Phlomisflavosides A and B, New Flavonol Bisglycosides from *Phlomis spinidens*

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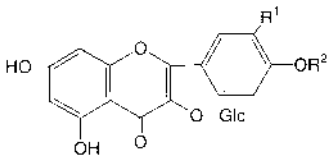
From the aerial parts of *Phlomis spinidens*, two new flavonol bisglycosides, phlomisflavosides A (1) and B (2), were isolated together with the known compounds, astragalin, isoquercitrin, lamiridoside, phlomoside A, shanzhiside methyl ester, 8-*O*-acetylshanzhiside methyl ester, phlorigidoside C, rodioloside (=salidroside), forsythoside B, citroside A and lariciresinol-4′-*O*-β-D-glucoside. The structures of the new compounds were elucidated based on spectral and chemical evidence.

Key words *Phlomis spinidens*; Labiatae; phlomisflavoside A; phlomisflavoside B; flavonol bisglycoside

The plants classified to the genus *Phlomis* (Labiatae) have been known to contain several classes of compounds: iridoid glucosides,[1)] phenyl-ethanoid glycosides,[2)] flavonoid glycosides,[3)] diterpene glycosyl ester,[4)] and nortriterpenes.[5)] During the course of our studies on the constituents of traditional medicine and related plant material in the Uzbekistan Republic, we examined the glycosidic constituents of *Phlomis spinidens* NEVSKI (local name: Kuz kulok) which was used for treatment of allergy,[6)] and isolated two new flavonol bisglycosides, termed phlomisflavosides A (**1**) and B (**2**) together with the known compounds, astragalin (**3**),[7)] isoquercitrin (**4**),[8)] lamiridoside,[9)] phlomoside A,[1a)] shanzhiside methyl ester,[10)] 8-*O*-acetylshanzhiside methyl ester,[11)] phlorigidoside C,[1d)] rodioloside (=salidroside),[12)] forsythoside B,[13)] citroside A[14)] and lariciresinol-4′-*O*-β-D-glucoside.[15)] This paper describes isolation and structure elucidation of the new compounds.

Compound **1** was isolated as yellow colored amorphous powder, $[\alpha]_D$ −140° (50% aq. pyridine) and gave a positive coloration in the Mg–HCl test. The molecular formula was assigned as $C_{26}H_{28}O_{16}$ based on its negative ion high resolution (HR)-FAB-MS. The UV spectrum showed maxima at 257 and 351 nm, and the IR spectrum exhibited absorption bands ascribed to hydroxyls (3400 cm^{-1}), α,β-unsaturated ketone (1655 cm^{-1}) and aromatic rings (1606, 1502 cm^{-1}). Thus, **1** was suggested to be flavonol glycoside from its characteristic color reaction and spectral properties. In systematic investigation of the UV spectra, bathochromic shifts were observed on addition of sodium acetate and aluminum chloride, indicating that hydroxyl groups are located at C-5 and C-7 positions. Acetylation of **1** gave the decaacetate (**1a**) [δ_H 1.92, 2.00, 2.03, 2.07, 2.12, 2.14, 2.16, 2.34, 2.37, 2.45 (each 3H, s)]. The ^{1}H-NMR spectrum of **1** in DMSO-d_6 showed an ABX system due to 1,3,4-trisubstituted aromatic ring and two *meta*-coupled doublets assigned to H-6 and H-8. Thus, the aglycone part of **1** was analyzed as quercetin. The ^{1}H-NMR spectrum also showed signals due to anomeric protons at δ 5.37 (1H, d, J=7.7 Hz, H-1″) and 5.58 (1H, d, J=2.9 Hz, H-1‴). The ^{13}C-NMR spectrum (Table 1) showed, in addition to the signals due to those of the aglycone part, the presence of β-glucopyranose and β-apiofuranose moieties which are linked to different oxygen atoms. GC analysis of the methanolysis product of **1** revealed the presence of glucose and apiose moieties in the structure.[16)] The ^{13}C-signals due to the aglycone part and β-glucopyranose unit are essentially the same as those of **4**, whereas the signals due to ring B are slightly different from those of **4**. On irradiation of the anomeric proton of apiofuranose moiety [δ_H 5.58], a differential nuclear Overhauser enhancement (NOE) was observed for the proton at δ 7.10 (H-5′) confirming that the apiofuranose unit was connected to *O*-4′. A heteronuclear multiple bond correlation (HMBC) experiment also supported these results. Thus, phlomisflavoside A was elucidated as shown as **1**. In fact, partial hydrolysis of **1** with HCl-dioxane gave **4**.

