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A new phenylpropanoid and an alkylglycoside from *Piper retrofractum* leaves with their antioxidant and α-glucosidase inhibitory activity

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ABSTRACT

Two new compounds, piperoside (**1**) and isoheptanol 2(*S*)-O-β-D-xylopyranosyl (1→6)-O-β-D-glucopyranoside (**11**), along with 10 known compounds 3,4-dihydroxyallylbenzene (**2**), 1,2-di-O-β-D-glucopyranosyl-4-allylbenzene (**3**), tachioside (**4**), benzyl-O-β-D-glucopyranoside (**5**), icariside F_2 (**6**), dihydrovomifoliol-3′-O-β-D-glucopyranoside (**7**), isopropyl O-β-D-glucopyranoside (**8**), isopropyl primeveroside (**9**), *n*-butyl O-β-D-glucopyranoside (**10**), isoheptanol 2(*S*)-O-β-D-apiofuranosyl-(1→6)-O-β-D-glucopyranoside (**12**), were isolated from the leaves of *Piper retrofractum*. Their structures were determined from 1D-NMR, 2D-NMR, and HR-ESI-MS spectral, a modified Mosher's method, and comparisons with previous reports. All of the isolated compounds showed modest α-glucosidase inhibitory (4.60 ± 1.74% to 11.97 ± 3.30%) and antioxidant activities under the tested conditions.

Piper retrofractum is widely distributed in tropical and subtropical regions of the world and is used medicinally in variety of preparations. In traditional medicine, *P. retrofractum* is often used as an anti-flatulent, expectorant, or antitussive agent. It exhibits antifungal, uterus-contractile, sedative-hypnotic, appetite-inducing, and counter-irritant properties and has been used to treat digestive and intestinal disorders.[1] The roots and fruits of *P. retrofractum* can act as stimulants and are used to treat asthma, bronchitis, hemorrhoids, fever, liver diseases, jaundice, edema, and abdominal pain.[1,2] Both the unripe and ripe fruits of *P. retrofractum* have been used as a spice in curries, preserves, and pickles. Phytochemical studies have characterized neurotrophic compounds,[2] as well as anti-obesity effects of alkaloids,[3] and the anti-leishmanial activity of amides and lignans found in *P. retrofractum*.[4] As part of an ongoing research program studying the bioactive components in *Piper* species, the methanolic extract of *P. retrofractum* was repeatedly fractionated through various column chromatographies (CC) containing silica gel, YMC C-18, and Diaion HP-20 resin, to isolate 12 compounds (see Fig. 1). Among them, two of which (**1** and **11**) are new discoveries. In addition, the α-glucosidase inhibitory and antioxidant activities of all of the isolated compounds were evaluated.

Compound **1**[5] was obtained as a pale yellow powder. The HR-ESI-MS spectrum showed a pseudo-molecular ion peak at *m/z* 383.1316 $[M+Na]^+$ (Calcd for $C_{16}H_{24}O_9Na$, 383.1318) which indicated a molecular formula of $C_{16}H_{24}O_9$. In addition, an ESI-MS/MS experiment on ion 383.1316 showed fragments $[M+Na-H_2O]^+$ at *m/z* 365.12, $[M+Na-C_6H_{10}O_5]^+$ at *m/z* 221.07, and $[M+Na-C_6H_{10}O_5-H_2O]^+$ at *m/z* 203.06 . The ^1H NMR spectrum contained signals corresponding to three aromatic protons H-2′ (δ_H 6.89, d, J = 1.8 Hz), H-5′ (δ_H 7.06, d, J = 8.4 Hz) and H-6′ (δ_H 6.76, dd, J = 1.8, 8.4 Hz), which indicate a 1,3,4-trisubtituted benzene ring system. Two double doublet methylene proton signals at δ_H 2.76 and 2.61 were assigned to benzylic methylene protons (H_2-3). The signals from an anomeric proton H-1″ (δ_H 4.82, d, J = 7.8 Hz) and carbinol protons at δ_H 3.36–3.84 indicated the presence of a sugar unit in the structure of **1** (see Table 1). The ^{13}C NMR spectrum showed signals from 16 carbons atoms, which is in good agreement with its molecular formula of $C_{16}H_{24}O_9$. Among these, a methoxy carbon (δ_C 56.7, 3′-OCH_3), two methylene carbons [δ_C 66.5 (C-1) and 40.5 (C-3)], an oxygenated methine carbon (δ_C 74.9, C-2), and six aromatic carbons (δ_C 135.2,

