Rhodiolosides A—E, Monoterpene Glycosides from *Rhodiola rosea*

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Five new monoterpene glycosides, rhodiolosides A—E (1—5), were isolated from the roots of *Rhodiola rosea* (Crassulaceae). Their structures were elucidated as (2*E*,6*E*,4*R*)-4,8-dihydroxy-3,7-dimethyl-2,6-octadienyl β-D-glucopyranoside (1), (2*E*,4*R*)-4-hydroxy-3,7-dimethyl-2,6-octadienyl α-D-glucopyranosyl(1→6)-β-D-glucopyranoside (2), (2*E*,4*R*)-4-hydroxy-3,7-dimethyl-2,6-octadienyl β-D-glucopyranosyl(1→3)-β-D-glucopyranoside (3), (2*E*,4*R*)-4,7-dihydroxy-3,7-dimethyl-2-octenyl β-D-glucopyranoside (4), and (2*E*)-7-hydroxy-3,7-dimethyl-2-octenyl α-L-arabinopyranosyl(1→6)-β-D-glucopyranoside (5), on the basis of various spectroscopic analyses and chemical degradation.

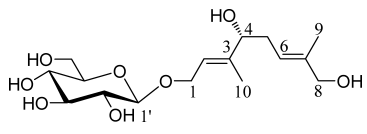
Key words *Rhodiola rosea*; Crassulaceae; monoterpene; glycoside; rhodioloside

Rhodiola rosea L. (Crassulaceae), also known as golden root or rose root, is a perennial herbaceous plant widely distributed at high altitudes in the arctic and mountainous regions throughout Europe and Asia. The roots of *R. rosea* are traditionally used as a tonic and adaptpgen in Russia, and also as a hemostatic in Tibetan folk medicine. Various pharmacological effects of the roots of *R. rosea* have been reported, such as improvement of the memory and learning abilities, anti-stress and anticancer effects, *etc*.[1,2] Previous chemical investigation on *R. rosea* has demonstrated the occurrence of over thirty compounds, belonging to the phenylethanoids, phenylpropanoides, flavonoids, phenolic acids, cyanoglycosides, monoterpenoids, and triterpenes.[1—5] Although several monoterpenoids have been reported in other *Rhodiola* species,[6,7] only one monoterpenoid, rosiridol and its glucoside, rosiridin have been isolated from *R. rosea*.[3,8] Our continuing phytochemical investigations on Chinese medicinal plants[9—12] have resulted in the isolation of five new monoterpene glycosides, rhodiolosides A—E (**1**—**5**) from the roots of *R. rosea*. This paper deals with the isolation and structure elucidation of these new compounds.

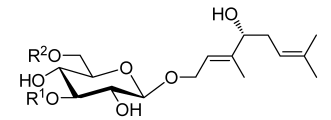
Results and Discussion

The air-dried roots of *R. rosea* were extracted with 80% aqueous EtOH. The extract was concentrated, suspended in H_2O and then partitioned successively with $CHCl_3$, EtOAc and *n*-BuOH. The *n*-BuOH-soluble fraction was evaporated under reduced pressure and fractionated using silica gel and ODS columns. Further purification by repeated reversed-phase HPLC afforded five new monoterpene glycosides, rhodiolosides A—E (**1**—**5**).

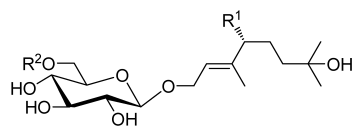
Rhodioloside A (**1**) was isolated as a colorless viscous oil. The molecular formula was established as $C_{16}H_{28}O_8$ by high-resolution (HR)-FAB-MS. On acidic hydrolysis, **1** afforded D-glucose, which was identified by gas-liquid chromatography (GLC) analysis of its trimethylsilyl thiazolidine derivative.[13] The ^{1}H-NMR spectrum of **1** (Table 1) revealed signals assignable to a β-glucopyranosyl moiety, with the anomeric proton resonanced at δ 4.29 (d, J=7.8 Hz). Further, the ^{1}H-NMR spectrum showed two olefinic proton signals at δ 5.59 (dd, J=7.2, 6.2 Hz, H-2) and 5.40 (t, J=6.9 Hz, H-6), and the signals of two oxygenated methylenes at δ 4.37 (dd, J=12.4, 6.2 Hz, H_a-1), 4.30 (dd, J=12.4, 7.2 Hz, H_b-1) and 3.92 (s, H_2-8), one oxygenated methine at δ 4.02 (t, J=6.6 Hz, H-4), one aliphatic methylene at δ 2.30 (t, J=6.9 Hz, H_2-5) and two tertiary methyls at δ 1.68 (s, H_3-10) and 1.66 (s, H_3-9). These protons were assigned to their respective carbons by analysis of the ^{1}H-detected heteronuclear multiple quantum coherence (HMQC) data. In addition to the protonated carbon signals, the ^{13}C-NMR spectrum also showed two olefinic quaternary carbon signals at δ 142.9 (C-3) and 137.7 (C-7), which could be confirmed from the distortionless enhancement by polarization transfer (DEPT) data. Analysis of the double quantum filter correlation spectroscopy (DQFCOSY) data defined two spin systems as shown in Fig. 1, indicating the presence of two partial structures, one for C-1 to C-2 and one for C-4 to C-6. Further careful analysis of the ^{1}H-detected heteronuclear multiple bond connectivity (HMBC) correlations led to the construction of the planar structure of **1** (Fig. 1). The connection of the two partial structures