Compound **2** was also isolated as yellow colored amorphous powder, $[\alpha]_D$ −93.5° (50% aq. pyridine). The molecular formula was assigned as $C_{26}H_{28}O_{15}$ based on its negative ion HR-FAB-MS, which is one oxygen less than that of **1**. The ^{1}H-NMR spectrum of **2** exhibited A_2X_2 type signals at δ 7.10 and 8.08 (each 2H, d, J=9.0 Hz) instead of ABX type signals observed in **1**, and the other signals were very similar to those of **1**. GC analysis of the methanolysis product of **2** revealed the presence of glucose and apiose moieties in the structure,[16)] and the ^{13}C-NMR spectrum (Table 1) also reflected the above mentioned differences. Acetylation of **2** gave nonaacetate (**2b**) [δ 1.92, 2.00, 2.02, 2.08, 2.11, 2.15, 2.16, 2.34, 2.45 (each, 3H, s)]. On irradia-



(**1**) R^1=OH ; R^2=Api
(**2**) R^1=H ; R^2=Api
(**3**) R^1=R^2=H
(**4**) R^1=OH ; R^2=H

Glc : β-D-glucopyranosyl
Api : β-apiofuranosyl

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Table 1. ^{13}C-NMR Data for **1**, **2** and **4**

C	**1**[a)]	**2**[b)]	**4**[b)]
2	155.6 (158.4)	158.4	158.2
3	134.2 (136.0)	135.9	135.6
4	177.3 (179.5)	179.4	179.3
5	161.1 (163.0)	162.9	162.8
6	99.3 (100.0)	100.1	99.9
7	166.0 (166.1)	166.2	165.9
8	94.0 (94.8)	94.9	94.8
9	156.8 (158.4)	158.4	158.9
10	103.6 (105.8)	105.7	105.5
1′	124.5 (125.8)	125.1	123.2
2′	116.7 (116.7)	132.0	116.0
3′	146.8 (147.7)	116.9	145.7
4′	147.0 (148.6)	160.6	149.8
5′	116.4 (118.0)	116.9	117.6
6′	121.1 (122.7)	132.0	122.9
1″	101.7 (104.2)	104.2	104.6
2″	74.2 (75.7)	75.7	75.7
3″	76.6 (78.0)[c)]	78.0[d)]	78.0
4″	70.2 (71.2)	71.3	71.1
5″	77.3 (78.2)[c)]	78.3[d)]	78.2
6″	61.2 (62.6)	62.6	62.5
1‴	108.1 (109.4)	108.4	
2‴	76.5 (78.3)[c)]	78.4[d)]	
3‴	78.7 (80.4)	80.4	
4‴	74.6 (75.9)	75.8	
5‴	63.4 (64.9)	64.8	

a) Measured in DMSO-d_6. The figures in parentheses are for CD_3OD solution. *b*) Measured in CD_3OD. *c*—*d*) May be interchanged.

tion at δ 5.60 due to the anomeric proton of apiofuranose moiety, a differential NOE for the signal at δ 7.10 was observed. Thus, phlomisflavoside B was elucidated as shown as **2**. In fact, partial hydrolysis of **2** with 2% HCl-MeOH gave **3**.