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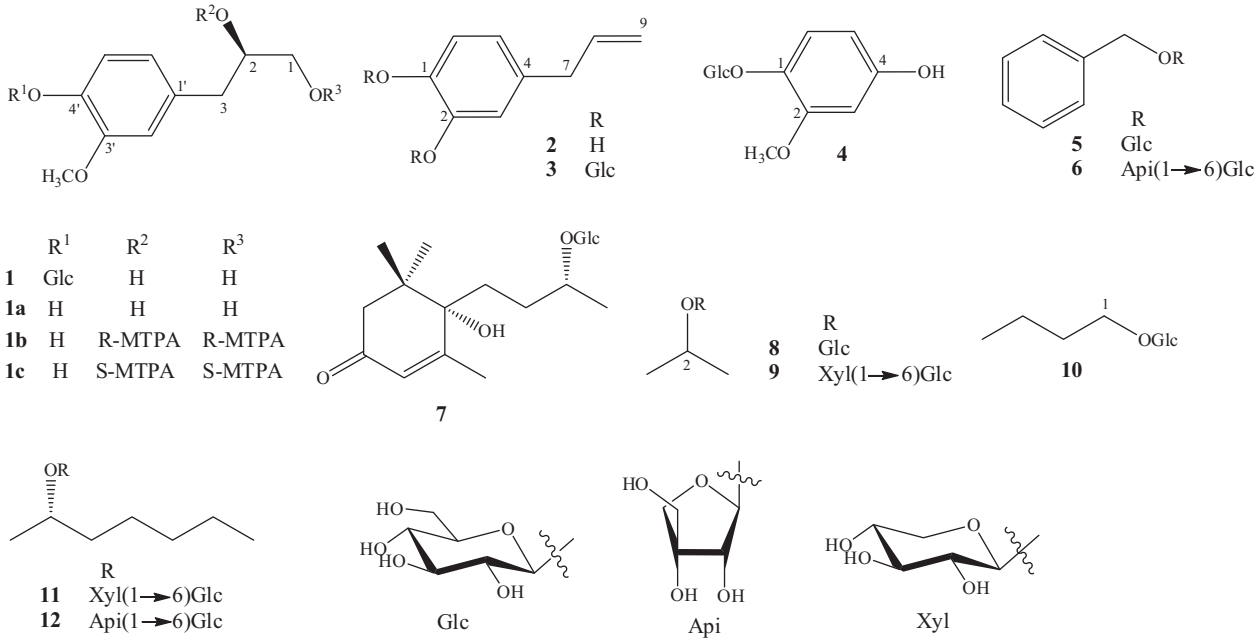

Figure 1. The structures of isolated compounds **1**–**12** from the leaves of *Piper retrofractum*.

Table 1
The NMR spectroscopic data for compounds **1**, **11**, and **12** (in CD_3OD)

