Phenolic Glycosides from the Chinese Liverwort *Reboulia hemisphaerica*

by **Li-Ning Wang**[a]), **Dong-Xiao Guo**[a]), **Shu-Qi Wang**[a]), **Chang-Sheng Wu**[a]), **Mujeeb Ur Rehman**[a])[b]), and **Hong-Xiang Lou***[a])

[a]) Department of Natural Products Chemistry, School of Pharmaceutical Sciences, Shandong University, No. 44 West Wenhua Road, Jinan 250012, P. R. China
(phone: +86-531-88382012; fax: +86-531-88382019; e-mail: louhongxiang@sdu.edu.cn)
[b]) H.E.J. Research Institute of Chemistry, International Center for Chemical and Biological Science, University of Karachi, Karachi 75270, Pakistan

Four new phenolic glycosides, named rebouosides A – D (**1** – **4**, resp.), along with three known ones 2-(3,4-dihydroxyphenyl)ethyl 2-*O*-*α*-L-rhamnopyranosyl-*β*-D-allopyranoside (**5**), 2-(3,4-dihydroxyphenyl)ethyl *β*-D-allopyranoside (**6**), 2-(3,4-dihydroxyphenyl)ethyl *β*-D-glucopyranoside (**7**), and a nucleoside, inosine (**8**), were isolated from Chinese liverwort *Reboulia hemisphaerica*. Their structures were elucidated by acidic hydrolysis and extensive spectroscopic methods, including 2D-NMR techniques.

Introduction. – *Reboulia hemisphaerica* (L.) RADDI. is a thalloid liverwort of the Aytoniaceae, widely distributed in moist areas of low altitude around the world [1]. It is traditionally used in China as a folk medicine for the treatment of skin ulcer, burns, pain, and swelling from injuries, external bleeding, and related diseases [2]. Samples of *R. hemisphaerica* from various origins have been chemically investigated previously [1][3–14], and a series of sesquiterpenoids and bis-bibenzyls have been isolated from its lipophilic fractions [3][4]. In our continuing effort to search for new biologically active natural products from liverworts [15–17], the phytochemical investigation of the H_2O-soluble portion of *R. hemisphaerica* led to the isolation and identification of four new phenolic glycosides, named rebouosides A – D (**1** – **4**), together with the four known compounds **5** – **8** (*Fig. 1*). This is the third report on the isolation and structural elucidation of H_2O-soluble phenylethanoid glycosides (=2-arylethyl glycosides) from liverworts. Similar compounds were isolated from *Marchantia polymorpha* and *Ricciocarpos natans* [18][19].

Results and Discussion. – Dried plant material of *R. hemisphaerica* was extracted with 95% EtOH and then partitioned with Et_2O and H_2O. The H_2O extract was repeatedly chromatographed on silica gel and *Sephadex LH-20* and then further separated by HPLC on a reversed-phase column to yield compounds **1** – **8**.

Compound **1** was obtained as a colorless, amorphous powder. Its molecular formula was established as $C_{19}H_{28}O_{12}$ by the quasimolecular-ion peak at *m*/*z* 471.1465 ($[M + Na]^+$) in the positive-ion-mode HR-ESI-MS. The IR spectrum (KBr) showed absorption bands of OH groups (3424 cm^{-1}) and aromatic rings (1610, 1523, and 1446 cm^{-1}). The ^{1}H-NMR spectrum of **1** (*Table 1*) exhibited characteristic signals attributable to a 2-(3,4-dihydroxyphenyl)ethoxy moiety, *i.e.*, three aromatic H-atoms

