Iridoid Glycosides from *Eremostachys glabra*

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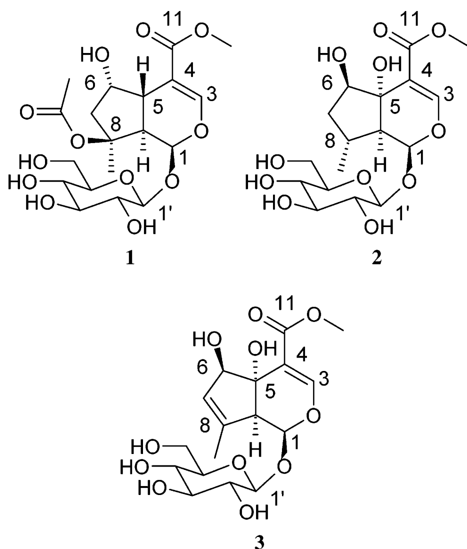
Reversed-phase preparative HPLC of a methanol extract of the rhizomes of *Eremostachys glabra* yielded three new iridoid glycosides, namely, 6,9-*epi*-8-*O*-acetylshanziside methyl ester (**1**), 5,9-*epi*-penstemoside (**2**), and 5,9-*epi*-7,8-didehydropenstemoside (**3**). Their structures were elucidated on the basis of spectroscopic data interpretation. The free-radical scavenging activity of these compounds was assessed using the DPPH assay.

Eremostachys glabra Boiss. (Lamiaceae), one of the 60 species of the genus *Eremostachys*, occurs mainly in central Asian countries.[1,2] In Iran, rhizomes of *E. glabra* have been used traditionally as a local analgesic and anti-inflammatory. While there is no report on any previous phytochemical investigation on *E. glabra* available to date, phytochemical studies on a few other species of *Eremostachys* have revealed the presence of flavonoids[1] and monoterpene glycosides.[3,4] We report herein on the isolation, structure elucidation, and assessment of free-radical scavenging activity (in the DPPH assay) of three new iridoid glycosides (**1**−**3**) from the rhizomes of *E. glabra*.

Preparative HPLC of a SepPak fraction (40% MeOH in water) of the MeOH extract of the rhizomes of *E. glabra* provided three new iridoid glycosides, for which the structures were deduced by UV, MS, and 1D and 2D NMR spectral data analyses.



The UV absorption spectra of **1**−**3** revealed their λ_{max}, respectively, at 236, 234, and 237 nm, indicative of the presence α,β-unsaturated carbonyl moiety within each of these molecules. Their ^{1}H NMR spectra (Table 1) displayed the signals (δ 7.44−7.55, H-3; δ 3.72−3.73, COOMe) corresponding to an enol ether system conjugated with a carbomethoxy group as found in various iridoid glycosides.[5−8] In the ^{1}H NMR spectrum (Table 1) of **1**, in addition to the signals attributable to a glucose moiety, an acetyl group, and an enol ether system with a carbomethoxy group, there were signals for the protons of two oxymethines (δ 5.91 and 4.33), two other methines (δ 3.06 and 2.99), a methylene group (δ 2.04 and 2.20), and a methyl group (δ 1.51). The ^{13}C NMR spectral data (Table 1) indicated the presence of signals for 18 carbons including four quaternary, 10 CH, two CH_2, and three CH_3 carbons. Among them, the signals at δ 100.5, 78.5, 78.3, 74.8, 71.8, and 63.2 were characteristic for a β-D-glucopyranosyl moiety. Signals at δ 173.0 and 22.4 could be assigned to an acetyl group, while resonances at δ 169.2, 153.8, 109.9, and 51.9 corresponded to an enol ether system with a carbomethoxy group. The remaining signals were assignable to two oxymethines (δ 95.9 and 76.1), an oxygenated quaternary (δ 89.9), a methylene (δ 47.8), two other methines (δ 42.5 and 50.1), and a methyl (δ 22.4). The deshielded nature of the methine (δ_H 5.91 and δ_C 95.9) was indicative of a methine linked directly to two oxygen atoms and was characteristic for the C-1 oxymethine of iridoid 1-glucosides.[5,8] Similar deshielding of the signal for the oxygenated quaternary at δ 89.9 confirmed its linkage to the acetyl group. In the HMBC spectrum (Table S1, Supporting Information), the ^3J correlations between δ_H 5.91 and δ_C 100.5 and between δ_H 4.63 and δ_C 95.9 confirmed the glucosylation at C-1. All these ^{1}H and ^{13}C NMR signals were comparable to those of 8-*O*-acetylshanziside methyl ester.[7] However, the ^{1}H NMR signal assigned to H-1 (δ_H 5.91) appeared as a clear doublet (J = 2.5 Hz) in **1** as opposed to a singlet in the reported ^{1}H NMR data for 8-*O*-acetylshanziside methyl ester.[5] The signals for H-9 and H-5 were double doublets (J = 2.5, 9.0 and 1.5, 9.0 Hz, respectively) in **1**, not broad singlets as was observed in 8-*O*-acetylshanziside methyl ester. These differences in coupling patterns observed for H-1, H-5, and H-9 indicated that the relative stereochemistry at the carbons C-1, C-5, and C-9 and the dihedral angle between H-1 and H-5 and between H-1 and H-9 in **1** could be different from that in 8-*O*-acetylshanziside methyl ester. The ^{1}H−^{1}H NOESY spectrum (Table S2, Supporting Information) of **1** revealed strong NOE interactions between