1



2 R^1 = H R^2 = α-D-glucopyranosyl
3 R^1 = β-D-glucopyranosyl R^2 = H



4 R^1 = OH R^2 = H
5 R^1 = H R^2 = α-L-arabinopyranosyl

Chart 1

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Table 1. ^{1}H-NMR Data (500 MHz) for **1**—**5** in Methanol-d_4

Position	1	2	3	4	5
1	4.37 (dd, 12.4, 6.2)	4.36 (dd, 12.4, 6.2)	4.37 (dd, 12.2, 6.2)	4.38 (dd, 12.3, 6.2)	4.35 (dd, 11.7, 6.5)
	4.30 (dd, 12.4, 7.2)	4.28 (dd, 12.4 7.3)	4.30 (dd, 12.2, 7.3)	4.31 (dd, 12.3, 7.2)	4.21 (dd, 11.7, 7.4)
2	5.59 (dd, 7.2, 6.2)	5.58 (dd, 6.2, 7.3)	5.57 (t, 6.9)	5.59 (dd, 7.2, 6.2)	5.39 (t, 6.9)
4	4.02 (t, 6.6)	3.97 (t, 7.0)	3.97 (t, 6.7)	3.94 (t, 6.6)	2.05 (t, 7.2)
5	2.30 (t, 6.9)	2.24 (t, 6.6)	2.24 (t, 6.7)	1.61 (dt, 9.4, 6.6)	1.52 (m)
6	5.40 (t, 6.9)	5.10 (m)	5.10 (t, 7.1)	1.53 (m), 1.36 (m)	1.43 (m)
8	3.92 (s)	1.62 (s)	1.62 (s)	1.18 (s)[b]	1.17 (s)
9	1.66 (s)	1.69 (s)	1.69 (s)	1.17 (s)[b]	1.17 (s)
10	1.68 (s)	1.67 (s)	1.67 (s)	1.67 (s)	1.69 (s)
Sugar					
1′	4.29 (d, 7.8)	4.34 (d, 7.8)	4.37 (d, 7.8)	4.30 (d, 7.8)	4.29 (d, 7.8)
2′	3.18 (dd, 8.9, 7.8)	3.20 (dd, 9.0, 7.8)	3.39 (t, 8.0)	3.18 (dd, 9.1, 7.8)	3.18 (dd, 9.4, 7.8)
3′	3.35 (t, 8.9)	3.36 (m)	3.54 (t, 8.7)	3.35[a]	3.33[a]
4′	3.28 (t, 8.9)	3.43 (t, 9.6)	3.42 (t, 9.6)	3.28 (t, 9.4)	3.35[a]
5′	3.25 (ddd, 8.9, 5.6, 2.0)	3.44 (m)	3.30 (m)	3.25 (m)	3.40 (ddd, 8.9, 5.6, 2.3)
6′	3.86 (dd, 11.9, 2.0)	4.00 (dd, 10.7, 4.1)	3.88 (dd, 11.8, 2.0)	3.86 (dd, 11.4, 2.0)	4.09 (dd, 11.3, 2.3)
	3.66 (dd, 11.9, 5.6)	3.71 (dd, 10.7, 1.6)	3.69 (dd, 11.8, 5.6)	3.67 (dd, 11.4, 5.5)	3.73 (dd, 11.4, 5.6)
1″		4.84 (d, 3.6)	4.55 (d, 7.5)		4.32 (d, 6.7)
2″		3.37 (dd, 9.6, 3.6)	3.28 (dd, 8.0, 9.4)		3.59 (dd, 8.7, 6.7)
3″		3.66 (t, 8.9)	3.39 (t, 8.6)		3.52 (dd, 8.7, 3.3)
4″		3.68 (t, 9.9)	3.31[a]		3.81 (td, 3.3, 1.9)
5″		3.30 (m)	3.32 (m)		3.86 (dd, 12.4, 3.3)
					3.53 (dd, 12.4, 1.9)
6″		3.80 (dd, 9.4, 4.3)	3.88 (dd, 11.8, 2.0)		
		3.69[a]	3.65 (dd, 11.8, 6.2)		

a) Overlapped siganls. *b*) Signals may be exchangeable.