Pos.	**1**		Pos.	**11**		**12**	
	δ_C[a]	δ_H[b] (mult., *J* in Hz)		δ_C[a]	δ_H[b] (mult., *J* in Hz)	δ_C[a]	δ_H[b] (mult., *J* in Hz)
1	66.5	3.46* 3.43*	1	22.1	1.20 (d, 6.6)	22.1	1.24 (d, 6.0)
2	74.9	3.17 (m)	2	77.8	3.78 (m)	77.9	3.78*
3	40.5	2.76 (dd, 6.0; 13.8) 2.61 (dd, 7.8; 13.8)	3	37.7	1.61 (m) 1.43*	37.7	1.63 (m) 1.44*
1′	135.2	—	4	33.2	1.30* 1.43*	33.2	1.31*
2′	115.0	6.89 (d, 1.8)	5	26.1	1.43* 1.33*	26.1	1.44* 1.34*
3′	150.5	—	6	23.7	1.33*	23.7	1.34*
4′	146.4	—	7	14.4	0.90 (t, 7.2)	14.4	0.92 (t, 7.8)
5′	118.1	7.06 (d, 8.4)	2-*O*-Glc			2-*O*-Glc	
6′	123.0	6.76 (dd, 1.8; 8.4)	1′	104.0	4.31 (d, 7.8)	104.0	4.31 (d, 7.8)
4′-*O*-Glc			2′	75.2	3.13*	75.2	3.16 (dd, 7.8, 9.0)
1″	103.0	4.82 (d, 7.8)	3′	78.0	3.30*	78.0	3.35 (t, 9.0)
2″	74.4	3.77*	4′	71.4	3.34*	71.7	3.27 (t, 9.0)
3″	78.1	3.36*	5′	76.9	3.39 (m)	76.7	3.40 (m)
4″	71.3	3.66*	6′	69.7	4.05 (dd, 2.4, 11.7) 3.73 (dd, 6, 11.1)	68.7	3.98* 3.60*
5″	77.8	3.44*	6′-*O*-Xyl			6′-*O*-Api	
6″	62.5	3.84* 3.67*	1″	105.5	4.33 (d, 7.2)	110.9	5.01 (d, 2.4)
3′-OMe	56.7	3.83 s	2″	74.8	3.18*	78.0	3.90 (d, 3.0)
			3″	77.7	3.30*	80.5	—
			4″	71.2	3.48 (m)	74.9	3.97* 3.77*
			5″	66.9	3.18* 3.85 (dd, 4.8, 11.7)	65.6	3.59*

Assignments were done by DEPT, HMQC, HMBC and COSY experiments.
[a] Measured at 150 MHz.
[b] Measured at 600 MHz.
* Overlapped signals.

115.0, 150.5, 146.4, 118.1, and 123.0) were detected. Basically, the 1D NMR spectral patterns of **1** were similar to those of Guaiacylglycerol 4-*O*-β-D-glucopyranoside with the exception of the appearance of methylene group and the loss of one hydroxyl group at C-3.[6] Careful examination of HMBC spectra revealed a correlation between the methoxy proton (δ_H 3.83) and C-3′ (δ_C 150.5). Furthermore, HMBC correlations H-2′ (δ_H 6.89)/C-3′ (δ_C 150.5), C-4′ (δ_C 146.4), C-6′ (δ_C 123.0), and C-3 (δ_C 40.5); H-5′ (δ_H 7.06)/C-3′ (δ_C 150.5), C-4′ (δ_C 146.4), and C-1′ (δ_C 135.2); and H-6′ (δ_H 6.76)/C-2′ (δ_C 115.0), C-4′ (δ_C 146.4), C-3 (δ_C 40.5) were also observed (see Fig. 2). These indicated the structure of a 3-(4′-hydroxy-3′-methoxyphenyl)propan-1,2-diol. The position of the glucosyl linkage in **1** was supported by an HMBC correlation between the anomeric proton H-1″ (δ_H 4.82, d, *J* = 7.8 Hz) and C-4′ (δ_C 146.4).

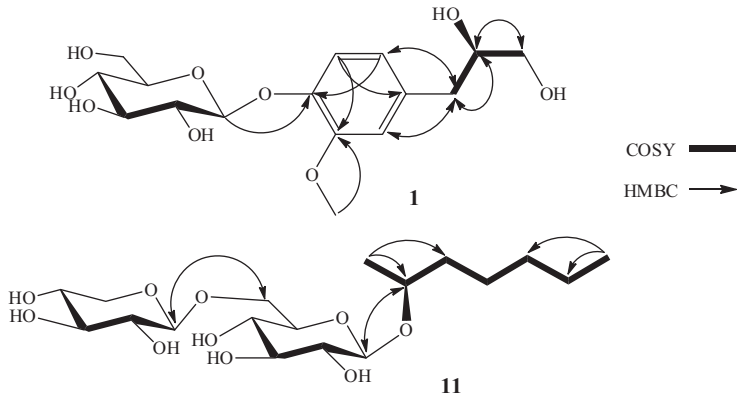

Figure 2. Important HMBC and COSY correlations for compounds **1** and **11**.