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Table 1. ^{1}H (500 MHz, coupling constants J in Hz in parentheses) and ^{13}C (125 MHz) NMR Data of Iridoid Glycosides **1–3**

	δ_H			δ_C		
position	**1**	**2**	**3**	**1**	**2**	**3**
1	5.91 d (2.5)	5.81 s	5.83 d (3.0)	95.9	95.9	95.1
3	7.44 d (1.5)	7.55 s	7.51 s	153.8	155.3	155.3
4				109.9	113.6	112.9
5	3.06 dd (1.5, 9.0)			42.5	73.6	73.8
6	4.33 m	4.28 t (4.5)	4.51 m	76.1	76.8	79.0
7	2.04 br dd	1.47 ddd (5.0, 6.5, 11.5)	5.53 m	47.8	40.6	129.1
	2.20 br d	1.80 ddd (4.5, 7.0, 11.5)				
8		2.60		89.9	31.5	143.6
9α	2.99 dd (2.5, 9.0)	2.57[a]	3.11 m	50.1	50.7	57.0
10α	1.51 s	0.94 d (7.0)	1.81 d (1.0)	22.4	16.6	15.9
11				169.2	168.3	168.4
OMe-11	3.72 s	3.73 s	3.72 s	51.9	51.7	51.8
OCO*CH*$_3$-8	2.01 s			22.4		
O*C*OCH$_3$-8				173.0		
1′	4.63 d (8.0)	4.57 d (8.0)	4.57 d (8.0)	100.5	99.8	100.1
2′	3.17 dd (8.0, 9.0)	3.18 dd (8.0, 9.0)	3.20 dd (8.0, 9.0)	74.8	74.4	74.5
3′	3.36 t (9.0)	3.37 t (9.0)	3.37 t (9.0)	78.5	77.5	77.6
4′	3.26 t (9.0)	3.25 t (9.0)	3.28 t (10.0)	71.8	71.7	71.8
5′	3.30[a]	3.30[a]	3.30[a]	78.3	78.5	78.7
6′	3.89 dd (2.0, 12.0)	3.91 dd (2.0, 12.0)	3.91 dd (2.5, 12.0)	63.2	62.9	63.0
	3.66 dd (6.0, 12.0)	3.65 dd (6.0, 12.0)	3.65 dd (6.0, 12.0)			

[a] Overlapped peaks identified from $^{1}H-^{1}H$ COSY and $^{1}H-^{13}C$ HMQC.

H-1 and H-9, H-1 and CH$_3$-10, H-9 and CH$_3$-10, and one of the methylene protons (H-7α, δ_H 2.04) and CH$_3$-10. These NOE interactions confirmed that H-1, H-9, CH$_3$-10, and H-7α (δ_H 2.04) were on the same face of the molecule. The NOE interactions H-5 ↔ H-6 ↔ H-7β (δ_H 2.20) ↔ OCOCH$_3$ (δ_H 2.01) ↔ H-6 established that H-5, H-6, H-7β, and the acetyl group were on the other face of the molecule. As most of the naturally occurring iridoid glycosides have been reported to have an α orientation for H-1,[5,8] in the structure of **1**, H-1, H-9, CH$_3$-10, and H-7α (δ_H 2.04) have been designated as α, and H-5, H-6, H-7β (δ_H 2.20), and OCOCH$_3$ as β. According to molecular models, there is greater rigidity and less flexibility in the *trans*-fused system than in the usual *cis*-fused iridoids, and hence the NOE interactions observed in the NOESY spectrum of **1** should be considered conclusive. The ESIMS revealed the [M + Na]$^+$ ion at *m/z* 471 in the positive-ion mode and the [M − H]$^-$ ion at *m/z* 447 in the negative-ion mode, which confirmed a molecular mass of 448 Da for **1**. Thus, the structure of **1** was proposed as 6,9-*epi*-8-*O*-acetylshanziside methyl ester. The *trans*-fused cyclopentanopyran ring system, as in **1**, has previously been found in *Penstemon* species.[9–11] However, in those compounds, unlike **1**, H-5 and H-9 were depicted respectively as α and β. It has been hypothesized that in the biosynthesis of *trans*-fused iridoid glycosides, deoxyloganic acid possibly serves as a precursor, and the inversion of relative stereochemistry at C-5 and C-9 takes place after the formation of the cyclopentanopyran ring system, not during the cyclization step from a monoterpene precursor.[9,10]