Table 2. ^{13}C-NMR Data (125 MHz) for **1**—**5** in Methanol-d_4

Position	1	2	3	4	5
1	66.1	66.4	66.1	66.2	66.6
2	122.9	122.7	122.7	123.0	121.7
3	142.9	143.3	143.2	143.2	142.0
4	77.6	78.0	78.0	78.5	41.1
5	34.4	34.9	34.8	30.7	23.5
6	122.7	121.6	121.6	40.1	44.4
7	137.7	134.2	134.1	71.2	71.4
8	68.9	18.1	18.1	29.3[a]	29.3
9	14.0	26.0	26.0	29.2[a]	29.3
10	12.1	12.2	12.1	11.9	16.5
Sugar					
1′	102.9	103.1	102.4	103.0	103.1
2′	75.1	75.1	74.4	75.2	75.1
3′	78.2	78.2	88.2	78.2	78.1
4′	71.7	71.4	70.1	71.8	71.7
5′	78.0	76.4	77.7	78.1	76.9
6′	62.8	67.3	62.7	62.9	69.5
1″		100.0	105.3		105.2
2″		73.9	75.5		72.4
3″		75.4	77.8		74.2
4″		73.6	71.6		69.5
5″		71.7	78.2		66.6
6″		62.6	62.7		

a) Signals may be exchangeable.

through a quaternary carbon (C-3) with a methyl group (C-10) was determined by the HMBC correlations between H_a-1/C-3, H_b-1/C-3, H_2-5/C-3, H_3-10/C-2, and H_3-10/C-4. The locations of the hydroxymethyl and the methyl at C-7 were elucidated by the HMBC correlations between H-6/C-8, and H-6/C-9. The β-D-glucopyranosyl moiety at C-1 was determined by the HMBC correlation between Glc-H-1′/C-1. Furthermore, the geometry of the $\Delta^{2,3)}$ olefin was determined to be *E* from the fact that the ^{13}C-NMR chemical shift of C-10

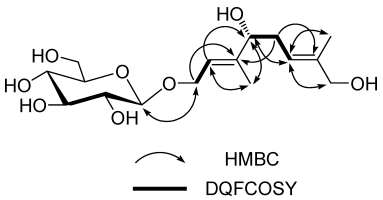
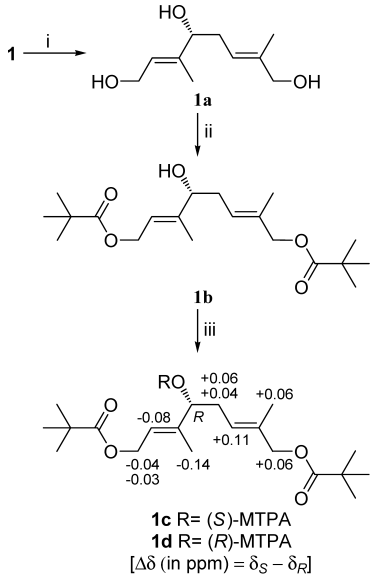


Fig. 1. Key DQFCOSY and HMBC Correlations of **1**

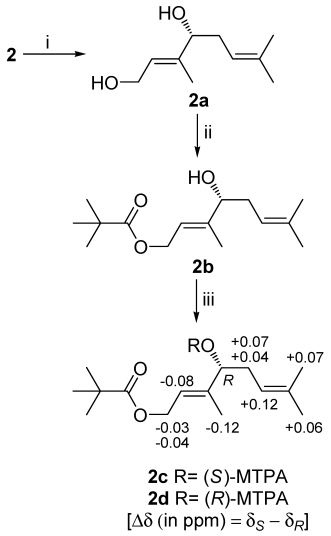
was observed at δ 12.1, which was very close to that of the structurally similar compounds, rosiridin (δ 12.0) and sachalinoside A (δ 13.0),[7] while in the case of the *Z*-type compound sacranoside B, it was observed at δ 23.7.[6] The $\Delta^{6,7)}$ olefin was determined to be *E* by the nuclear Overhauser effect (NOE) difference experiments. The enhancement of H-6 was observed by 9% when H_2-8 was irradiated, and H_2-5 by 6% when H_3-9 was irradiated. The absolute configuration of C-4 was determined to be *R* by applying the modified Mosher's method.[14] Enzymatic hydrolysis of **1** afforded the aglycone **1a**, which was a new monoterpene, and thus named rhodiolol A. The 1,8-dipivaloyl ester (**1b**), which was obtained by selective protection of the 1,8-primary alcohol in **1a** with pivaloyl chloride, was derived to the (*S*)- and (*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl (MTPA) esters (**1c**, **d**). As shown in Chart 2, the $\Delta\delta$ value ($\delta_S - \delta_R$) suggested the *R* configuration of C-4. On the basis of the above evidence, rhodioloside A (**1**) was unambiguously established as (2*E*,6*E*,4*R*)-4,8-dihydroxy-3,7-dimethyl-2,6-octadienyl β-D-glucopyranoside.