Thus, the glucose unit was bound to C-4′. Acid hydrolysis of **1** followed by TLC, GC analysis, and comparisons with authentic D-glucose, further confirmed the presence of D-glucose moiety in **1** (see Supporting information). Absolute configuration at C-2 of **1** was determined using a modified Mosher's method.[7,8] After acid hydrolysis, an aglycone **1a**[9] was individually reacted with (+) and (−) methoxytrifluoromethylphenylacetyl chlorides (MTPA-Cl) to obtain the (*R*)- and (*S*)-MTPA esters (**1b** and **1c**),[10,11] respectively (see Supporting information). The differences in the proton chemical shifts between the (*S*)-MTPA ester and the (*R*)-MTPA ester of **1a** (see Fig. 3) indicated an '*R*' configuration at C-2.[8] Consequently, compound **1** was identified as 2(*R*)-3-(4′-*O*-β-D-glucopyranosyl-3′-methoxyphenyl)propane-1,2-diol, a new phenylpropanoid glycoside that we have named piperoside.

Compound **11**[12] was obtained as a colorless oil. The HR-ESI-MS spectrum showed a pseudo-molecular ion peak at *m*/*z* 445.1848 $[M+Cl]^-$ (Calcd. for $C_{18}H_{34}O_{10}Cl$, 445.1846), which indicate a molecular formula of $C_{18}H_{34}O_{10}$. The ^1H NMR spectra of **11** contained signals corresponding to two methyl protons, which appeared as a doublet H-1 (δ_H 1.20, d, J = 6.6 Hz) and a triplet H-7 (δ_H 0.90, t, J = 7.2 Hz), an oxygenated methine proton H-2 (δ_H 3.78, m) and long chain methylene proton signals at δ_H 1.30 through 1.61. The signals of two anomeric protons H-1′ (δ_H 4.31, d, J = 7.8 Hz) and H-1″ (δ_H 4.33, d, J = 7.2 Hz) indicated the presence of two sugar units. The ^{13}C NMR spectra displayed seven carbon signals corresponding to aglycone moiety, including two methyls (δ_C 14.4, 22.1), four methylenes (δ_C 23.7, 26.1, 33.2, 37.7) and an oxygenated methine carbon atom (δ_C 77.8), together with eleven carbon resonant signals of the sugar moiety (δ_C 66.9 through 105.5). The 1D-NMR spectra of **11** was similar to those of Shimaurinoside B with the exception of the appearance of two more methylene groups.[13] Three individual correlations for the spin systems of H-1/H-2/H-3/H-4/H-5/H-6/H-7, H-1′/H-2′/H-3′/H-4′/H-5′/H-6′, and H-1″/H-2″/H-3″/H-4″/H-5″ were observed in the COSY spectra of **11**, which supports the backbone proton assignments of the aglycone moiety and the two sugar units. HMBC correlations of xylose H-1″ (δ_H 4.33)/glucose C-6′ (δ_C 69.7) and glucose H_2-6′ (δ_H 4.05, 3.73)/xylose C-1″ (δ_C 105.5) suggested the structure of a xylosyl(1→6)glucose disaccharide. The position of the sugar moiety in **11** was identified as C-2 based on HMBC correlations of the anomeric proton H-1′ (δ_H 4.31)/C-2 (δ_C 77.8) and H-2 (δ_H 3.78)/C-1′ (δ_C 104.0). In addition, acid hydrolysis experiments confirmed the presence of D-glucose and D-xylose in **11**. This conclusion was further supported by TLC, GC analysis, and comparisons with authentic D-glucose and D-xylose samples (see Supporting information). The stereochemistry at C-2 of **11** was determined by comparing the ^{13}C NMR data with those of previous reports. Agreement of the ^{13}C NMR chemical shift at C-2 (δ_C 77.8) of **11** with those of 2(*S*)- and 2(*R*)-pentanol-2-*O*-β-D-glucopyranoside [δ_C 78.2 for 2(*S*) and δ_C 75.1 for 2(*R*)] suggested an '*S*' configuration at C-2.[13] Thus, compound **11** was identified as 2(*S*) isoheptanol 2-*O*-β-D-xylopyranosyl (1→6)-*O*-β-D-glucopyranoside.