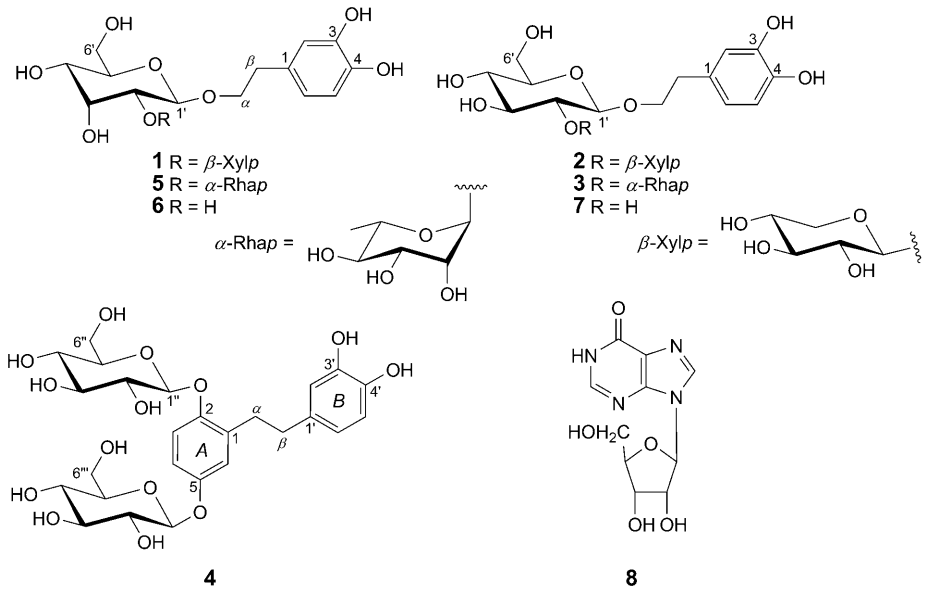

Fig. 1. *Compounds* **1**–**8**, *isolated from* Reboulia hemisphaerica

(*ABX* systems), a $CH_2(\beta)$ group at δ(H) 2.71–2.68 (*m*), and two nonequivalent H-atoms of $CH_2(\alpha)$ at δ(H) 3.97–3.93 and 3.63–3.59 (2*m*) derived from the aglycon. Compound **1** thus belonged to the phenylethanoid class of natural products. Additionally, two anomeric H-atom resonances appeared at δ(H) 4.70 (*d*, $J = 7.8$ Hz, H–C(1′)) of an allose (All) unit and at δ(H) 4.39 (*d*, $J = 7.2$ Hz, H–C(1″)) of a xylose (Xyl) unit, indicating an *O*-glycosylglycoside structure of **1**. The ^{13}C-NMR data (*Table 2*) confirmed the *O*-glycosylglycoside sugar chain of **1** by exhibiting two anomeric-C-atom resonances at δ(C) 100.3 and 102.5, which showed HSQC cross-peaks with the anomeric H-atoms of the All and Xyl unit, respectively. In the HMBC spectrum of **1**, the cross-peaks (*Fig. 2*) between the anomeric H-atom of the All unit at δ(H) 4.70 (H–C(1′)) and the C-atom at δ(C) 71.9 (C(α) of the arylethyl moiety), in combination with those between the H-atom at δ(H) 3.51 (H–C(2′) of All) and the anomeric C-atom of the Xyl unit at δ(C) 102.5 (C(1″)) determined the 2-*O*-glycosylglycoside chain linkage. Accordingly, the structure of **1** was established as 2-(3,4-dihydroxyphenyl)ethyl 2-*O*-β-D-xylopyranosyl-β-D-allopyranoside[1]), for which the trivial name rebouoside A is proposed.

Compound **2** was isolated as a colorless, amorphous powder, with the molecular formula $C_{19}H_{28}O_{12}$, as determined from the HR-ESI-MS quasimolecular-ion peak at *m*/*z* 471.1466 ($[M + Na]^+$) together with analysis of NMR data (*Table 1* and *2*). Analysis of the ^{1}H- and ^{13}C-NMR spectra indicated that **2** also possessed a 2-(3,4-dihydroxyphenyl)ethoxy moiety and two sugar units, while acid hydrolysis afforded xylose and glucose (Glc). Moreover, the clear correlations (*Fig. 2*) C(α)/H–C(1′) and

[1]) The absolute configurations D or L of the sugar moieties are tentative.

Table 1. *^{1}H-NMR Data* (600 Mz) *of Compounds* **1**–**4**. δ in ppm, J in Hz.