Experimental

Optical rotations were measured on a JASCO DIP-360 digital polarimeter. IR spectra were measured on a Horiba Fourier transform infrared spectrometer and UV spectra on a JASCO V-530 SR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were taken on a JEOL JNM EX-400 or α-400 spectrometer at 400 and 100 MHz with tetramethylsilane as an internal standard. HR-FAB-MS were performed on a JEOL JMS SX-102 spectrometer with polyethylene glycol-400 or 600 as calibration matrices. Column chromatography was performed on Diaion HP-20 (Mitsubishi Chemical Co. Ltd., Tokyo), silica gel 60 (230—400 mesh, Merck) and Lober LiChroprep RP-18 column (40—63 μm, ϕ=25 mm, L=310 mm, Merck), and TLC and preparative TLC were performed on precoated silica gel plate 60 F_{254} (0.25 and 0.5 mm in thickness, Merck). HPLC was performed on octadecylsilica gel (Cosmosil 5C18AR, Nacalai Tesque, Kyoto, ϕ=20 mm, L=250 mm) with a mixture of H_2O and MeOH at a flow rate of 6 ml/min, and the eluate was monitored by UV (230 nm).

Plant Material The aerial parts of *Phlomis spinidens* Nevski were harvested in June, 1997, in Uzbekistan Republic and identified by Dr. F. O. Khassanof of the Institute of Botany, Academy of Sciences, Uzbekistan Republic. A voucher specimen (97B051) is deposited in the Herbarium of the Graduate School of Pharmaceutical Sciences, Kyoto University.

Extraction and Isolation The dried aerial parts (2.7 kg) of *P. spinidens* were extracted with MeOH (27 l×2) for 3 weeks at room temperature. The MeOH extract was concentrated *in vacuo* to give a residue which was dissolved in 90% MeOH (1 l). The 90% MeOH solution was washed with *n*-hexane (1 l×3) and then concentrated *in vacuo*. The residue was suspended in H_2O (1 l) and the suspension was extracted with EtOAc (1 l×3) and *n*-BuOH (1 l×3), successively. The *n*-BuOH extract was concentrated *in vacuo* to give a residue (56.7 g) which was chromatographed over Diaion HP-20 (ϕ=11 cm, L=35 cm) with a mixture of H_2O and MeOH with increasing MeOH content. Six liters of 0, 10, 30, 40, 50, 70% aqueous MeOH and MeOH were eluted collecting 1 l fractions. Fraction Nos. 14—20 were combined and concentrated *in vacuo* to give a residue (5.95 g) which was chromatographed over silica gel (400 g) with a mixture of $CHCl_3$ and MeOH with increasing amount of MeOH content. $CHCl_3$ (2.4 l), $CHCl_3$–MeOH (19 : 1, 2 l), $CHCl_3$–MeOH (9 : 1, 2.4 l), $CHCl_3$–MeOH (4 : 1, 3.4 l), $CHCl_3$–MeOH (3 : 1, 2.4 l) and $CHCl_3$–MeOH (7 : 3, 3.4 l) were eluted successively, collecting 200 ml fractions. Fraction Nos. 34—39 gave a residue (489 mg), an aliquot (101 mg) of which was separated by HPLC (solvent: MeOH–H_2O 1 : 4) to give shanzhiside methyl ester[10] (8.7 mg), phlorigidoside C[1d] (18.9 mg) and rodioloside (=salidroside)[12] (2.5 mg). Fraction Nos. 40—42 gave a residue (488 mg), an aliquot (100 mg) of which was separated by HPLC as above to give phlomoside A[12] (50.8 mg), shanzhiside methyl ester[10] (30.4 mg) and citroside A[14] (3.7 mg). Fraction Nos. 43—47 gave a residue (418 mg), an aliquot (200 mg) of which was separated by HPLC as above to give lamiridoside[9] (59.0 mg). Fraction Nos. 21—32 in the HP-20 chromatography were combined and concentrated *in vacuo* to give a residue (24.3 g) which was chromatographed over silica gel (1 kg) with a mixture of $CHCl_3$ and MeOH with increasing amounts of MeOH content. $CHCl_3$ (7.5 l), $CHCl_3$–MeOH (97 : 3, 7.5 l), $CHCl_3$–MeOH (19 : 1, 7.5 l), $CHCl_3$–MeOH (93 : 7, 5 l), $CHCl_3$–MeOH (9 : 1, 5 l), $CHCl_3$–MeOH (22 : 3, 7.5 l), $CHCl_3$–MeOH (17 : 3, 7.5 l), $CHCl_3$–MeOH (4 : 1, 7.5 l), $CHCl_3$–MeOH (7 : 3, 7.5 l) and MeOH (2.5 l) were eluted, collecting 500 ml fractions. Fraction Nos. 34—58 were combined and evaporated *in vacuo* to give a residue which was separated by chromatography over silica gel (solvent: $CHCl_3$–MeOH with increasing amount of MeOH) to give 8-*O*-acetylshanzhiside methyl ester[11] (116 mg). Fraction Nos. 101—130 were combined and evaporated *in vacuo* to give a residue (5.09 g) which was further separated by repeated chromatography over silica gel (solvent : $CHCl_3$–MeOH with increasing amounts of MeOH) and Lobar RP-18 (solvent: MeOH–H_2O, 7 : 13) to give phlomisflavoside A (**1**) (398 mg) and phlomisflavoside B (**2**) (56.6 mg). Fraction Nos. 33—35 in the HP-20 chromatography gave a residue (10.6 g) on evaporation *in vacuo* which was separated by repeated silica gel chromatography (solvent: $CHCl_3$–MeOH with increasing amount of MeOH content) and HPLC (solvent: MeOH–H_2O, 2 : 3) to give additional **1** (31.3 mg) and **2** (48.9 mg) together with astragalin (**3**)[7] (15.0 mg), isoquercitrin (**4**)[8] (74.3 mg), forsythoside B[13] (58.4 mg) and laricresinol-4′-*O*-β-D-glucoside[15] (5.2 mg). Compounds **1** and **2** showed *Rf* values (0.16 and 0.24, respectively) on silica gel TLC (solvent: $CHCl_3$–MeOH–H_2O, 15 : 6 : 1). Known compounds isolated were identified by comparisons of spectral data with those reported.

