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NEW CYANOGLYCOSIDES, HYDRACYANOSIDES D, E, AND F, FROM THE LEAVES OF *HYDRANGEA MACROPHYLLA*

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Abstract —Three new cyanoglycosides named hydracyanosides D (**1**), E (**2**), and F (**3**) were isolated from the leaves of *Hydrangea macrophylla* cultivated in China together with 17 known constituents including hydracyanoside A (**4**). Their structures were elucidated on the basis of chemical and physicochemical evidence.

In the course of our characterization studies on bioactive constituents from *Hydrangea* species,[1-6] we have reported the isolation and absolute stereostructure elucidation of three cyanogenic glycosides, hydracyanosides A (**4**), B, and C from *H. macrophylla* (Thunb.) Ser. (Saxifragaceae).[1] As a continuing study on the leaves of *H. macrophylla*, we have isolated three new cyanoglycosides named hydracyanosides D (**1**), E (**2**), and F (**3**) together with 17 known constituents. In this paper, we describe the isolation and structure elucidation of these three new constituents.

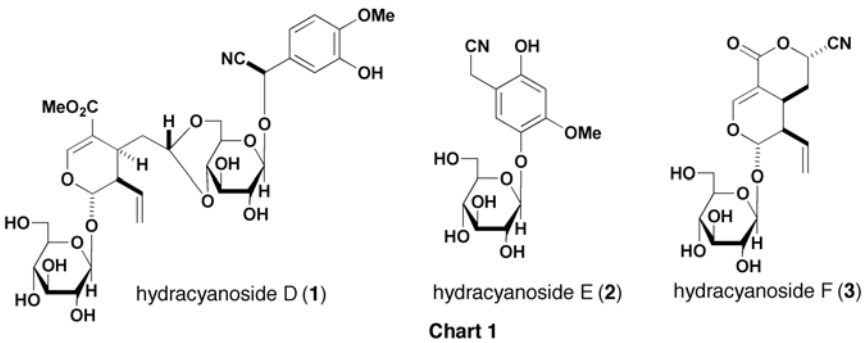

Chart 1

The leaves of *H. macrophylla* were finely cut and treated with MeOH to furnish a MeOH extract (26.0%). The MeOH extract was partitioned into an EtOAc–H_2O (1:1, v/v) mixture to furnish an EtOAc-soluble fraction (8.4%) and an aqueous phase. The aqueous phase was further extracted with *n*-BuOH to give an *n*-BuOH- and a H_2O-soluble fraction (6.5% and 11.1%, respectively).[1] The *n*-BuOH-soluble fraction was separated by normal- and reversed-phase column chromatography, and finally HPLC to give hydracyanosides D (**1**, 0.00071%), E (**2**, 0.00020%), F (**3**, 0.00023%), together with hydracyanoside A (**4**, 0.09%),[1] (2*R*)-taxiphyllin (**5**, 0.00028%),[7,8] tachioside (**6**, 0.00061%),[9] isotachioside (**7**, 0.00072%),[9] 3-(*β*-D-glucopyranosyloxy)-4-methoxybenzaldehyde (**8**, 0.00093%),[10] 2-phenylethyl-*β*-D-glucopyranoside (**9**, 0.00032%),[11] salidroside (**10**, 0.00014%),[12] icariside

F_2 (**11**, 0.00022%),[13] loganin (**12**, 0.0015%),[14] 8-*epi*-loganin (**13**, 0.0011%),[15] secoxyloganin (**14**, 0.00070%),[16] vogeloside (**15**, 0.0023%),[17] *epi*-vogeloside (**16**, 0.00038%),[17] thymidine (**17**, 0.00037%),[18,19] adenosine (**18**, 0.00055%),[20] (–)-methyl shikimate (**19**, 0.00023%),[21] *Z*-hex-3-en-1-ol *β*-D-xylopyranosyl(1-6)-*β*-D-glucopyranoside (**20**, 0.00051%)[22] (Chart 1, 2).