	1[a])	**2**[a])	**3**[b])	**4**[c])
H–C(2)	6.64 (*d*, *J* = 2.4)	6.68 (*d*, *J* = 1.9)	6.71 (*d*, *J* = 1.7)	
H–C(3)				7.05 (*d*, *J* = 8.9)
H–C(4)				6.83 (*dd*, *J* = 2.4, 8.9)
H–C(5)	6.61 (*d*, *J* = 8.4)	6.66 (*d*, *J* = 8.0)	6.72 (*d*, *J* = 8.1)	
H–C(6)	6.52 (*dd*, *J* = 2.4, 8.4)	6.56 (*dd*, *J* = 1.9, 8.0)	6.62 (*dd*, *J* = 1.7, 8.1)	6.75 (*d*, *J* = 2.4)
$CH_2(\alpha)$	3.97–3.93 (*m*),	4.04–4.00 (*m*),	3.95–3.91 (*m*),	2.92–2.87 (*m*),
	3.63–3.59 (*m*)[d])	3.67–3.64 (*m*)	3.76–3.72 (*m*)	2.85–2.80 (*m*)
$CH_2(\beta)$	2.71–2.68 (*m*)	2.70 (*t*, *J* = 7.3)	2.71 (*t*, *J* = 7.3)	2.74–2.65 (*m*)
	All:	Glc:	Glc:	
H–C(1′)	4.70 (*d*, *J* = 7.8)	4.40 (*d*, *J* = 7.8)	4.39 (*d*, *J* = 7.9)	
H–C(2′)	3.51 (*dd*, *J* = 2.6, 7.8)	3.40–3.36 (*m*)	3.23–3.20 (*m*)	6.60 (*d*, *J* = 1.8)
H–C(3′)	4.18 (*t*, *J* = 2.6)	3.24–3.20 (*m*)[d])	3.44–3.42 (*m*)	
H–C(4′)	3.45 (*dd*, *J* = 2.6, 9.6)	3.35–3.32 (*m*)[d])	3.26–3.24 (*m*)[d])	
H–C(5′)	3.69–3.67 (*m*)	3.55–3.52 (*m*)	3.26–3.24 (*m*)[d])	6.59 (*d*, *J* = 7.8)
$CH_2(6')$ or H–C(6′)	3.79 (*dd*, *J* = 2.4, 11.2),	3.85 (*dd*, *J* = 1.9, 12.1),	3.74 (*dd*, *J* = 1.5, 11.3),	6.45 (*dd*, *J* = 1.8, 7.8)
	3.63–3.59 (*m*)[d])	3.66 (*dd*, *J* = 5.7, 12.1)	3.56 (*dd*, *J* = 4.2, 11.3)	
	Xyl:	Xyl:	Rha:	Glc:
H–C(1″)	4.39 (*d*, *J* = 7.2)	4.52 (*d*, *J* = 7.4)	4.95 (*d*, *J* = 1.7)	4.61 (*d*, *J* = 7.8)
H–C(2″)	3.27–3.25 (*m*)[d])	3.24–3.20 (*m*)[d])	3.82 (*dd*, *J* = 1.7, 3.4)	3.43–3.38 (*m*)[d])
H–C(3″)	3.31–3.29 (*m*)[d])	3.35–3.31 (*m*)[d])	3.60 (*dd*, *J* = 3.4, 9.8)	3.47–3.45 (*m*)[d])
H–C(4″)	3.50–3.48 (*m*)	3.51–3.47 (*m*)	3.30 (*t*, *J* = 9.7)	3.36–3.31 (*m*)[d])
$CH_2(5'')$ or H–C(5″)	3.85 (*dd*, *J* = 5.2, 11.5),	3.87 (*dd*, *J* = 5.2, 11.5),	3.81–3.78 (*m*)	3.36–3.31 (*m*)[d])
	3.17–3.14 (*m*)	3.60 (*dd*, *J* = 10.3, 11.5)		
$Me(6'')$ or $CH_2(6'')$			1.08 (*d*, *J* = 6.2)	3.86–3.81 (*m*)
H–C(1‴)				4.76 (*d*, *J* = 7.8)
H–C(2‴)				3.43–3.38 (*m*)[d])
H–C(3‴)				3.47–3.45 (*m*)[d])
H–C(4‴)				3.36–3.31 (*m*)[d])
H–C(5‴)				3.36–3.31 (*m*)[d])
$CH_2(6''')$				3.68–3.64 (*m*)

[a]) Recorded in CD_3OD. [b]) Recorded in D_2O. [c]) Recorded in $(D_6)DMSO$. [d]) Overlapping signals.