Rhodioloside B (**2**) was isolated as a colorless viscous oil. The molecular formula of **2** was determined to be $C_{22}H_{38}O_{12}$ by HR-FAB-MS. Acid hydrolysis of **2** afforded D-glucose as the component sugar. The ^{1}H-NMR spectrum indicated the presence of a β-glucopyranosyl moiety with the anomeric



(i) Naringinase, 0.1 M acetate buffer, 40 °C, 12 h;
(ii) Pivaloyl chloride, dry pyridine, rt, 12 h;
(iii) (*R*) or (*S*)-MTPA chloride, dry pyridine, rt, 4 h.

Chart 2



(i) Naringinase, 0.1 M acetate buffer, 40 °C, 12 h;
(ii) Pivaloyl chloride, dry pyridine, rt, 12 h;
(iii) (*R*) or (*S*)-MTPA chloride, dry pyridine, rt, 4 h.

Chart 3

proton resonanced at δ 4.34 (d, J=7.8 Hz), and an α-glucopyranosyl moiety with the anomeric proton resonanced at δ 4.84 (d, J=3.6 Hz). The ^{1}H- and ^{13}C-NMR signals of the aglycon part of **2** were similar to those of **1** except for the replacement of the hydroxymethyl (δ_C 68.9) in **1** by a methyl (δ_C 18.1) in **2**, which was supported by the HMBC correlations between δ_H 5.10 (H_2-6), 1.69 (H_3-9) and δ_C 18.1 (C-8). Comparison of the ^{1}H- and ^{13}C-NMR data between **2** and rosiridin suggested the identical NMR signals due to the aglycon. The β-glucopyranosyl moiety linked to C-1 was determined by the HMBC correlation between δ_H 4.34 (β-Glc-H-1′) and δ_C 66.4 (C-1). On further comparing the ^{13}C-NMR data of **2** with that of rosiridin, glycosylation shifts were observed at C-6′ (+4.5 ppm) of the β-glucopyranosyl, suggesting the α-glucopyranosyl moiety was connected to C-6′ of the β-glucopyranosyl. This linkage was supported by the HMBC correlation between δ_H 4.84 (α-Glc-H-1″) and δ_C 67.3 (β-Glc-C-6′). Enzymatic hydrolysis of **2** afforded the aglycon as (−)-rosiridol (**2a**) ([α]$_D^{24}$ −7.1° in acetone; ref.: −7.7° in acetone).[15] The absolute configuration of C-4 in (−)-rosiridol had been determined to be *S* by chemical transformation into (−)-eldanolide by Hong *et al.*[15] However, this conclusion was contrary to those structurally related monoterpene glycosides previously reported from *Rhodiola* species.[7] To establish the absolute configuration of C-4 in **2**, the modified Mosher's method was applied as shown in Chart 3 by the same strategy as **1**. On the basis of the data of $\Delta\delta_{S-R}$, the absolute configuration of C-4 was determined to be *R*. Thus, rhodioloside B (**2**) was determined as (2*E*,4*R*)-4-hydroxy-3,7-dimethyl-2,6-octadienyl α-D-glucopyranosyl(1→6)-β-D-glucopyranoside.

Rhodioloside C (**3**) was isolated as a colorless viscous oil. The HR-FAB-MS data determined the same molecular formula, $C_{22}H_{38}O_{12}$, as that of **2**. On acid hydrolysis, **3** afforded D-glucose as the component sugar. In the ^{1}H-NMR spectrum, two anomeric proton signals at δ 4.37 and 4.55 were observed with the large $^3J_{H1,H2}$ coupling constant values (7.8, 7.5 Hz), suggesting the β-configuration of both glucopyranosyl moieties. Comparison of the NMR data between **3** and **2** suggested the aglycon was identical, which was confirmed by enzymatic hydrolysis of **3** to produce (−)-rosiridol. Further comparison of the ^{1}H- and ^{13}C-NMR between **3** and rosiridin suggested the terminal glucopyranosyl moiety was connected to C-3′ from the glycosylation shifts observed at C-3′ (+10.3 ppm) of the inner glucosyl moiety. This sugar linkage was also supported by the HMBC correlation between δ_H 4.55 (glc-H-1″) and δ_C 88.2 (glc-C-3′). Thus, rhodioloside C (**3**) was elucidated as (2*E*,4*R*)-4-hydroxy-3,7-dimethyl-2,6-octadienyl β-D-glucopyranosyl(1→3)-β-D-glucopyranoside.