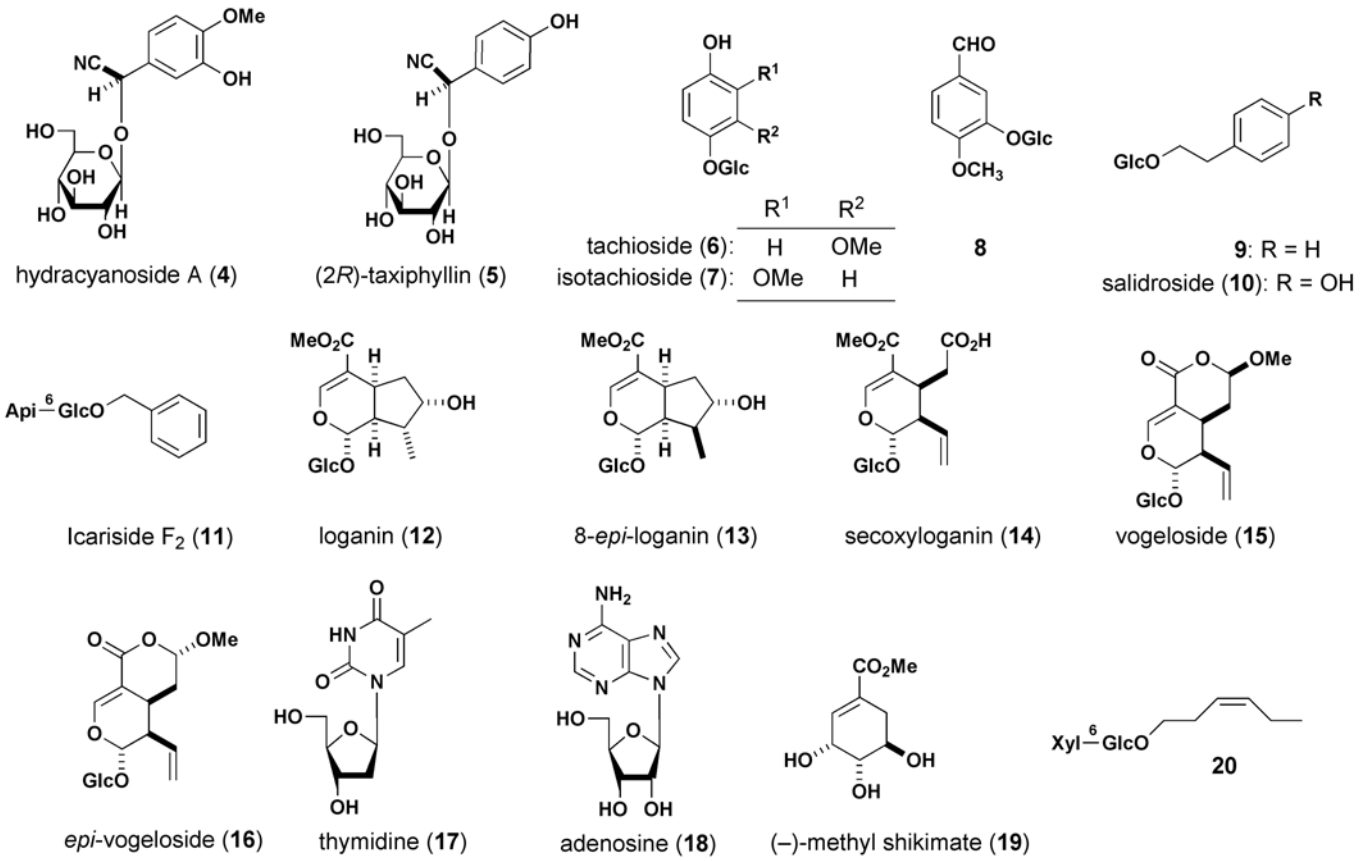

Chart 2

Hydracyanoside D (**1**) was isolated as a white powder with negative optical rotation ($[a]_D^{23}$ –111.6° in MeOH). The molecular formula $C_{32}H_{41}NO_{17}$ of **1** was clarified from the positive-ion FABMS [*m/z* 734 $(M+Na)^+$] and by HRFABMS measurement. The IR spectrum showed the presence of cyano group (2365 cm^{-1}), ester (1701 cm^{-1}), olefin (1655 cm^{-1}), and an oligoglycoside structure (3420 and 1078 cm^{-1}). Acid hydrolysis of **1** with 1 M HCl liberated D-glucose, which was identified by HPLC analysis using an optical rotation detector.[23,24] The ^{1}H-(CD_3OD) and ^{13}C-NMR (Table 1) spectra of **1**, which were assigned by various NMR experiments,[25] showed signals assignable to a methoxy group [*δ* 3.87 (3H, s)], a carbomethoxy group [*δ* 3.70 (3H, s)], a methine bearing a cyano functional group [*δ* 5.60 (1H, s, 2-H)], four olefinic protons [*δ* 5.24 (1H, br d, *J* = 11.0 Hz, 10'''a-H), 5.30 (1H, br d, *J* =

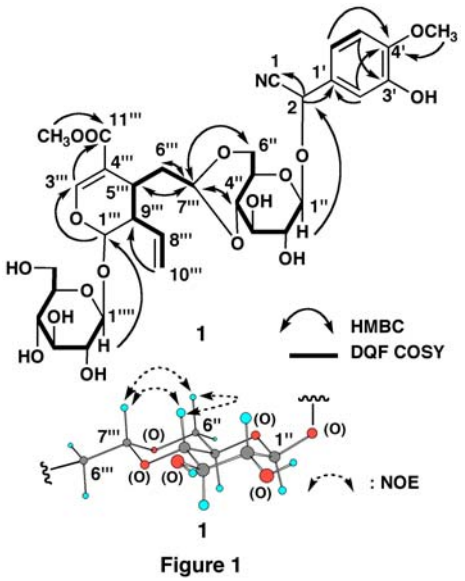

Figure 1

