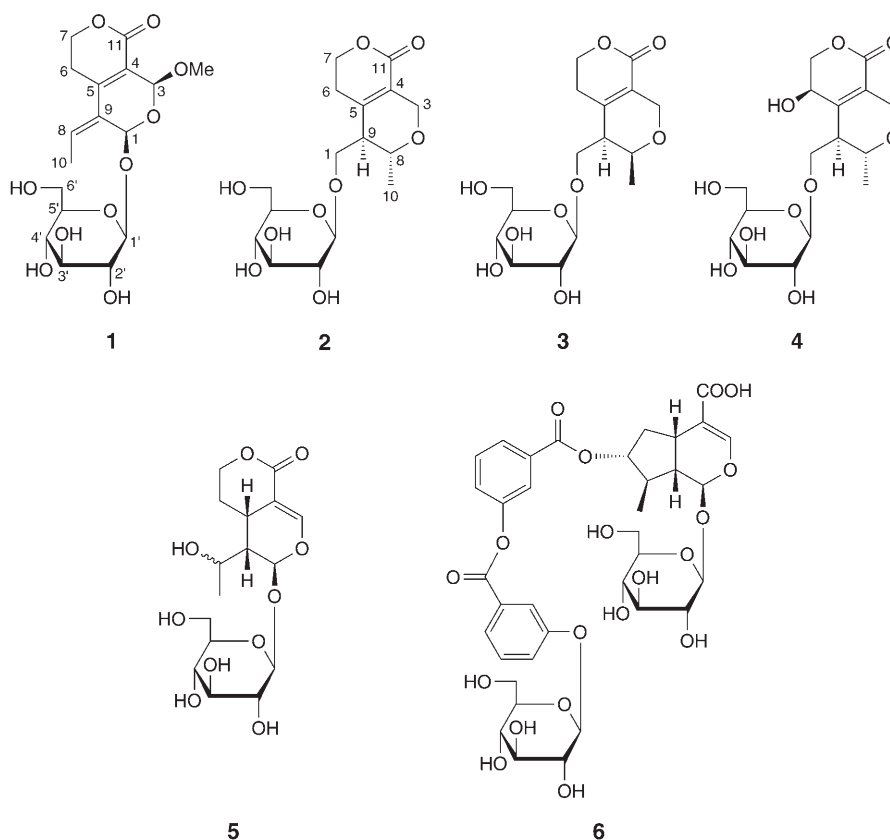

Furthermore, one anomeric signal (δ(H) 4.83 ($d, J = 7.8$)) was recognized. The coupling constant of the anomeric signal indicated that the glucosyl linkage has β-configuration. The ^{13}C-NMR spectrum of **1** (in CD_3OD; *Table 1*) showed signals due to one fully substituted C=C bond (δ(C) 119.7, 147.3) and one C=O group (δ(C) 165.7). The ^{1}H,^{1}H-COSY spectrum of **1** (*Fig. 1*) implied connectivities of CH_2(6) to CH_2(7)[1]), and of H−C(8) to Me(10). The HMBC spectrum (*Fig. 1*) showed correlations between H−C(1) and C(5) and C(8), between H−C(3) and C(1), C(5), and C(11), between CH_2(6) and C(4), between CH_2(7) and C(11), between H−C(8) and C(5), between H−C(1′) and C(1), and between MeO and C(3), respectively. With these correlations, the constitution of **1** could be deduced. The relative configuration of **1** was determined by NOESY experiments. The NOE cross-peaks observed between H_α−C(1) and H_α−C(3), and between the MeO group at C(3) and H−C(1′) implied that the Glc moiety at C(1) and the MeO group at C(3) occurred on the same face (β) of the ring system (*Fig. 2*). The C(8)=C(9) bond was (Z)-configured, based on a NOESY cross-peak between H_α−C(1) and Me(10) (*Fig. 2*). From these data, the structure of **1** was

[1]) Arbitrary atom numbering, see Formula collection.

Table 1. *^{1}H- and ^{13}C-NMR Spectral Data of* **1**. At 400/100 MHz, resp., in CD_3OD; δ in ppm, J in Hz.