Rhodioloside D (**4**) was isolated as a colorless viscous oil. The molecular formula of **4** was determined to be $C_{16}H_{30}O_8$ by HR-FAB-MS. Acid hydrolysis of **4** afforded D-glucose as the component sugar. The presence of the β-glucopyranosyl moiety was confirmed from the ^{1}H- and ^{13}C-NMR data. The ^{1}H- and ^{13}C-NMR data of the aglycon were close to that of **2** except for the replacement of signals due to an olefin in **2** by one methylene [δ_H 1.53 (m), 1.36 (m) and δ_C 40.1] and one quaternary oxygenated carbon (δ_C 71.2) in **4**. Enzymatic hydrolysis afforded the aglycon **4a**, which was identified as (2*E*,4*R*)-4,7-dihydroxy-3,7-dimethyl-2-octene (sachalinol A) by comparison of their ^{1}H-NMR data and optical rotation values (**4a**: −17.0° in MeOH; ref.: −17.1° in MeOH).[7] The β-D-glucopyranosyl moiety was determined to be located at C-1 by the HMBC correlation between δ_H 4.30 (Glc-H-1′) and δ_C 66.2 (C-1). Thus, rhodioloside D (**4**) was determined as (2*E*,4*R*)-4,7-dihydroxy-3,7-dimethyl-2-octenyl β-D-glucopyranoside.

Rhodioloside E (**5**) was isolated as a colorless viscous oil. The molecular formula was established as $C_{21}H_{38}O_{11}$ by HR-FAB-MS. Acid hydrolysis of **5** afforded DD-glucose and L-arabinose as component sugars. The ^{1}H- and ^{13}C-NMR spectra showed the signals assignable to the β-glucopyranosyl and α-arabinopyranosyl moieties. The ^{1}H- and ^{13}C-NMR signals

of the aglycon moiety of **5** were similar to those of **4** except for the absence of the oxygenated methylene (δ_H 3.94, δ_C 78.5) and the presence of an additional aliphatic methylene (δ_H 2.05, δ_C 41.1). Comprehensive collation of 2D NMR data from DQFCOSY, HMQC, total correlation spectroscopy (TOCSY) and HMBC experiments led to the construction of a (2*E*)-7-hydroxy-3,7-dimethyl-2-octene as the aglycone. The β-D-glucopyranosyl moiety linked to C-1 of the aglycon and the α-L-arabinopyranosyl moiety linked to the C-6 of the β-D-glucopyranosyl moiety were established by the HMBC correlations between δ_H 4.29 and δ_C 66.6, and δ_H 4.32 and δ_C 69.5. Thus, the structure of rhodioloside E (**5**) was determined as (2*E*)-7-hydroxy-3,7-dimethyl-2-octenyl α-L-arabinopyranosyl(1→6)-β-D-glucopyranoside.

Since *R. rosea* has been reported to have aniticancer effect,[1,2] we routinely tested the cytotoxic activity of these compounds **1**—**5** against three human cancer cell lines: human myeloid leukemia HL60 cells, human stomach KATO-III adenocarcinoma and human lung A_{549} adenocarcinoma,[16] but compounds **1**—**5** did not show any significant activity. Other biological testing is under way.

Experimental

General Experimental Procedures The IR spectra were measured with a JASCO FT/IR-300E (by a KBr disk method) spectrophotometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter in a 0.5-dm length cell. FAB-MS and HR-FAB-MS were taken on a JEOL JMS-700 MStation mass spectrometer. The ESI-MSs were taken on an LCQ mass spectrometer. The ^{1}H- and ^{13}C-NMR spectra were measured with a JEOL ECP-500 spectrometer or JEOL AL-400 spectrometer with TMS as the internal reference, and chemical shifts are expressed in δ (ppm). Column chromatography was carried out on silica gel H (Qingdao Factory of Marine Chemical Industry, P. R. China) and ODS (Chromatorex, 100—200 mesh, Fuji Sylisia Chemical, Ltd., Aichi, Japan). Preparative HPLC was performed using an ODS column (YMC-Pack Pro C18, 10 mm i.d.×250 mm, YMC Co., Ltd., Kyoto, Japan). GLC was carried out on a Perkin-Elmer Clarus 500 GC-MS instrument.

Plant Material The air-dried roots of *R. rosea* were collected at Tacheng, Xin-Jiang, P. R. of China, in October, 2003. The plant materials were identified by one of the authors (D.S.).