Compound 1 Yellow colored amorphous powder, $[\alpha]_D^{21}$ −140° (*c*= 0.55, 50% aq. pyridine). UV λ_{max} (MeOH) nm (log ε): 257 (4.39), 351 (4.24); λ_{max} (+$AlCl_3$) nm: 263, 273, 355, 398; λ_{max} (+$AlCl_3$+HCl) nm: 263, 273, 354, 398; λ_{max} (+NaOAc) nm: 274, 320, 368; (+CH_3ONa) nm: 272, 384; λ_{max} (+H_3BO_3) nm: 257, 351. IR ν_{max} (KBr) cm^{-1}: 3400, 1655, 1606, 1502. ^{1}H-NMR (DMSO-d_6, 90 °C) δ: 3.16 (1H, m, H-4″), 3.26 (2H, H-2″, 3″), 3.40 (1H, dd, *J*=11.8, 5.2 Hz, Ha-6″), 3.49 and 3.53 (each 1H, d, *J*=11.2 Hz, H-5‴), 3.59 (1H, dd, *J*=11.8, 2.0 Hz, H_b-6″), 3.78 and 4.08 (each 1H, d, *J*=9.4 Hz, H-4‴), 4.21 (1H, d, *J*=2.9 Hz, H-2‴), 5.37 (1H, d, *J*=7.7 Hz, H-1″), 5.58 (1H, d, *J*=2.9 Hz, H-1‴), 6.16 (1H, d, *J*=2.0 Hz, H-6), 6.34 (1H, d, *J*=2.0 Hz, H-8), 7.10 (1H, d, *J*=9.1 Hz, H-5′), 7.60 (1H, dd, *J*=9.1, 2.2 Hz, H-6′), 7.61 (1H, br s, H-2′), 12.37 (br s, 5-OH); (CD_3OD) δ: 3.22 (1H, m, H-5″), 3.33 (1H, dd, *J*=9.3, 9.3 Hz, H-4″), 3.42 (1H, dd, *J*=9, 9 Hz, H-3″), 3.47 (1H, dd, *J*=9.3, 7.3 Hz, H-2″), 3.56 (1H, dd, *J*=12.0, 5.4 Hz, H_a-6″), 3.68 (2H, s, H_2-5‴), 3.72 (1H, dd, *J*=12.0, 2.0 Hz, H_b-6″), 3.91 and 4.15 (each 1H, d, *J*=9.5 Hz, H-4‴), 4.35 (1H, br s, H-2‴), 5.29 (1H, d, *J*=7.3 Hz, H-1″), 5.66 (1H, br s, H-1‴), 6.20 (1H, br s, H-6), 6.39 (1H, br s, H-8), 7.18 (1H, d, *J*=8.5 Hz, H-5′), 7.64 (1H, dd, *J*=8.5, 1.5 Hz, H-6′), 7.71 (1H, br s, H-2′), ^{13}C-NMR: given in Table 1. HR-FAB-MS (negative) *m/z*: 595.1340 [M−H]$^-$ (Calcd for $C_{26}H_{27}O_{16}$: 595.1299).