Position	δ(H)	δ(C)
1	6.22 (d, $J=0.7$)	91.2
3	5.38 (d, $J=1.2$)	95.9
4		119.7
5		147.3
6	2.66 (ddd, $J=17.3$, 4.4, 4.0, H_β), 2.76 ($dddd$, $J=17.3$, 11.0, 5.6, 1.0, H_α)	23.8
7	4.36 (ddd, $J=11.2$, 11.0, 4.4, H_β), 4.48 (ddd, $J=11.2$, 5.6, 4.0, H_α)	66.8
8	6.42 (q, $J=7.3$)	136.9
9		130.6
10	1.97 (d, $J=7.3$)	14.4
11		165.7
1′	4.83 (d, $J=7.8$)	99.2
2′	3.20 (dd, $J=9.0$, 7.8)	75.0
3′	3.45 (t, $J=9.0$)	78.6
4′	[a])	71.8
5′	3.37–3.41 (m)	78.0
6′	3.68 (dd, $J=11.7$, 6.1), 3.92 (dd, $J=11.7$, 2.2)	63.0
3-MeO	3.58 (s)	58.2

[a]) Overlapped by the solvent signal.

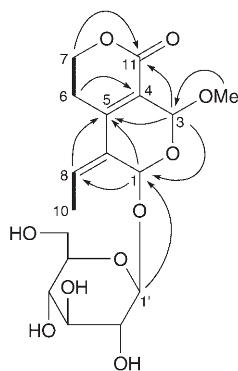

Fig. 1. *^{1}H,^{1}H-COSY* (bold line) *and HMBC* (full-line arrows) *correlations for* **1**

elucidated as (5Z,6S*,8S*)-5-ethylidene-6-(β-D-glucopyranosyloxy)-4,5,6,8-tetrahydro-8-methoxy-1H,3H-pyrano[3,4-c]pyran-1-one, the absolute configuration of which remains to be established.

Swertiajaposides D (**2**) and E (**3**) gave the same molecular formula, $C_{16}H_{24}O_9$, by positive HR-FAB-MS (**2**, m/z 383.1293 ($[M+Na]^+$, calc. 383.1318); **3**, m/z 383.1288 ($[M+Na]^+$, calc. 383.1318)). Acid hydrolysis of **2** and **3** each gave D-glucose, as described above for **1**. Both compounds showed closely similar ^{1}H- and ^{13}C-NMR spectral features (in CD_3OD; *Table 2*). In the ^{1}H-NMR spectrum, each compound exhibited signals due to one Me group, two CH (one oxygenated) and four CH_2 (three oxygenated). Furthermore, one anomeric signal (**2**, δ(H) 4.22 (d, $J=7.8$); **3**, δ(H) 4.26

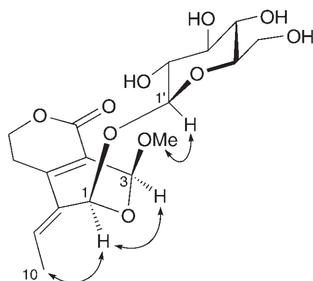

Fig. 2. *NOESY* (full-line arrows) *Correlations for* **1**

Table 2. *¹H- and ¹³C-NMR Spectral Data of* **2** *and* **3**. At 400/100 MHz, resp., in CD_3OD; δ in ppm, J in Hz.

Position	**2**		**3**	
	δ(H)	δ(C)	δ(H)	δ(C)
1	3.78 (*dd*, J = 10.5, 4.4, H_a), 4.08 (*dd*, J = 10.5, 3.4, H_b)	67.6	3.67 (*dd*, J = 10.0, 5.6, H_a), 4.26 (*dd*, J = 10.0, 5.9, H_b)	68.3
3	4.21 (br. *d*, J = 15.9, H_β), 4.30 (br. *d*, J = 15.9, H_α)	63.7	4.28 (br. *d*, J = 15.4, H_α), 4.38 (br. *d*, J = 15.4, H_β)	65.6
4		125.1		124.4
5		153.5		155.1
6	2.37–2.41 (*m*, H_β), 2.78–2.86 (*m*, H_α)	26.9	2.44–2.46 (*m*, H_β), 2.79–2.85 (*m*, H_α)	28.8
7	4.37 (*ddd*, J = 11.0, 10.5, 4.4, H_β), 4.43 (*ddd*, J = 11.0, 5.4, 5.4, H_α)	67.8	4.39–4.42 (*m*, 2 H)	67.9
8	3.83 (*qd*, J = 6.3, 6.3)	71.8	3.79 (*qd*, J = 6.6, 2.9)	72.7
9	2.35–2.37 (*m*)	46.5	2.44–2.46 (*m*)	43.8
10	1.31 (*d*, J = 6.3)	19.3	1.30 (*d*, J = 6.6)	18.1
11		166.0		165.7
1′	4.22 (*d*, J = 7.8)	104.6	4.26 (*d*, J = 7.8)	102.0
2′	3.13 (*dd*, J = 9.0, 7.8)	74.9	3.15 (*dd*, J = 9.3, 7.8)	75.1
3′	[a])	78.2	[a])	78.1
4′	[a])	71.7	[a])	71.7
5′	[a])	78.1	[a])	78.1
6′	3.66 (*dd*, J = 11.7, 5.6), 3.87 (*dd*, J = 11.7, 1.5)	62.8	3.65 (*dd*, J = 12.0, 5.6), 3.88 (*dd*, J = 12.0, 1.7)	62.9