Compound **12** was isolated as a colorless oil. In general, the ^1H and ^{13}C NMR data of **12** were similar to those of **11**. The differences between the spectra of **11** and **12** were with regard to the sugar moiety. The presence of an anomeric proton signal H-1″ (δ_H 5.01, d, J = 2.4 Hz), an anomeric carbon signal C-1″ (δ_C 110.9), together with four other carbinol carbon signals C-2″ (δ_C 78.0), C-3″ (δ_C 80.5), C-4″ (δ_C 74.9), and C-5″ (δ_C 65.6) suggested the presence of an β-D-apiofuranose unit.[14] In addition, acid hydrolysis of **12** followed by TLC, GC analysis, and comparisons with authentic D-apiose, further confirmed the presence of D-apiose in **12** (see Supporting information). Thus, the xylose unit in **11** was replaced by an apiose moiety in **12**. The apiosyl(1→6)glucose disaccharide moiety was also confirmed by HMBC correlations H-1″ (δ_H 5.01)/C-6′ (δ_C 68.7) and H_2-6′ (δ_H 3.60, 3.98)/C-1″ (δ_C 110.9). Therefore,

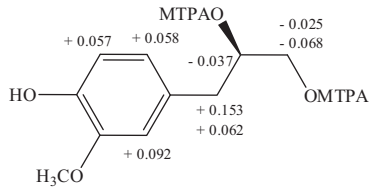

Figure 3. $\Delta\delta$ values ($\Delta\delta = \delta_S - \delta_R$ in ppm) obtained for MTPA esters **1b**/**1c**.

Table 2
Rat intestinal α-glucosidase inhibitory activities of compounds **1**–**12**

Compounds	% Enzyme inhibition
1	11.74 ± 2.58
2	9.08 ± 3.78
3	7.02 ± 5.49
4	4.60 ± 1.74
5	11.97 ± 3.30
6	7.93 ± 4.50
7	6.90 ± 4.39
8	7.31 ± 1.29
9	7.49 ± 4.50
10	9.75 ± 4.58
11	8.54 ± 2.94
12	8.62 ± 4.54
Acarbose*	50.96 ± 2.97

Percentage of enzyme inhibition at the concentration of 50 μM.
* Acarbose was used as positive controls. Data presented is the mean ± SD of samples run in triplicate.

Table 3
Antioxidant activities of compounds **1–12**

Compounds	$ORAC^{*}_{RCOO}$ (TE, μM)		Reduction power (Copper(I) ion, μM)		Cu^{2+} chelating activity (% vs control)
	1 μM	10 μM	1 μM	10 μM	10 μM
1	0.55 ± 0.18	2.88 ± 0.17	0.29 ± 0.19	0.96 ± 0.03	24.21 ± 1.18
1a	3.59 ± 0.80	28.20 ± 0.28	9.01 ± 0.06	43.82 ± 0.57	25.00 ± 0.90
2	2.55 ± 0.12	16.26 ± 0.50	1.55 ± 0.06	22.77 ± 0.28	20.48 ± 1.14
3	0.17 ± 0.20	1.71 ± 0.11	0.32 ± 0.11	0.65 ± 0.06	21.80 ± 0.35
4	0.21 ± 0.06	1.65 ± 0.14	0.21 ± 0.06	0.63 ± 0.31	21.42 ± 0.64
5	0.18 ± 0.17	1.83 ± 0.17	0.41 ± 0.12	0.69 ± 0.04	22.39 ± 0.55
6	0.15 ± 0.10	1.61 ± 0.22	0.46 ± 0.06	0.84 ± 0.11	19.30 ± 0.46
7	0.12 ± 0.23	0.92 ± 0.09	0.21 ± 0.06	0.34 ± 0.23	20.50 ± 0.31
8	0.22 ± 0.17	1.79 ± 0.15	0.29 ± 0.23	0.54 ± 0.15	20.97 ± 0.29
9	0.31 ± 0.22	2.13 ± 0.16	0.27 ± 0.09	0.63 ± 0.07	21.67 ± 1.43
10	0.62 ± 0.07	3.64 ± 0.05	0.18 ± 0.06	1.68 ± 0.09	18.04 ± 0.72
11	0.48 ± 0.08	2.26 ± 0.18	0.17 ± 0.08	0.59 ± 0.04	20.58 ± 0.37
12	1.04 ± 0.13	3.07 ± 0.12	0.34 ± 0.26	1.13 ± 0.13	19.63 ± 1.24