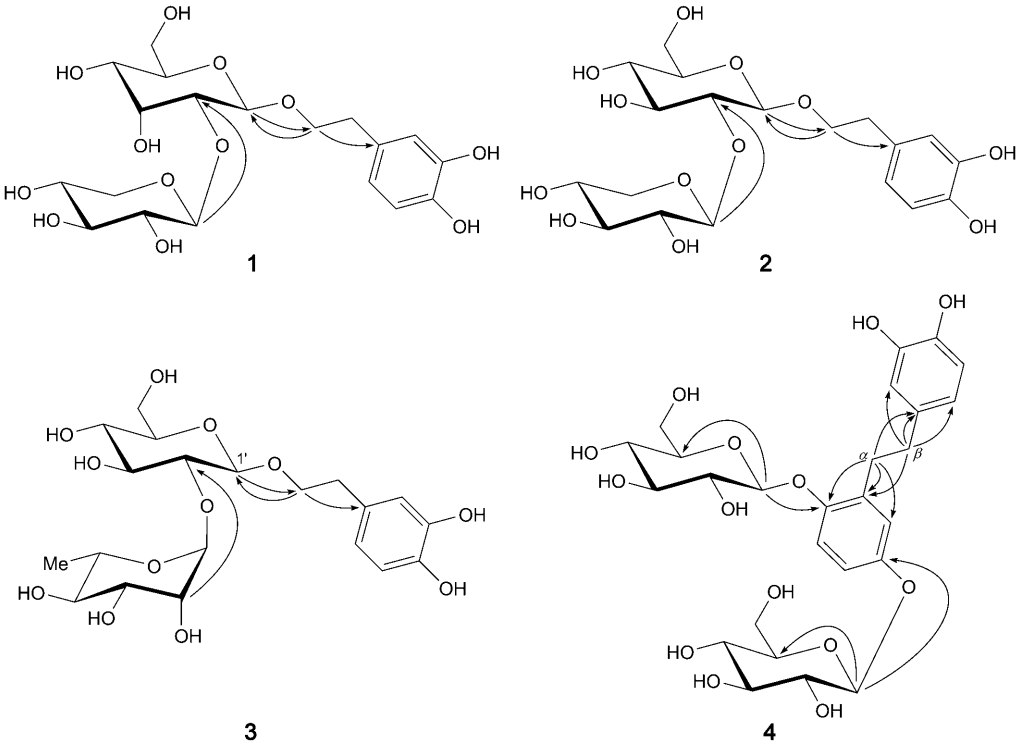

Fig. 2. *Key HMBCs* (H → C) *of* **1**–**4**

C(2′)/H–C(1″), indicated that the Xyl unit was attached to C(2′) of the Glc unit and the latter to C(α) of the arylethyl moiety [20]. Therefore, the structure of compound **2** (rebouoside B) was established as 2-(3,4-dihydroxyphenyl)ethyl 2-*O*-β-D-xylopyranosyl-β-D-glucopyranoside[1]).

Compound **3** was obtained as a colorless, amorphous powder. The molecular formula was determined as $C_{20}H_{30}O_{12}$ from the HR-ESI-MS quasimolecular-ion peak at *m*/*z* 485.1617 ([*M* + Na]$^+$). Analysis of the ^{1}H- and ^{13}C-NMR spectra (*Table 1* and *2*) and the acid hydrolysis experiment suggested the presence of three fragments, including a 2-(3,4-dihydroxyphenyl)ethoxy, a β-glucose, and an α-rhamnose (Rha) unit. The sugar moieties were assigned according to the coupling-constant values of the sugar H-atoms and their ^{13}C-NMR data (*Table 2*) [21]. In the HMBC spectrum of **3**, the correlations H–C(1′) (Glc)/C(α), H–C(1″) (Rha)/C(2′) (Glc) were observed (*Fig. 2*). On the basis of these results, **3** was established as 2-(3,4-dihydroxyphenyl)-ethyl 2-*O*-α-L-rhamnopyranosyl-β-D-glucopyranoside[1]), and named rebouoside C.