[a]) Overlapped by the solvent signal.

(*d*, J = 7.8)) was recognized. The coupling constant of the anomeric signal indicated that the glucosyl linkage has β-configuration. In the ¹³C-NMR spectrum, each compound showed signals due to one fully substituted C=C bond (**2**, δ(C) 125.1, 153.5; **3**, δ(C) 124.4, 155.1) and one C=O group (**2**, δ(C) 166.0; **3**, δ(C) 165.7). The ¹H,¹H-COSY spectrum of **2** and **3** (*Fig. 3*) implied connectivities of CH_2(1) to H–C(9), of CH_2(6) to CH_2(7), of H–C(8) to H–C(9), and of H–C(8) to Me(10). The HMBC spectrum of **2** and **3** (*Fig. 3*) showed correlations between H–C(1) and C(5), between H–C(3) and C(5), between CH_2(6) and C(4), between CH_2(7) and C(11), between H–C(8) and C(3) and C(5), and between H–C(1′) and C(1). From these data, the constitutional

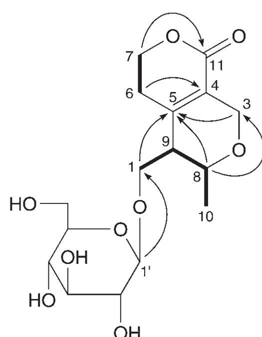

Fig. 3. *$^1H,^1H$-COSY* (bold line) *and HMBC* (full-line arrows) *correlations for* **2** *and* **3**

formulae of **2** and **3** could be deduced. The relative configuration of **2** and **3** was determined as follows. In the ^{1}H-NMR spectrum of **2**, H–C(8) has a large coupling constant ($J(8\beta,9\alpha) = 6.3$). In an NOE experiment, irradiation of H–C(8) enhanced the signals of H_b–C(1) (1.46%) and H_β–C(3) (3.94%), and irradiation of Me(10) enhanced the signal of H_b–C(1) (1.01%). These observations revealed that **2** takes a conformation as shown in *Fig. 4*, and Me(10) and the (β-D-glucopyranosyloxy)methyl group at C(9) were on the α- and β-faces of the ring system, respectively (*Fig. 4*). On the other hand, in the ^{1}H-NMR spectrum of **3**, H–C(8) has a small coupling constant ($J(8\alpha,9\alpha) = 2.9$). In an NOE experiment, irradiation of H–C(8) enhanced the signal of H_α–C(3) (7.83%), and irradiation of Me(10) enhanced the signals of H_a–C(1) (1.32%) and H_b–C(1) (2.31%). These observations revealed that **3** takes a conformation as shown in *Fig. 5*, and Me(10) and the (β-D-glucopyranosyloxy)methyl group at C(9) occurred on the same face (β) of the ring system (*Fig. 5*). Accordingly, the structures of **2** and **3** were assigned as (5*R**,6*R**)-5-[(β-D-glucopyranosyloxy)methyl]-4,5,6,8-tetrahydro-6-methyl-1*H*,3*H*-pyrano[3,4-*c*]pyran-1-one and (5*R**,6*S**)-5-[(β-D-glucopyrano-