17.8 Hz, 10'''b-H), 5.73 (1H, ddd, J = 8.2, 11.0, 17.8 Hz, 8'''a-H), 7.45 (1H, s, 3'''-H)], an aromatic ring [δ 6.95 (1H, dd, J = 2.1, 8.3 Hz, 6'-H), 6.96 (1H, d, J = 8.3 Hz, 5'-H), 7.00 (1H, d, J = 2.1 Hz, 2'-H)], two β-D-glucopyranosyl moieties [δ 4.40 (1H, d, J = 8.0 Hz, 1''-H), 4.67 (1H, d, J = 7.6 Hz, 1''-H)], and a cyano group (δc 119.4, 1-C). The double quantum filter correlation spectroscopy (DQF COSY) experiment on **1** indicated the presence of partial structures written in bold lines, and in the heteronuclear multiple bond connectivity spectroscopy (HMBC) experiment, long-range correlations were observed between the following protons and carbons: 2-H and 1, 1'-C; 2'-H and 1', 4'-C; 5'-H and 3'-C; 6'-H and 4'-C; 1''-H and 2-C; 4''-H and 7'''-C; 6''-H and 7'''-C; 1'''-H and 3'''-C; 3'''-H and 11'''-C; 5'''-H and 7'''-C; 6'''-H and 7'''-C; 7'''-H and 4'', 6''-C; -OCH_3 and 4'-C; -COOCH_3 and 11'''-C (Figure 1). Furthermore, the NOESY spectrum showed NOE correlations between the following proton pairs (4''-H and 6''β, 7'''-H; 6''β -H and 7'''-H), so that the stereostructure of **1** was characterized. Finally, methanolysis of **1** with mild conditions was carried out to give hydracyanoside A (**4**)[1] and secoxyloganin dimethylacetal.[17] Consequently, the structure of hydracyanoside D (**1**) was determined as shown.