Extraction and Isolation The air-dried roots of *R. rosea* (6 kg) were refluxed twice with 80% aqueous EtOH (60 l, 48 l). The extract was concentrated, suspended in H_2O, and then partitioned with $CHCl_3$, EtOAc and *n*-BuOH, successfully. Evaporation of the *n*-BuOH yielded an *n*-BuOH fraction (700 g). The *n*-BuOH fraction (300 g) was subjected to silica gel column chromatography, and eluted with the mixture of $CHCl_3$–MeOH in gradient to give 8 fractions, A—H. Fr. D ($CHCl_3$–MeOH, 5 : 1) was further chromatographed on a silica gel column with $CHCl_3$–MeOH–H_2O (8 : 2 : 0.2 and 6 : 4 : 1) to furnish 4 fractions. The preparative HPLC separation of Fr. D2 with MeOH–H_2O (2 : 8) yielded compounds **4** (100 mg) and **1** (15 mg). Fr. D3 was further separated by HPLC with MeOH–H_2O (35 : 65) to give compounds **3** (69 mg) and **5** (36 mg). Fr. E was purified by HPLC with MeOH–H_2O (35 : 65) to give compound **2** (27 mg).

Rhodioloside A (**1**): Colorless viscous oil; $[\alpha]_D^{24}$ −32.3° (*c*=1.2, MeOH). IR (KBr) ν_{max} cm^{-1}: 3401, 2923, 1632, 1565, 1382, 1038. ^{1}H-NMR (CD_3OD, 500 MHz) and ^{13}C-NMR (CD_3OD, 125 MHz): see Tables 1 and 2. FAB-MS (positive) *m/z* 371 $[M+Na]^+$; HR-FAB-MS (positive) *m/z* 371.1681 $[M+Na]^+$ (Calcd for $C_{16}H_{28}O_8Na$, 371.1682).

Rhodioloside B (**2**): Colorless viscous oil; $[\alpha]_D^{24}$ +24.0° (*c*=1.0, MeOH). IR (KBr) ν_{max} cm^{-1}: 3416, 2925, 1632, 1565, 1382, 1029. ^{1}H-NMR (CD_3OD, 500 MHz) and ^{13}C-NMR (CD_3OD, 125 MHz): see Tables 1 and 2. FAB-MS (positive) *m/z* 517 $[M+Na]^+$; HR-FAB-MS (positive) *m/z* 517.2272 $[M+Na]^+$ (Calcd for $C_{22}H_{38}O_{12}Na$, 517.2261).

Rhodioloside C (**3**): Colorless viscous oil, $[\alpha]_D^{24}$ −18.3° (*c*=0.8, MeOH). IR (KBr) ν_{max} cm^{-1}: 3408, 2922, 1633, 1565, 1382, 1041. ^{1}H-NMR (CD_3OD, 500 MHz) and ^{13}C-NMR (CD_3OD, 125 MHz): see Tables 1 and 2. FAB-MS (positive) *m/z* 517 $[M+Na]^+$; HR-FAB-MS (positive) *m/z* 517.2252 $[M+Na]^+$ (Calcd for $C_{22}H_{38}O_{12}Na$, 517.2261).

Rhodioloside D (**4**): Colorless viscous oil, $[\alpha]_D^{24}$ −25.2° (*c*=0.9, MeOH). IR (KBr) ν_{max} cm^{-1}: 3392, 2925, 1632, 1565, 1382, 1075. ^{1}H-NMR (CD_3OD, 500 MHz) and ^{13}C-NMR (CD_3OD, 125 MHz): see Tables 1 and 2. FAB-MS (positive) *m/z* 373 $[M+Na]^+$; HR-FAB-MS (positive) *m/z* 373.1849 $[M+Na]^+$ (Calcd for $C_{16}H_{30}O_8Na$, 373.1838).

Rhodioloside E (**5**): Colorless viscous oil, $[\alpha]_D^{24}$ −36.4° (*c*=1.0, MeOH). IR (KBr) ν_{max} cm^{-1}: 3401, 2925, 1632, 1565, 1381, 1041. ^{1}H-NMR (CD_3OD, 500 MHz) and ^{13}C-NMR (CD_3OD, 125 MHz): see Tables 1 and 2. FAB-MS (positive) *m/z* 489 $[M+Na]^+$; HR-FAB-MS (positive) *m/z* 489.2324 $[M+Na]^+$ (Calcd for $C_{21}H_{38}O_{11}Na$, 489.2312).