Compound **4** was obtained as a colorless, amorphous powder. Its molecular formula $C_{26}H_{34}O_{14}$ was deduced from the [*M* + Na]$^+$ peak at *m*/*z* 593.1840 in the HR-ESI-MS. The IR spectrum showed absorptions of OH groups (3355 cm^{-1}) and aromatic rings (1614, 1516, and 1456 cm^{-1}). The ^{1}H- and ^{13}C-NMR, COSY, and HMQC data (*Tables 1* and *2*) of **4** showed the presence of two *ABX* systems at δ(H) 7.05 (*d*, *J* = 8.9 Hz,

Table 2. *^{13}C-NMR Data* (150 MHz) *of Compounds* **1**–**4**. δ in ppm.

	1[a])	**2**[a])	**3**[b])	**4**[c])
C(1)	131.9	131.7	131.0	134.4
C(2)	117.4	117.3	116.5	152.5
C(3)	144.9	144.8	143.8	117.9
C(4)	146.3	146.3	142.2	116.2
C(5)	116.3	116.4	116.2	154.4
C(6)	121.6	121.4	121.0	120.0
C(α)	71.9	72.3	70.6	36.9
C(β)	36.7	36.8	34.4	33.9
	All:	Glc:	Glc:	
C(1′)	100.3	103.2	100.8	135.4
C(2′)	77.8	83.7	78.7	116.5
C(3′)	70.3	77.9	75.6	144.3
C(4′)	68.8	71.4	69.4	145.9
C(5′)	75.5	78.0	75.6	121.2
C(6′)	63.2	62.7	60.6	117.1
	Xyl:	Xyl:	Rha:	Glc:
C(1″)	102.5	106.1	100.9	103.2
C(2″)	74.7	75.9	70.0	75.3
C(3″)	77.6	77.5	69.4	78.3
C(4″)	70.3	71.3	71.8	71.5
C(5″)	67.1	67.3	68.9	78.1
C(6″)			16.5	62.6
C(1‴)				103.2
C(2‴)				75.1
C(3‴)				78.5
C(4‴)				71.6
C(5‴)				78.1
C(6‴)				62.6

[a]) Recorded in CD_3OD. [b]) Recorded in D_2O. [c]) Recorded in (D_6)DMSO.

H–C(3)), 6.83 (*dd*, $J = 8.9$, 2.4 Hz, H–C(4)), and 6.75 (*d*, $J = 2.4$ Hz, H–C(6)) for a 2,5-disubstituted phenyl moiety (ring *A*), and at δ(H) 6.60 (*d*, $J = 1.8$ Hz, H–C(2′)), 6.59 (*dd*, $J = 1.8$, 7.8 Hz, H–C(6′)), and 6.45 (*d*, $J = 7.8$ Hz, H–C(5′)) for a 3,4-dihydroxyphenyl moiety (ring *B*). The NMR data of **4** were similar to those reported for α,β-dihydrostilbene-2,4′,5-triol 2,5-di(β-D-glucopyranoside) [18]. Rings *A* and *B* of **4** were connected *via* the fragment $CH_2(\alpha)CH_2(\beta)$, based on the HMBCs (*Fig. 2*) of $CH_2(\alpha)$ at δ(H) 2.92–2.87 and 2.85–2.80 with C(1), C(2), and C(6) at δ(C) 134.4, 152.5, and 120.0, respectively, and correlations of $CH_2(\beta)$ at δ(H) 2.74–2.65 with C(1′), C(2′), and C(6′) at δ(C) 135.4, 116.5, and 117.1, respectively. Thus, the aglycone of **4** was deduced to be bibenzyl-2,3′,4′,5-tetrol (=4-[2-(2,5-dihydroxyphenyl)ethyl]benzene-1,2-diol). The acid hydrolysis afforded only glucose. Two anomeric H-atoms at δ(H) 4.61 (H–C(1″)) and 4.76 (H–C(1‴)) displayed long-range correlations with C(2) (δ(C) 152.5) and C(5) (δ(C) 154.4), respectively, in the HMBC plot, which determined that the glucose units were connected with the bibenzyl moiety at C(2) and C(5). Finally, **4**

was determined as α,β-dihydrostilbene-2,3′,4′,5-tetrol 2,5-di(β-D-glucopyranoside)[1]), which was given the trivial name rebouoside D.