Table 1. ^{13}C-NMR data for **1**

Position		Position	
1	119.4	1'''	97.7
2	69.1	3'''	153.7
1'	127.3	4'''	111.5
2'	115.7	5'''	29.6
3'	148.3	6'''	35.1
4'	150.5	7'''	102.7
5'	112.6	8'''	135.8
6'	120.7	9'''	45.4
4'-OCH_3	56.5	10'''	119.9
1''	103.1	11'''	169.3
2''	75.6	COOCH_3	51.9
3''	74.5	1''	100.0
4''	81.6	2''	74.7
5''	67.9	3''	78.0
6''	69.2	4''	71.6
	-	5''	78.4
	-	6''	62.8

Measured in CD_3OD at 150 MHz

Hydracyanoside E (**2**), $[\alpha]_D^{24}$ –29.4° (MeOH), was isolated as a white powder. The IR spectrum of **2** showed absorption bands at 3570, 2257, and 1074 cm^{-1} ascribable to hydroxyl, cyano, and ether functional groups. The molecular formula $C_{15}H_{19}NO_8$ was determined from the positive-ion FABMS at m/z 364 $(M+Na)^+$ and by HRFABMS measurement. Acid hydrolysis of **2** liberated D-glucose, which was identified by HPLC analysis using an optical rotation detector.[23,24] The ^{1}H- (CD_3OD) and ^{13}C-NMR (Table 2) spectra[25] of **2** indicated the presence of a methoxy group [δ 3.81 (3H, s)], a methylene [δ 3.65 (1H, s, 2-H_2)], an aromatic ring [δ 6.54 (1H, s, 3'-H), 7.13 (1H, s, 6'-H)], a β-D-glucopyranosyl moiety [δ 4.72 (1H, d, J = 7.6 Hz, 1''-H)], and a cyano group (δc 119.8, 1-C). Next, long-range correlations in the HMBC experiment were observed between the following proton and carbon: 2-H_2 and 1, 1', 2', 6'-C; 3'-H and 1', 2', 5'-C; 6'-H and 2, 2', 4'-C; 1''-H and 5'-C; -OCH_3 and 4'-C (Figure 2). Furthermore, the NOESY spectrum showed NOE correlations between the following proton pairs (1''-H and 6'-H; -OCH_3 and 3'-H). On the basis of this evidence, the structure of **2** was elucidated as shown.

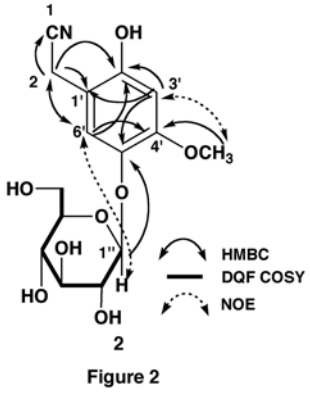

Figure 2

Table 2. ^{13}C-NMR data for **2**

Position		Position	
1	119.8	1''	104.3
2	18.1	2''	75.1
1'	109.9	3''	77.9
2'	152.5	4''	71.4
3'	101.7	5''	78.2
4'	152.0	6''	62.5
5'	140.9		
6'	121.1		
4'-O-CH_3	56.7		