Compound 2 Yellow colored amorphous powder, $[\alpha]_D^{22}$ −93.5° (*c*= 0.64, 50% aq. pyridine). UV λ_{max} (MeOH) nm (log ε): 265 (4.21), 344 (4.02); λ_{max} (+$AlCl_3$) nm: 275.5, 300, 341, 395; λ_{max} (+$AlCl_3$+HCl): 276, 300, 341, 395; λ_{max} (+NaOAc) nm: 274, 357.5; λ_{max} (+CH_3ONa) nm: 276, 372; λ_{max} (+H_3BO_3) nm: 265, 344. IR ν_{max} (KBr) cm^{-1}: 3402, 1655, 1606, 1502. ^{1}H-NMR (DMSO-d_6, 90 °C): 3.13—3.28 (3H, H-2″, 3″, 4″), 3.38 (1H, dd, *J*=11.7, 4.9 Hz, H_a-6″), 3.44, 3.49 (each 1H, d, *J*=11.1 Hz, H-5‴), 3.58 (1H, dd, *J*=11.7, 2.2 Hz, H_b-6″), 3.78, 4.07 (each 1H, d, *J*=9.3 Hz, H-4‴), 4.14 (1H, d, *J*=3.2 Hz, H-2‴), 5.36 (1H, d, *J*=7.1 Hz, H-1″), 5.60 (1H, d, *J*=3.2 Hz, H-1‴), 6.12 (1H, d, *J*=2.0 Hz, H-6), 6.31 (1H, d, *J*=2.0 Hz, H-8), 7.10 (2H, d, *J*=9.0 Hz, H-3′, 5′), 8.08 (2H, d, *J*=9.0 Hz, H-2′, 6′), 12.34 (1H, br s, 5-OH); (CD_3OD) δ: 3.21 (1H, m, H-5″), 3.39—3.46 (2H, H_2-2, 3), 3.53 (1H, dd, *J*=11.7, 5.4 Hz, H_a-6″), 3.65 (2H, s, H-5‴), 3.71 (1H, br d, *J*=11.7 Hz, H_b-6″), 3.91, 4.13 (each 1H, d, *J*=9.8 Hz, H-4‴), 4.26 (1H, br s, H-2‴), 5.26 (1H, d, *J*=7.3 Hz, H-1″), 5.68 (1H, br s, H-1‴), 6.20 (1H, br s, H-6), 6.40 (1H, br s, H-8), 7.13 (2H, d, *J*=8.3 Hz, H-3′, 5′), 8.12 (2H, d,

J=8.3 Hz, H-2′, 6′). ^{13}C-NMR: given in Table 1. HR-FAB-MS (negative) *m/z*: 579.1346 $[M-H]^-$ (Calcd for $C_{26}H_{27}O_{15}$: 579.1350).