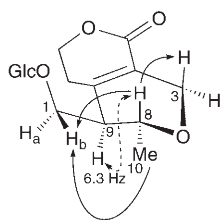

Fig. 4. *Selected coupling constant* (dotted arrows) *and NOEs* (full-line arrows) *for* **2**

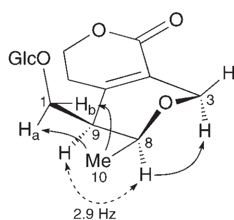

Fig. 5. *Selected coupling constant* (dotted arrows) *and NOEs* (full-line arrows) *for* **3**

syloxy)methyl]-4,5,6,8-tetrahydro-6-methyl-1*H*,3*H*-pyrano[3,4-*c*]pyran-1-one, respectively. The absolute configuration of **2** and **3** could not be determined yet.

Swertiajaposide F (**4**) was obtained as an amorphous powder. Acid hydrolysis of **4** gave D-glucose as described above. Compound **4** showed a very similar signal pattern to that of **2** in the ^{13}C-NMR spectrum (in CD_3OD; *Table 3*). However, in contrast to **2**, one more oxygenated CH signal was observed instead of a CH_2 signal. The molecular formula was determined as $C_{16}H_{24}O_{10}$ based on the positive HR-FAB-MS (*m/z* 377.1460 ($[M+H]^+$, calc. 377.1448). Consequently, **4** was deduced to be a compound in which a H-atom in **2** was replaced by an OH group. The resonance for C(6) at δ(C) 26.9 of **2** was shifted downfield to δ(C) 62.1 in **4**, suggesting that an additional OH group was located at C(6). This was confirmed by the ^{1}H,^{1}H-COSY spectrum in which a cross-peak was observed between H–C(6) and CH_2(7). The relative configuration of the OH group at C(6) was determined to be β from an NOE experiment, in which irradiation of H_α–C(9) enhanced the signal of H_α–C(6) (4.97%). The absolute configuration of **4** was determined as (6*R*,8*R*,9*R*)[1]), based on the circular dichroism (CD) spectrum, in which a negative *Cotton* effect was observed at 231 nm ($\Delta\varepsilon = -7.20$) [17][18]. Accordingly, the structure of **4** was elucidated as (4*R*,5*R*,6*R*)-5-[(β-D-glucopyranosyloxy)methyl]-4,5,6,8-tetrahydro-4-hydroxy-6-methyl-1*H*,3*H*-pyrano[3,4-*c*]pyran-1-one.

Table 3. *^{1}H- and ^{13}C-NMR Spectral Data of* **4**. At 400/100 MHz, resp., in CD_3OD; δ in ppm, *J* in Hz.

Position	δ(H)	δ(C)
1	3.87 (*dd*, *J* = 10.2, 5.4), 4.07 (*dd*, *J* = 10.2, 3.9)	69.2
3	4.17 (*dt*, *J* = 16.6, 2.0, H_β), 4.38 (*dd*, *J* = 16.6, 2.0, H_α)	62.0
4		126.3
5		152.3
6	4.46–4.49 (*m*)	62.1
7	4.32 (*dd*, *J* = 11.5, 3.7, H_β), 4.50 (*dd*, *J* = 11.5, 3.7, H_α)	72.9
8	3.97 (*qd*, *J* = 6.3, 6.3)	71.0
9	2.55–2.59 (*m*)	42.9
10	1.30 (*d*, *J* = 6.3)	18.6
11		164.5
1′	4.26 (*d*, *J* = 7.8)	104.6
2′	3.15 (*dd*, *J* = 9.0, 7.8)	74.6
3′	[a])	78.2
4′	[a])	71.6
5′	[a])	78.1
6′	3.66 (*dd*, *J* = 11.7, 5.4), 3.86 (*dd*, *J* = 11.7, 3.2)	62.8

[a]) Overlapped by the solvent signal.

The known compounds **5** and **6** were identified on the basis of their optical rotation values, NMR, and MS data as 8-hydroxy-10-hydrosweroside [19][20] and senburiside IV [21][22], respectively. This is the first report of compounds **5** and **6** from *S. japonica*.

We are grateful to Mr. *S. Satoh* and Mr. *T. Matsuki* for NMR and MS measurements.