The four known compounds were identified as 2-(3,4-dihydroxyphenyl)ethyl 2-*O*-α-L-rhamnopyranosyl-β-D-allopyranoside (**5**) [18], 2-(3,4-dihydroxyphenyl)ethyl β-D-glucopyranoside (**6**) [22], 2-(3,4-dihydroxyphenyl)ethyl β-D-allopyranoside (**7**) [23], and inosine (**8**), based on comparison of their NMR and MS data with those reported. They were all obtained for the first time from this plant species.

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Experimental Part

General. TLC: precoated silica gel GF_{254} plates (*Qingdao Marine Chemical Industry*); eluent $CHCl_3$/MeOH 2:1. Column chromatography (CC): silica gel (SiO_2; 200–300 mesh; *Qingdao Marine Chemical Industry*), *Sephadex* LH-20 gel (*Pharmacia Biotech*), *MCI* gel (*CHP20P*, 75–150 μm; *Mitsubishi Chemical Industries Ltd.*), silica gel *100* C_{18}-reversed phase (40–63 μm; *Sigma–Aldrich.*). Semi-prep. HPLC: *YMC-Pack ODS-A* column (250 × 20 mm, 10 μm (spherical), 12 nm), with *Agilent-1100-G1310A* isopump and *Agilent-1100-G1314* detector (210 nm); mobile phase MeOH/H_2O 15:85, flow rate 1.8 ml/min. Optical rotations: *Perkin-Elmer-241MC* polarimeter. UV Spectra: *Shimadzu-UV-2450* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Thermo-Nicolet-670* spectrophotometer; KBr disks; $\tilde{\nu}_{max}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker-Avance-DRX-600* spectrometer; at 600 (^1H) or 150 MHz (^{13}C); in CD_3OD, (D_6)DMSO, or D_2O; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz; 2D spectra recorded with standard pulse programs and acquisition parameters. MS: *API-4000* triple-stage quadrupole instrument for electrospray ionization (ESI) and *Finnigan LC-*Q^{DECA} mass spectrometer for HR-ESI; in *m*/*z*.

Plant Material. *R. hemisphaerica* was collected from Libo, Guizhou Province, P. R. China, in August 2008, and authenticated by Prof. *Yuan-Xin Xiong* (School of Agricultural Sciences, Guizhou University, P. R. China). A voucher specimen has been deposited with the School of Pharmaceutical Sciences, Shandong University (accession number: TX-18-200807-RH), Shandong, P. R. China.

Extraction and Isolation. The air-dried parts of *R. hemisphaerica* (380 g) were ground and extracted four times exhaustively with (each 2.0 l) 95% aq. EtOH at r.t. The combined EtOH extract was concentrated to yield a semi-solid (32.2 g). The residue was partitioned between Et_2O (5 × 200 ml) and H_2O (200 ml). The aq. portion (10.3 g) was purified further by CC (*MCI* gel, $H_2O \rightarrow$ MeOH) to give fractions eluting with H_2O (6.4 g) and MeOH (3.5 g). A portion (3.4 g) of the MeOH fraction was subjected to CC (SiO_2, gradient cyclohexane/acetone 100:10 → 0:100): *Fractions 1–6*. *Fr. 3* (0.23 g) was subjected to CC (*Sephadex LH-20*, $CHCl_3$/MeOH 1:1): *Frs. 3.1–3.6*. *Fr. 3.3* (25 mg) was further fractionated by semi-prep. HPLC (see *General*): **6** (3.2 mg; t_R 25.3 min), **7** (2.4 mg; t_R 27.1 min), and **8** (2.1 mg; t_R 30.5 min). *Fr. 4* (0.18 g) was applied to CC (*Sephadex LH-20*, $CHCl_3$/MeOH 1:1): *Frs. 4.1–4.5*. *Fr. 4.3* (24 mg) was further fractionated by semi-prep. HPLC (see *General*): **1** (2.1 mg; t_R 33.8 min), **2** (2.4 mg; t_R 38.6 min), **3** (5.6 mg; t_R 40.1 min), and **5** (6.3 mg; t_R 47.9 min). *Fr. 5* (0.12 g) was subjected to CC (*Sephadex LH-20*, $CHCl_3$/MeOH 1:1): *Frs. 5.1–5.4*. *Fr. 5.2* (3.2 mg) was further fractionated by semi-prep. HPLC (see *General*): **4** (1.3 mg).