Measured in CD_3OD at 150 MHz

Hydracyanoside F (**3**), $[\alpha]_D^{25}$ –106.2° (MeOH), was isolated as a white powder. The IR spectrum showed the presence of cyano group (2361 cm^{-1}), ester (1719 cm^{-1}), olefin (1655 cm^{-1}), and a glycoside structure (3420 and 1074 cm^{-1}). The molecular formula $C_{17}H_{21}NO_9$ was determined from the positive-ion FABMS at *m/z* 406 $(M+Na)^+$ and by HRFABMS measurement. Acid hydrolysis of **3** liberated D-glucose.[23,24] The ^{1}H- (CD_3OD) and ^{13}C-NMR (Table 3) spectra[25] of **3** indicated the presence of a methine bearing a cyano functional group [δ 5.59 (1H, dd, *J* = 2.0, 5.5 Hz, 7-H)], four olefinic protons [δ 5.31 (1H, dd, *J* = 2.1, 10.3 Hz, 10a-H), 5.36 (1H, dd, *J* = 2.1, 17.3 Hz, 10b-H), 5.54 (1H, ddd, *J* = 9.7, 10.3, 17.3 Hz, 8-H), 7.70 (1H, br s, 3-H)], a β-D-glucopyranosyl moiety [δ 4.75 (1H, d, *J* = 7.6 Hz, 1'-H)], and a cyano group (δc 118.0). The proton and carbon signals in the ^{1}H- and ^{13}C-NMR of **3** were similar to those of *epi*-vogeloside (**16**)[17] except for the signals around the 7-position. The connectivity of a sugar part in **3** was characterized by HMBC experiment, which showed long-range correlations between the 1'-proton and the 1-carbon (Figure 3). Furthermore, the NOESY spectrum showed NOE correlations between the following proton pairs (1β-H and 8-H; 5-H and 6α, 9-H; 6α-H and 7-H; 6β-H and 7-H). On the basis of this evidence, the structure of **3** was elucidated as shown.

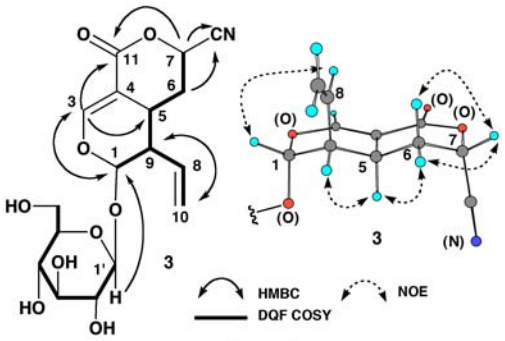

Figure 3

Table 3. ^{13}C-NMR data for **3**

Position		Position	
1	98.7	1'	100.6
3	156.0	2'	74.6
4	103.7	3'	78.1
5	25.6	4'	71.5
6	28.4	5'	78.5
7	66.8	6'	62.7
8	132.8		
9	43.1		
10	121.8		
11	165.0		
*C*N	118.0		

Measured in CD_3OD at 150 MHz

EXPERIMENTAL

The following instruments were used to obtain physical data: specific rotations, Horiba SEPA-300 digital polarimeter (*l* = 5 cm); UV spectra, Shimadzu UV-1600; IR spectra, Shimadzu FTIR-8100 spectrophotometer; FABMS and high-resolution FABMS, JEOL JMS-SX 102A mass spectrometer; ^{1}H-NMR spectra, JEOL EX-270 (270 MHz), JNM-LA500 (500 MHz), and JEOL ECA-600K (600 MHz) spectrometers; ^{13}C-NMR spectra, JEOL EX-270 (68 MHz), JNM-LA500 (125 MHz), and JEOL ECA-600K (150 MHz) spectrometers with tetramethylsilane as an internal standard; HPLC detector, Shimadzu RID-6A refractive index and SPD-10A*vp* UV-VIS detectors; and HPLC column, Cosmosil 5C_{18}-MS-II (250 x 4.6 mm i.d.) and (250 x 20 mm i.d.) columns were used for analytical and preparative purposes, respectively. The following experimental materials were used for chromatography: normal-phase silica gel column chromatography, Silica gel BW-200 (Fuji Silysia Chemical, Ltd., 150–350 mesh); reversed-phase silica gel column chromatography, Chromatorex ODS DM1020T (Fuji Silysia Chemical, Ltd., 100–200 mesh); TLC, precoated TLC plates with Silica gel 60F_{254} (Merck, 0.25 mm) (ordinary phase) and Silica gel RP-18 F_{254S} (Merck, 0.25 mm) (reversed phase); reversed-phase HPTLC, precoated TLC

plates with Silica gel RP-18 WF_{254S} (Merck, 0.25 mm); and detection was achieved by spraying with 1% $Ce(SO_4)_2$–10% aqueous H_2SO_4 followed by heating.