Enzymatic Hydrolysis of 1, 2, 3 and 4 A solution of **1** (7.0 mg) in 0.1 M acetate buffer (pH 4.0, 1.0 ml) was treated with naringinase (Sigma Chemical Co., 2 units), and then the reaction mixture was stirred at 40 °C for 12 h. The reaction mixture was passed through a Diaion HP-20 column, and washed with H_2O and MeOH. The MeOH fraction was chromatographed over a silica gel column to give the aglycon rhodiolol A (**1a**, 2.8 mg, eluted with $CHCl_3$–MeOH, 92 : 8). Through a similar procedure, enzymatic hydrolysis of **2** (8.0 mg), **3** (7.1 mg) and **4** (9.9 mg) was carried out to afford the aglycons, (−)-rosilidol (**2a**, 1.9 mg; **3a**, 0.5 mg) and sachalinol A (**4a**, 3.7 mg).

Rhodiolol A (**1a**): $[\alpha]_D^{24}$ −1.5° (*c*=0.3, MeOH); IR (KBr) ν_{max} cm^{-1}: 3424, 2924, 1632, 1440, 1016. ^{1}H-NMR (CD_3OD, 500 MHz) δ: 5.55 (1H, t, *J*=6.7 Hz, H-2), 5.39 (1H, t, *J*=7.0 Hz, H-6), 4.12 (2H, d, *J*=6.7 Hz, H_2-1), 3.99 (1H, t, *J*=6.7 Hz, H-4), 3.92 (2H, br s, H_2-8), 2.29 (2H, t, *J*=6.9 Hz, H_2-5), 1.65 (3H, s, H_3-9), 1.65 (3H, s, H_3-10); ^{13}C-NMR (CD_3OD, 125 MHz) δ: 140.6 (C-3), 137.7 (C-7), 126.3 (C-2), 122.9 (C-6), 77.9 (C-4), 68.9 (C-8), 59.3 (C-1), 34.5 (C-5), 14.0 (C-9), 11.9 (C-10). ESI-MS (positive) *m/z* 209 $[M+Na]^+$.

Compounds **2a** and **3a**: $[\alpha]_D^{24}$ −7.1° (*c*=0.1, acetone); $[\alpha]_D^{24}$ −21.1° (*c*=0.1, $CHCl_3$); ref.: $[\alpha]_D^{24}$ −7.7° (*c*=1.0, acetone).[15] The ^{1}H-NMR spectra of **2a** and **3a** were identical with that in reference.[15]

Compound **4a**: $[\alpha]_D^{24}$ −17.0° (*c*=0.4, MeOH); ref.: $[\alpha]_D^{24}$ −17.1° (*c*=1.0, MeOH).[7] The ^{1}H-NMR spectrum of **4a** was identical with that in reference.[7]

Pivaloylation of 1a and 2a A solution of **1a** (2.1 mg) in dry pyridine (1.0 ml) was treated with pivaloyl chloride (13 μl), and the mixture was stirred at room temperature for 12 h. After addition of H_2O (1 ml), the mixture was extracted with EtOAc (2 ml×3), dried over Na_2SO_4, and purified with silica gel column chromatography ($CHCl_3$) to give the pivaloyl ester **1b** (3.7 mg). Through a similar procedure, pivaloylation of **2a** (1.9 mg) afforded the pivaloyl ester **2b** (1.3 mg).

Compound **1b**: ^{1}H-NMR ($CDCl_3$, 400 MHz): δ: 5.59 (1H, t, *J*=6.7 Hz, H-2), 5.44 (1H, t, *J*=7.0 Hz, H-6), 4.62 (2H, d, *J*=6.7 Hz, H_2-1), 4.47 (2H, br s, H_2-8), 4.09 (1H, t, *J*=6.7 Hz, H-4), 2.33 (2H, t, *J*=7.0 Hz, H_2-5), 1.72 (3H, s, H_3-9), 1.67 (3H, s, H_3-10).

Compound **2b**: ^{1}H-NMR ($CDCl_3$, 400 MHz): δ: 5.59 (1H, t, *J*=6.7 Hz, H-2), 5.10 (1H, t, *J*=7.4 Hz, H-6), 4.62 (2H, d, *J*=6.7 Hz, H_2-1), 4.03 (1H, t, *J*=6.4 Hz, H-4), 2.27 (2H, t, *J*=7.1 Hz, H_2-5), 1.73 (3H, s, H_3-9), 1.71 (3H, s, H_3-10), 1.64 (3H, s, H_3-8).

(*S*)- and (*R*)-MTPA Derivatives of 1b and 2b A solution of **1b** (1.0 mg) in dry pyridine (0.1 ml) was added (−)-MTPA chloride (10 ml) at room temperature. After being stirred at room temperature for 4 h, the mixture was evaporated to dryness and purified by RP-HPLC with 90% MeOH to give (*S*)-MTPA ester **1c** (1.22 mg). Using a similar procedure, treatment of **1b** (1.0 mg) with (+)-MTPA chloride afforded (*R*)-MTPA ester **1d** (1.28 mg). (*S*)-MTPA ester **2c** (0.6 mg) and (*R*)-MTPA ester **2d** (0.9 mg) were obtained from **2b** (each 0.6 mg).