Rebouoside A (=*2-(3,4-Dihydroxyphenyl)ethyl 2*-O-β-D-*Xylopyranosyl-*β-D-*allopyranoside*[1]); **1**): Colorless, amorphous powder. $[\alpha]_D^{20} = -36$ ($c = 0.5$, MeOH). UV (MeOH): 202 (3.84), 274 (3.17). IR (KBr): 3424, 1610, 1523, 1446. ^1H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS (neg.): 447 ($[M-H]^-$). HR-ESI-MS: 471.1465 ($[M+Na]^+$, $C_{19}H_{28}NaO_{12}^+$; calc. 471.1473).

Rebouoside B (=*2-(3,4-Dihydroxyphenyl)ethyl 2*-O-β-D-*Xylopyranosyl-*β-D-*glucopyranoside*[1]); **2**): Colorless, amorphous powder. $[\alpha]_D^{20} = -27$ ($c = 0.9$, MeOH). UV (MeOH): 202 (3.96), 274 (3.16). IR (KBr): 3423, 1610, 1523, 1446. ^1H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS (neg.): 447 ($[M-H]^-$). HR-ESI-MS: 471.1466 ($[M+Na]^+$, $C_{19}H_{28}NaO_{12}^+$; calc. 471.1473).

Rebouoside C (=*2-(3,4-Dihydroxyphenyl)ethyl 2*-O-*(6-Deoxy-α*-L-*mannopyranosyl)-β*-D-*glucopyranoside*[1]); **3**): Colorless, amorphous powder. $[\alpha]_D^{20} = -56$ ($c = 0.9$, MeOH). UV (MeOH): 202 (3.82), 274 (3.14). IR (KBr): 3423, 1609, 1522, 1446. ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS (neg.): 461 ($[M-H]^-$). HR-ESI-MS: 485.1617 ($[M + Na]^+$, $C_{20}H_{30}NaO_{12}^+$; calc. 485.1629).

Rebouoside D (=*α,β-Dihydrostilbene-2,3′,4′,5-tetrol 2,5-Di(β*-D-*glucopyranoside)* = *2-[2-(3,4-Dihydroxyphenyl)ethyl]-1,4-phenylene Bis(β*-D-*glucopyranoside)*[1]); **4**): Colorless, amorphous powder. $[\alpha]_D^{20} = -37$ ($c = 0.9$, MeOH). UV (MeOH): 202 (3.94), 274 (3.74). IR (KBr): 3355, 1614, 1516, 1456. ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS (pos.): 593 ($[M+Na]^+$). HR-ESI-MS: 593.1840 ($[M + Na]^+$, $C_{26}H_{34}NaO_{14}^+$; calc. 593.1841).

Acid Hydrolysis of Compounds **1**–**4**. Each compound **1**–**4** (each 0.5 mg) was hydrolyzed with 0.5N HCl for 3 h at 100°. The mixture was then diluted with H_2O (10 ml) and extracted with CH_2Cl_2 (3 × 5 ml). The aq. layer was lyophilized to give a residue. The sugars were identified by co-TLC with a authentic samples. TLC ($CHCl_3$/AcOH/H_2O 30 : 35 : 5): R_f value of glucose 0.26, of allose 0.33, of xylose 0.50, and of rhamnose 0.75.

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