Plant Material

The fresh leaves of *H. macrophylla*, which were cultivated in Sichuan province of China, were collected in 2008. A voucher of the plant is on file in our laboratory (Phamacognosy-2008-HM).

Isolation of Constituents from the Leaves of *H. macrophylla*

The fresh leaves (2.2 kg) of *H. macrophylla* cultivated in Sichuan province of China were finely cut and extracted with MeOH under reflux to provide a MeOH extract (573 g, 26.0%). The MeOH extract (563 g) was partitioned into an EtOAc–H_2O (1:1, v/v) mixture to furnish an EtOAc-soluble fraction (182 g, 8.4%) and an aqueous phase. The aqueous phase was further extracted with *n*-BuOH to give an *n*-BuOH-soluble fraction (140 g, 6.5%) and a H_2O-soluble fraction (240 g, 11.1%). The *n*-BuOH-soluble fraction (140 g) was subjected to ordinary-phase silica gel column chromatography {3.0 kg, $CHCl_3$ → $CHCl_3$–MeOH–H_2O [(30:3:1, v/v/v, lower layer) → (10:3:1, v/v/v, lower layer) → (7:3:1, v/v/v, lower layer) → (6:4:1, v/v/v)] → MeOH} to give five fractions [Fr. 1 (20.0 g), Fr. 2 (10.9 g), Fr. 3 (60.3 g), Fr. 4 (30.7 g), Fr. 5 (12.7 g)]. Fraction 1 (20.0 g) was subjected to reversed-phase silica gel column chromatography [500 g, MeOH–H_2O (15:85 → 25:75 → 45:55 → 65:35 → 85:15, v/v) → MeOH → $CHCl_3$] to afford six fractions [Fr. 1-1, Fr. 1-2 (1.0 g), Fr. 1-3 (4.2 g), Fr. 1-4 (1.2 g), Fr. 1-5, Fr. 1-6]. Fraction 1-2 (1.0 g) was subjected to HPLC [MeOH–H_2O (15:85, v/v)] to afford thymidine (**17**, 8.1 mg, 0.00037%). Fraction 1-3 (4.2 g) was subjected to HPLC [MeCN–H_2O (7:93, v/v)] to afford nine fractions [Fr. 1-3-1, Fr. 1-3-2, Fr. 1-3-3 [= 3-(*β*-D-glucopyranosyloxy)-4-methoxybenzaldehyde (**8**, 20 mg, 0.00093%)], Fr. 1-3-4, Fr. 1-3-5, Fr. 1-3-6, Fr. 1-3-7 (23 mg), Fr. 1-3-8, Fr. 1-3-9 [= 2-phenylethyl-*β*-D-glucopyranoside (**9**, 7.0 mg, 0.00032%)]. Fraction 1-3-7 (23 mg) was further purified by HPLC [MeOH–H_2O (28:72, v/v)] to give hydracyanoside F (**3**, 5.0 mg, 0.00023%). Fraction 1-4 (1.2 g) was subjected to HPLC [MeOH–H_2O (32:68, v/v)] to afford four fractions [Fr. 1-4-1, Fr. 1-4-2 (100 mg), Fr. 1-4-3, Fr. 1-4-4]. Fraction 1-4-2 (100 mg) was further purified by HPLC [MeCN–H_2O (10:90, v/v)] to give vogeloside (**15**, 50 mg, 0.0023%), *epi*-vogeloside (**16**, 8.3 mg, 0.00038%). Fraction 3 (60 g) was subjected to reversed-phase silica gel column chromatography [1.2 kg, MeOH–H_2O (15:85 → 25:75 → 45:55 → 65:35 → 85:15, v/v) → MeOH → $CHCl_3$] to afford ten fractions [Fr. 3-1, Fr. 3-2, Fr. 3-3, Fr. 3-4 (4.9 g), Fr. 3-5 (1.5 g), Fr. 3-6, Fr. 3-7 (1.3 g), Fr. 3-8 (1.8 g), Fr. 3-9, Fr. 3-10 (580 mg)]. Fraction 3-4 (4.9 g) was subjected to HPLC [MeOH–H_2O (15:85, v/v)] to afford hydracyanoside A (**4**, 1.92 g, 0.09%), hydracyanoside E (**2**, 4.3 mg, 0.00020%), (2*R*)-taxiphyllin (**5**, 6.0 mg, 0.00028%), tachioside (**6**, 13 mg, 0.00061%), isotachioside (**7**, 16 mg, 0.00072%), salidroside (**10**, 3.1 mg, 0.00014%), adenosine (**18**, 12 mg, 0.00055%), (–)-methyl shikimate (**19**, 5.0 mg, 0.00023%). Fraction 3-5 (1.5 g) was subjected to HPLC [MeCN–H_2O (10:90, v/v)] to afford icariside F_2 (**11**, 4.8 mg, 0.00022%). Fraction 3-7 (1.3 g) was subjected to HPLC [MeOH–H_2O (37:63, v/v)] to afford 8-*epi*-loganin (**13**, 23 mg, 0.0011%), *Z*-hex-3-en-1-ol *β*-D-xylopyranosyl(1-6)-*β*-D-glucopyranoside (**20**, 11 mg, 0.00051%). Fraction 3-8 (1.8 g) was subjected to HPLC [MeOH–H_2O (55:45, v/v)] to afford loganin (**12**, 33 mg, 0.0015%), secoxyloganin (**14**, 15 mg, 0.00070%).