Phlomisflavoside A Decaacetate (1b) Compound **1** (3.3 mg) was dissolved in pyridine (0.1 ml) and Ac_2O (0.1 ml) and the solution was kept overnight at 60 °C. Excess MeOH was added to the solution and the solvent was removed *in vacuo* to give a residue which was purified by preparative TLC (solvent: $CHCl_3$–Me_2CO, 9 : 1) to give the decaacetate (**1b**) (4.0 mg). ^{1}H-NMR ($CDCl_3$) δ: 1.92, 2.00, 2.03, 2.07, 2.12, 2.14, 2.16, 2.34, 2.37, 2.45 (each 3H, s, 10×OAc), 3.60 (1H, m, H-5″), 3.91 (1H, dd, J=12.5, 2.4 Hz, H_a-6″), 4.01 (1H, dd, J=12.5, 4.4 Hz, H_b-6″), 4.31, 4.39 (each 1H, d, J=10.7 Hz, H-4‴), 4.58 and 4.90 (each 1H, d, J=12.5 Hz, H-5‴), 5.06 (1H, dd, J=9.8, 9.8 Hz, H-3″), 5.18 (1H, dd, J=9.8, 7.8 Hz, H-2″), 5.29 (1H, dd, J=9.8, 9.8 Hz, H-4″), 5.58 (1H, d, J=7.8 Hz, H-1″), 5.66 (1H, s, H-2‴), 5.71 (1H, s, H-1‴), 6.83, 7.30 (each 1H, d, J=2.0 Hz, H-6 and/or H-8), 7.30 (1H, d, J=7.3 Hz, H-5′), 7.77 (1H, d, J=2.2 Hz, H-2′), 7.98 (1H, dd, J=7.3, 2.2 Hz, H-6′), HR-FAB-MS (positive) *m/z*: 1039.2377 $[M+Na]^+$ (+NaI) (Calcd for $C_{46}H_{48}O_{26}Na$: 1039.2331).

Phlomisflavoside B Nonaacetate (2b) Compound **2** (2.7 mg) was acetylated and the product purified as above to give the nonaacetate (**2b**) (2.8 mg). ^{1}H-NMR ($CDCl_3$) δ: 1.92, 2.00, 2.02, 2.08, 2.11, 2.15, 2.16, 2.34, 2.45 (each 3H, 9×OAc), 3.60 (1H, m, H-5″), 3.91 (1H, dd, J=12.2, 2.4 Hz, H_a-6″), 3.99 (1H, dd, J=12.2, 4.2 Hz, H_b-6″), 4.29 and 4.42 (each 1H, d, J=10.5 Hz, H-4‴), 4.68 and 4.87 (each 1H, d, J=12.4 Hz, H-5‴), 5.06 (1H, dd, J=9.8, 9.8 Hz, H-3″), 5.17 (1H, dd, J=8.1, 9.8 Hz, H-2″), 5.29 (1H, dd, J=9.8, 9.8 Hz, H-4″), 5.55 (1H, d, J=8.1 Hz, H-1″), 5.67 (1H, s, H-2‴), 5.74 (1H, s, H-1‴), 6.82, 7.29 (each 1H, d, J=2.2 Hz, H-6 and/or H-8), 7.11 (2H, d, J=8.8 Hz, H-3′, 5′), 8.00 (2H, d, J=8.8 Hz, H-2′, 6′). HR-FAB-MS (positive) *m/z*: 981.2286 $[M+Na]^+$ (+NaI) (Calcd for $C_{44}H_{46}O_{24}Na$: 981.2276).

Partial Hydrolysis of 1 Compound **1** (38.5 mg) was dissolved in a mixture of 1 N aq. HCl (1.5 ml) and dioxane (1.5 ml) and the solution was warmed at 60 °C for 15 min and then stirred at room temperature for 1 h. The solution was neutralized by addition of Ag_2CO_3 and the insoluble material was filtered off. The filtrate was concentrated *in vacuo*. The residue was purified by chromatography over silica gel (7 g, $CHCl_3$–MeOH with increasing amount of MeOH content) and HPLC (solvent: MeOH–H_2O, 9 : 11) to give isoquercitrin (**4**) (4.1 mg).

Partial Hydrolysis of 2 Compound **2** (37.3 mg) was dissolved in 2% HCl–MeOH (5 ml) and the solution was kept at 40 °C for 1.5 h. After cooling, the solution was worked up as above to give a residue which was purified by chromatography over silica gel (as above) and finally HPLC (solvent: MeOH–H_2O, 2 : 3) to give astragalin (**3**) (9.0 mg).

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