Experimental Part

General. Column chromatography (CC): silica gel (SiO_2) (230–400 mesh; *Merck*), *Diaion HP-20* (250–300 μm; *Mitsubishi Chemical Corporation*), and *Sephadex LH-20* (18–111 μm; *GE Healthcare Bio-Sciences AB*). HPLC: *CCPM* pump (*Tosoh*), *RI-8020* refractive-index detector (*Tosoh*), *UV-8020* UV/VIS detector (*Tosoh*) and *JASCO* OR-2090 plus chiral detector. Optical rotations: *JASCO DIP-360* digital polarimeter. CD spectra: *JASCO J-720* spectropolarimeter; $\Delta\varepsilon$ in mdeg l mol^{-1} cm^{-1} (λ in nm). UV Spectra: *Beckman DU-64* spectrophotometer. IR Spectra: *Perkin-Elmer Spectrum-One-FT-IR* spectrometer. NMR Spectra: *JEOL JNM-LA 400* (^{1}H, 400 MHz; ^{13}C, 100 MHz) spectrometer; chemical shifts δ in ppm, rel. to Me_4Si, J in Hz. FAB- and HR-FAB-MS: *JEOL JMS-DX 303* mass spectrometer; glycerol as matrix; in m/z.

Plant Material. The dried whole plants of *Swertia japonica* were purchased from *Uchida Wakanyaku Co. Ltd.*, Japan, in 2002. A voucher specimen (SJ-2002-01) was deposited at the Laboratory of Molecular Structural Analysis, Tohoku Pharmaceutical University.

Extraction and Isolation. The dried whole plants (including roots, stems, leaves and flowers) of *Swertia japonica* (2.0 kg) were extracted three times (14 d each time) with MeOH (6 l) at r.t. and filtered. The MeOH extract was concentrated under reduced pressure, and the residue (474 g) was suspended in H_2O (1 l). This suspension was extracted with $CHCl_3$ (3 × 1 l), Et_2O (3 × 1 l), AcOEt (3 × 1 l), and BuOH (3 × 1 l).

The BuOH-soluble fraction was concentrated under reduced pressure to afford a residue (12.0 g), which was subjected to CC (SiO_2, $CHCl_3$/MeOH/H_2O 30 : 10 : 1): 92 fractions according to TLC. *Fr. 25*, on prep. HPLC (*TSKgel ODS-120T* column (300 × 7.8 mm, 10 μm, *Tosoh*); MeOH/H_2O 1 : 3, 1.0 ml/min) gave **1** (2.6 mg, t_R 37.3 min). *Fr. 42* on prep. HPLC (*Cosmosil 5C18AR* column (250 × 10 mm, 10 μm, *Nacalai Tesque*); MeOH/H_2O 1 : 8, 1.0 ml/min) gave **4** (10.5 mg, t_R 32.0 min) and **5** (3.5 mg, t_R 38.4 min). *Fr. 55* was purified over *Sephadex LH-20* (MeOH/H_2O 1 : 1) to afford **6** (113.7 mg).

The H_2O-soluble fraction was passed through *Diaion HP-20* column, and the adsorbed material was eluted with H_2O and MeOH. The MeOH eluate fraction was concentrated under reduced pressure to afford a residue (20.8 g), which was subjected to CC (SiO_2, $CHCl_3$/MeOH/H_2O 30 : 10 : 1): 12 fractions according to TLC. *Fr. 3* was further purified on prep. HPLC (*Cosmosil 5SL* column (250 × 10 mm, 10 μm, *Nacalai Tesque*); CH_2Cl_2/MeOH/H_2O 30 : 10 : 1, 1.0 ml/min) and gave **2** (10.4 mg, t_R 24.6 min) and **3** (26.1 mg, t_R 29.2 min).

Swertiajaposide C (= *(5*Z*,6*S**,8*S**)-5-Ethylidene-6-(β-*D*-glucopyranosyloxy)-4,5,6,8-tetrahydro-8-methoxy-1*H*,3*H*-pyrano[3,4-*c*]pyran-1-one*; **1**). Amorphous powder. $[\alpha]_D^{25} = -50.6$ ($c = 0.27$, MeOH). UV (MeOH): 270 (4.3). IR (KBr): 3450, 1710. ^{1}H- and ^{13}C-NMR: see *Table 1*. FAB-MS (pos.): 389 ($[M+H]^+$). HR-FAB-MS (pos.): 389.1442 ($[M+H]^+$, $C_{17}H_{25}O_{10}^+$; calc. 389.1447).