Fraction 3-10 (580 mg) was subjected to HPLC [MeOH–H_2O (75:25, v/v)] to afford hydracyanoside D (**1**, 15 mg, 0.00071%).

Hydracyanoside D (1): a white powder, $[a]_D^{23}$ –111.6° (*c* 0.07, MeOH). High-resolution positive-ion FABMS: Calcd for $C_{32}H_{41}NO_{17}Na$ $(M+Na)^+$: 734.2272. Found: 734.2269. UV [MeOH, nm, (logε)]: 282 (3.55), 236 (4.24). IR (KBr): 3420, 2923, 2365, 1701, 1655, 1078 cm^{-1}. ^{1}H-NMR (600 MHz, CD_3OD) δ: 3.54 (1H, dd, *J* = 9.6, 10.3 Hz, 6"β-H), 4.16 (1H, dd, *J* = 4.4, 10.3 Hz, 6"α-H), 3.70 (3H, s, COO*CH*$_3$), 3.87 (3H, s, O*CH*$_3$), 4.40 (1H, d, *J* = 8.0 Hz, 1"-H), 4.67 (1H, d, *J* = 7.6 Hz, 1""-H), 4.69 (1H, dd, *J* = 5.5, 7.0 Hz, 7""-H), 5.24 (1H, br d, *J* = 11.0 Hz, 10"'a-H), 5.30 (1H, br d, *J* = 17.8 Hz, 10"'b-H), 5.54 (1H, d, *J* = 6.2 Hz, 1"'-H), 5.60 (1H, s, 2-H), 5.73 (1H, ddd, *J* = 8.2, 11.0, 17.8 Hz, 8"'a-H), 6.95 (1H, dd, *J* = 2.1, 8.3 Hz, 6'-H), 6.96 (1H, d, *J* = 8.3 Hz, 5'-H), 7.00 (1H, d, *J* = 2.1 Hz, 2'-H), 7.45 (1H, s, 3"'-H). ^{13}C-NMR (150 MHz, CD_3OD) δ_C: given in Table 1. Positive-ion FABMS: *m/z* 734 $(M+Na)^+$.