the structure of **12** was proposed to be isoheptanol 2-*O*-β-D-apiofuranosyl (1→6)-*O*-β-D-glucopyranoside, a new alkylglycoside isolated from *Hedychium yunnanense*.[15] Although the structure of compound **12** has been reported previously, the absolute configuration at C-2 of **12** has not been identified. Similar to compound **11**, the absolute configuration at C-2 was proposed to be '*S*' based on a comparison of the chemical shift of C-2 (δ_C 77.9) with those of 2(*S*)- and 2(*R*)-pentanol-β-D-glucopyranoside ['*S*'-form (δ_C 78.2), '*R*'-form (δ_C 75.1)].[13] Compound **12** was therefore identified as 2(*S*) isoheptanol 2-O-β-D-apiofuranosyl (1→6)-O-β-D-glucopyranoside.

The remaining compounds were identified as 3,4-dihydroxyallylbenzene (**2**),[16] 1,2-di-O-β-D-glucopyranosyl-4-allylbenzene (**3**),[17] tachioside (**4**),[18] benzyl-O-β-D-glucopyranoside (**5**),[19] icariside F_2 (**6**),[20] dihydrovomifoliol-O-β-D-glucopyranoside (**7**),[21] isopropyl O-β-D-glucopyranoside (**8**),[22] isopropyl primeveroside (**9**),[23] and *n*-butyl O-β-D-glucopyranoside (**10**),[24] (see Fig. 1). Their structures were established based on spectroscopic and chemical evidence, which was in good agreement with those reported in literatures.

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by high blood glucose levels due to a deficiency in insulin secretion or/and insulin action. It has been estimated that diabetes affects approximately 4% of the worldwide population, which is expected to increase to 5.4% by 2025.[25] Intestinal α-glucosidase is found in the epithelium of the small intestine and is a key enzyme in carbohydrate digestion and glucose absorption. The inhibition of intestinal α-glucosidase can therefore delay the hydrolysis of carbohydrates and consequently reduce the incidence of postprandial hyperglycemia.[26,27] Therefore, administration of α-glucosidase inhibitors is a plausible treatment for DM-type 2 and obesity.[28,29] Compounds **1–12** were evaluated for their α-glucosidase inhibitory activity at a concentration of 50 μM. Acarbose was used as the positive control with an inhibition of 50.96 ± 2.97% at a concentration of 50 μM. The compounds isolated from *P. retrofractum* exhibited moderate α-glucosidase inhibitory activity. The percentage of enzyme inhibition ranged from 4.60 ± 1.74% (**4**) to 11.97 ± 3.30% (**5**) at the same concentration (see Table 2). The antioxidant activities of compounds **1–12** were then measured using the oxygen radical absorbance capacity (ORAC), cupric ion reducing antioxidant capacity (CUPRAC), and metal chelating activity assays. Compound **2** showed a moderate peroxyl radical scavenging activity and a reducing potential with ORAC and CUPRAC values of 16.26 ± 0.50, 22.77 ± 0.28 fold higher than those of the positive control (1.0 μM of Trolox), respectively. The other isolated compounds exhibited relatively weak activities under the test conditions. At a concentration of 50 μM, all of the compounds also exhibited weak metal chelating activities (see Table 3). According to previous study, aglycone **1a** was reported in a mixture of both S-form and R-form. S-form was presented as major component. This mixture exhibited potentially antioxidant activities.[30] Thus, **1a** was also evaluated for antioxidant activities using the same method. The results showed that **1a** exhibited greater peroxyl radical scavenging activity and a reducing potential activities than compound **1** with ORAC and CUPRAC values of 28.20 ± 0.28, 43.82 ± 0.57 at concentration of 10.0 μM, respectively. While **1a** also showed weak Cu^{2+} chelating activity at 50.0 μM (see Table 3). These implied that the present of glucose may decrease the peroxyl radical scavenging activity and a reducing potential activities but it do not effect for metal chelating activity on phenolic compound with a one hydroxy group on the aromatic ring.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.07.057.