Swertiajaposide D (= *(5*R**,6*R**)-5-[(β-*D*-Glucopyranosyloxy)methyl]-4,5,6,8-tetrahydro-6-methyl-1*H*,3*H*-pyrano[3,4-*c*]pyran-1-one*; **2**). Amorphous powder. $[\alpha]_D^{27} = +34.3$ ($c = 1.04$, MeOH). UV (MeOH): 224 (3.9). IR (KBr): 3445, 1725. ^{1}H- and ^{13}C-NMR: see *Table 2*. FAB-MS (pos.): 383 ($[M+Na]^+$). HR-FAB-MS (pos.): 383.1293 ($[M+Na]^+$, $C_{16}H_{24}NaO_9^+$; calc. 383.1318).

Swertiajaposide E (= *(5*R**,6*S**)-5-[(β-*D*-Glucopyranosyloxy)methyl]-4,5,6,8-tetrahydro-6-methyl-1*H*,3*H*-pyrano[3,4-*c*]pyran-1-one*; **3**). Amorphous powder. $[\alpha]_D^{27} = +74.1$ ($c = 2.61$, MeOH). UV (MeOH): 223 (3.9). IR (KBr): 3440, 1725. ^{1}H- and ^{13}C-NMR: see *Table 2*. FAB-MS (pos.): 383 ($[M+Na]^+$). HR-FAB-MS (pos.): 383.1288 ($[M+Na]^+$, $C_{16}H_{24}NaO_9^+$; calc. 383.1318).

Swertiajaposide F (= *(4*R*,5*R*,6*R*)-5-[(β-*D*-Glucopyranosyloxy)methyl]-4,5,6,8-tetrahydro-4-hydroxy-6-methyl-1*H*,3*H*-pyrano[3,4-*c*]pyran-1-one*; **4**). Amorphous powder. $[\alpha]_D^{25} = -26.3$ ($c = 1.05$, MeOH). CD (MeOH): +0.75 (262), −7.20 (231). UV (MeOH): 217 (4.0), 279 (2.8). IR (KBr): 3455, 1720. ^{1}H- and ^{13}C-NMR: see *Table 3*. FAB-MS (pos.): 377 ($[M+H]^+$). HR-FAB-MS (pos.): 377.1460 ($[M+H]^+$, $C_{16}H_{25}O_{10}^+$; calc. 377.1448).

8-Hydroxy-10-hydrosweroside (= *(4a*S*,5*R*,6*S*)-5-Ethenyl-6-(β-*D*-glucopyranosyloxy)-4,4a,5,6-tetrahydro-1*H*,3*H*-pyrano[3,4-*c*]pyran-1-one*; **5**). $[\alpha]_D^{24} = -150.7$ ($c = 0.35$, MeOH). UV (MeOH): 243 (3.8). ^{1}H- and ^{13}C-NMR: as reported [19]. FAB-MS (pos.): 377 ($[M+H]^+$).

Senburiside IV (= *3‴-*O*-Glucosylsenburiside II*; *(1*S*,4a*S*,6*R*,7*R*,7a*S*)-1,4a,5,6,7,7a-Hexahydro-1-(hexopyranosyloxy)-6-[(3-{[3-(hexopyranosyloxy)benzoyl]oxy}benzoyl)oxy]-7-methylcyclopenta[*c*]-*

pyran-4-carboxylic Acid; **6**). $[\alpha]_D^{25} = -80.5$ ($c = 1.10$, MeOH). ^{1}H- and ^{13}C-NMR: as reported [21][22]. FAB-MS (pos.): 779 ($[M + H]^+$).

Acid Hydrolysis of **1**–**4** *and Determination of the Absolute Configuration of the Sugar*. Each of the compounds, **1**–**4** (*ca.* 0.3 mg), was refluxed with 5% HCl for 5 h. The reaction mixture was neutralized with Ag_2CO_3 and filtered. The soln. was concentrated *in vacuo* and dried to give a sugar fraction. The sugar fraction was analyzed by HPLC (*Shodex SUGAR KS-801* column (300×8.0 mm, *Showa Denko*); H_2O, 1.0 ml/min, chiral detection): t_R 7.5 min (D-glucose, positive optical rotation).

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