Hydracyanoside E (2): a white powder, $[a]_D^{24}$ –29.4° (*c* 0.02, MeOH). High-resolution positive-ion FABMS: Calcd for $C_{15}H_{19}NO_8Na$ $(M+Na)^+$: 364.1009. Found: 364.1012. UV [MeOH, nm, (logε)]: 289 (3.55), 224 (3.84). IR (KBr): 3570, 2926, 2257, 1074 cm^{-1}. ^{1}H-NMR (600 MHz, CD_3OD) δ: 3.81 (3H, s), 3.70 (1H, dd, *J* = 5.2, 11.7 Hz, 6"a-H), 3.88 (1H, dd, *J* = 2.0, 11.7 Hz, 6"b-H), 3.65 (1H, s, 2-H_2), 4.72 (1H, d, *J* = 7.6 Hz, 1"-H), 6.54 (1H, s, 3'-H), 7.13 (1H, s, 6'-H). ^{13}C-NMR (150 MHz, CD_3OD) δ_C: given in Table 2. Positive-ion FABMS: *m/z* 364 $(M+Na)^+$.

Hydracyanoside F (3): a white powder, $[a]_D^{25}$ –106.2° (*c* 0.02, MeOH). High-resolution positive-ion FABMS: Calcd for $C_{17}H_{21}NO_9Na$ $(M+Na)^+$: 406.1114. Found: 406.1119. UV [MeOH, nm, (logε)]: 242 (3.73). IR (KBr): 3420, 2924, 2361, 1719, 1655, 1074 cm^{-1}. ^{1}H-NMR (600 MHz, CD_3OD) δ: 2.01 (1H, ddd, *J* = 5.5, 13.7, 14.5 Hz,, 6β-H), 2.11 (1H, ddd, *J* = 2.0, 4.8, 14.5 Hz,, 6α-H), 4.75 (1H, d, *J* = 7.6 Hz, 1'-H), 5.31 (1H, dd, *J* = 2.1, 10.3 Hz, 10a-H), 5.36 (1H, dd, *J* = 2.1, 17.3 Hz, 10b-H), 5.54 (1H, ddd, *J* = 9.7, 10.3, 17.3 Hz, 8-H), 5.59 (1H, dd, *J* = 2.0, 5.5 Hz, 7-H), 5.60 (1H, d, *J* = 5.5 Hz, 1-H), 7.70 (1H, br s, 3-H). ^{13}C-NMR (150 MHz, CD_3OD) δ_C: given in Table 3. Positive-ion FABMS: *m/z* 406 $(M+Na)^+$.

Acid Hydrolysis of 1–3. A solution of **1**, **2**, and **3** (each 1.0 mg) in 1.0 M aqueous HCl (2.0 mL) was heated under reflux for 3 h. After cooling, the reaction mixture was poured into ice-water and neutralized with Amberlite IRA-400 (OH^- form), and the resin was removed by filtration. Then, the filtrate was partitioned with EtOAc. The aqueous layer was subjected to HPLC analysis to identify the D-glucose under the following conditions: HPLC column, Kaseisorb LC NH_2-60-5, 4.6 mm i.d. × 250 mm (Tokyo Kasei Co., Ltd., Tokyo, Japan); detection, optical rotation [Shodex OR-2 (Showa Denko Co., Ltd., Tokyo, Japan)]; mobile phase, MeCN–H_2O (85:15, v/v); flow rate 0.8 mL/min; column temperature, room temperature. Identification of D-glucose present in the aqueous layer was carried out by comparison of its retention time and optical rotation with that of authentic sample. t_R: D-glucose, 13.5 min (positive optical rotation).

Methanolysis of 1

A solution of hydracyanoside D (**1**, 5 mg, 0.007 mmol) in MeOH containing 0.1M HCl (2mL) was stirred

at 70 °C for 2 h. The solution was neutralized with Amberlite IRA-400 (OH^- form) and the resin was removed by filtration. Evaporation of the solvent from the filtrate under reduced pressure gave a residue which was purified by HPLC [Cosmosil 5C_{18}-MS-II, MeOH–H_2O (30:70, v/v)] to afford hydracyanoside A (**4**, 0.4 mg) and secoxyloganin dimethylacetal (0.3 mg).

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