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5. *Piperoside* (***1***)*:* Pale yellow powder; $[\alpha]_D^{22}$ +186.6 (c 0.32, MeOH); UV (MeOH) λ_{max} (log ε): 274 (3.36) nm; IR (KBr) ν_{max}: 3357, 2927, 1655, 1512, 1072 cm^{-1}; HR-ESI-MS *m/z* 383.1316 $[M+Na]^+$ (Calcd for $C_{16}H_{24}O_9Na$, 383.1318); ^1H and ^{13}C NMR data are given in the Table 1.
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9. *3-(4-Hydroxy-3-methoxy-phenyl)propane-1,2-diol* (***1a***)*:* Colorless oil; $[\alpha]_D^{25}$ +29.1° (MeOH; *c* 0.15); ^1H NMR (CD_3OD, 400 MHz): δ 2.63 (1H, dd, *J* = 7.6; 13.8 Hz, H-3a), 2.76 (1H, dd, *J* = 5.6; 13.8 Hz, H-3b), 3.46 (1H, ddd, *J* = 4.0; 4.0; 12.0 Hz, H-1a), 3.53 (1H, ddd , *J* = 4.0; 4.0; 12.0 Hz, H-1b), 3.80 (1H, m, H-2), 3.87 (3H, s, 3′-OCH_3), 6.69 (1H, dd, *J* = 2.0; 8.0 Hz, H-6′), 6.73 (1H, d, *J* = 8.0 Hz, H-5′), 6.86 (1H, d, *J* = 2.0 Hz, H-2′). ^{13}C NMR (CD_3OD, 100 MHz): δ 40.5 (C-3), 56.4 (OCH_3), 66.6 (C-1), 74.7 (C-2), 114.2 (C-2′), 116.0 (C-5′), 122.9 (C-6′), 131.6 (C-1′), 145.9 (C-4′), 148.8 (C-3′).

10. *(R)-MTPA ester (**1b**):* Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.822 (1H, dd, J = 6.1; 13.8 Hz, H-3a), 2.913 (1H, dd, J = 7.2; 13.8 Hz, H-3b), 4.232 (1H, dd, J = 5.6; 12.3 Hz, H-1a), 4.676 (1H, dd, J = 2.8; 12.3 Hz, H-1b), 5.553 (1H, m, H-2), 6.623 (1H, dd, J = 1.7, 8.0 Hz, H-6′), 6.678 (1H, d, J = 1.7 Hz, H-2′), 6.849 (1H, d, J = 8.0 Hz, H-5′), 7.244–7.470 (H-MTPA).
11. *(S)-MTPA ester (**1c**):* Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.975 (2H, d, J = 7.2 Hz, H_2-3), 4.207 (1H, dd, J = 4.0; 12.2 Hz, H-1a), 4.608 (1H, dd, J = 1.2; 12.2 Hz, H-1b), 5.516 (1H, m, H-2), 6.681 (1H, dd, J = 2.0, 8.1 Hz, H-6′), 6.770 (1H, br s, H-2′), 6.906 (1H, d, J = 8.1 Hz, H-5′), 7.210–7.469 (H-MTPA).
12. *(2S)-Isoheptanol 2-O-β-D-xylopyranosyl (1→6)-O-β-D-glucopyranoside (**11**):* Colorless oil; $[\alpha]_D^{21}$ −74.4° (MeOH; *c* 0.04); IR (KBr) ν_{max}: 3372, 2930, 1074 cm^{-1}; HR-ESI-MS *m/z* 445.1848 $[M+Cl]^-$ (Calcd for $C_{18}H_{34}O_{10}Cl$, 445.1846); ^{1}H and ^{13}C NMR data are given in the Table 1.
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