(*S*)-MTPA Ester of **1b** (**1c**): ^{1}H-NMR ($CDCl_3$, 400 MHz): δ: 5.60 (1H, t, *J*=6.4 Hz, H-2), 5.38 (1H, t, *J*=5.5 Hz, H-4), 5.36 (1H, t, *J*=6.4 Hz, H-6), 4.59 (1H, dd, *J*=13.0, 6.4 Hz, H-1), 4.54 (1H, dd, *J*=13.0, 6.4 Hz, H-1), 4.42 (2H, br s, H_2-8), 2.56 (1H, m, H-5), 2.40 (1H, m, H-5), 1.64 (3H, s, H_3-9), 1.58 (3H, s, H_3-10).

(*R*)-MTPA Ester of **1b** (**1d**): ^{1}H-NMR ($CDCl_3$, 400 MHz): δ: 5.68 (1H, t, *J*=6.7 Hz, H-2), 5.40 (1H, dd, *J*=7.7, 6.0 Hz, H-4), 5.25 (1H, d, *J*=6.7 Hz, H-6), 4.63 (1H, dd, *J*=13.0, 6.7 Hz, H-1), 4.57 (1H, dd, *J*=13.0, 6.7 Hz, H-1), 4.36 (2H, br s, H_2-8), 2.50 (1H, m, H-5), 2.36 (1H, m, H-5), 1.72 (3H, s, H_3-10), 1.58 (3H, s, H_3-9).

(*S*)-MTPA Ester of **2b** (**2c**): ^{1}H-NMR ($CDCl_3$, 400 MHz): δ: 5.59 (1H, t, *J*=6.6 Hz, H-2), 5.33 (1H, dd, *J*=7.9, 5.7 Hz, H-4), 5.04 (1H, t, *J*=7.2 Hz, H-6), 4.60 (1H, dd, *J*=11.0, 5.5 Hz, H-1), 4.55 (1H, dd, *J*=11.0, 5.5 Hz, H-1), 2.49 (1H, m, H-5), 2.32 (1H, m, H-5), 1.70 (3H, s, H_3-9), 1.60 (3H, s, H_3-8), 1.60 (3H, s, H_3-10).

(*R*)-MTPA Ester of **2b** (**2d**): ^{1}H-NMR ($CDCl_3$, 400 MHz): δ: 5.67 (1H, t, *J*=6.5 Hz, H-2), 5.37 (1H, dd, *J*=7.6, 6.2 Hz, H-4), 4.92 (1H, t, *J*=7.3 Hz,

H-6), 4.63 (1H, dd, J=11.1, 6.5 Hz, H-1), 4.59 (1H, dd, J=11.1, 6.5 Hz, H-1), 2.42 (1H, m, H-5), 2.28 (1H, m, H-5), 1.72 (3H, s, H_3-10), 1.63 (3H, s, H_3-9), 1.54 (3H, s, H_3-8).

Acid Hydrolysis of 1—5 Each solution of **1**—**5** (each 0.5 mg), in 1 M HCl (dioxane–H_2O, 1 : 1, 200 ml) was heated at 100 °C for 1 h under an Ar atmosphere. After dioxane was removed, the solution was extracted with EtOAc (1 ml×3) to remove the aglycon. The aqueous layer was neutralized by passing through an ion-exchange resin (Amberlite MB-3, Organo, Tokyo, Japan) column, concentrated under reduced pressure to dryness, to give a residue of the sugar fraction. The residue was dissolved in pyridine (1 ml), to which 0.1 M L-cysteine methyl ester hydrochloride in pyridine (2 ml) was added. The mixture was kept at 60 °C for 1.5 h. After the reaction mixture was dried *in vacuo*, the residue was trimethylsilylated with 1-trimethylsilylimidazole (0.2 ml) for 2 h. The mixture was partitioned between *n*-hexane and H_2O (0.3 ml each) and the *n*-hexane extract was analyzed by GC-MS under the following conditions: capillary column, EQUITY^{TM}-1 (30 m× 0.25 mm×0.25 mm, Supelco); column temperature, 230 °C; injection temperature, 250 °C; carrier N_2 gas; detection in EI mode, ionization potential, 70 eV; ion-source temperature, 280 °C. D-Glucose and L-arabinose were confirmed by comparison of the retention times of their derivatives with those of D-glucose, L-glucose and L-arabinose derivatives prepared in a similar way.

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