The ESIMS of **2** revealed the [M + Na]$^+$ ion at *m/z* 429 in the positive-ion mode and the [M − H]$^-$ ion at *m/z* 405 in the negative-ion mode, which indicated a molecular mass of 406 Da for this compound. The ^{1}H and ^{13}C NMR spectra (Table 1) of **2** showed characteristic signals for an iridoid glycoside.[5–8] The ^{13}C NMR spectrum displayed signals for 17 carbons, including five oxymethines (δ 99.8, 78.5, 77.5, 74.4, and 71.7) and an oxymethylene (δ 62.9) for the glucosyl moiety, a C-4 carbomethoxy group (δ 168.4 and 51.7), and nine carbons (δ 155.3, 113.6, 95.9, 76.8, 73.6, 50.7, 40.6, 31.5, and 16.6) for the iridoid skeleton. Among the signals for the iridoid skeleton, δ 155.3, 113.6, and 95.9 were typical of C-3, C-4, and C-1, respectively. On the basis of COSY, HMQC, and HMBC (Table S1, Supporting Information) spectral analyses, the ^{13}C NMR signals, 76.8, 73.6, 50.7, 40.6, 31.5, and 16.6, could be assigned respectively to C-6, C-5, C-9, C-7, C-8, and CH$_3$-10. The spectroscopic data were almost identical to those published for penstemoside.[12,13] However, the $^{1}H-^{1}H$ NOESY spectrum of **2** revealed NOE interactions among the protons (Table S2, Supporting Information), leading to the identification of **2** as an epimer of penstemoside. Strong NOE interactions were observed between H-1 and H-9, H-1 and CH$_3$-10, H-9 and CH$_3$-10, one of the methylene protons (H-7α, δ_H 1.47) and CH$_3$-10, and H-7α and H-6. A weak interaction between H-6 and CH$_3$-10 was also observed. These NOE interactions confirmed that H-1, H-6, H-9, CH$_3$-10, and H-7α (δ_H 1.47) are on the same face of the molecule. The NOE interactions H-8 ↔ H-7β (δ_H 1.80) established that H-8 and H-7β (δ_H 1.80) are on the other face of the molecule. As most of the naturally occurring iridoid glycosides have been reported to have an α orientation for H-1,[5,8] in the structure of **2**, H-1, H-6, H-9, CH$_3$-10, and H$_2$-7 (δ_H 1.47) have been designated as α, and H-8 and H-7β (δ_H 1.80) as β. It has been observed previously that when H-9 and the OH at C-5 are on the same face, the chemical shift of H-9 is normally above δ 2.20 because of its close proximity to the electronegative oxygen atom, whereas if they are opposite each other (*trans*), the signal appears at a more upfield region.[8,14] The ^{1}H NMR chemical shift of H-9 of **2** appeared at δ 2.57, which confirmed the α orientation of the OH group at C-5. In terms of stability of the configuration of **2**, it is more likely to have two bulky groups such as OH at C-5 and C-6 in opposite directions to minimize the repulsive force between them. As from the NOESY experiment it was established that H-6 was on the α face, confirming the β orientation of OH at C-6, the OH at C-5 should be opposite, α. Thus, the structure of **2** was confirmed as 5,9-*epi*-penstemoside.

The ESIMS of **3** revealed the [M + Na]$^+$ ion at *m/z* 427 in the positive-ion mode and the [M − H]$^-$ ion at *m/z* 403 in the negative-ion mode, which indicated a molecular mass of 404 Da for this compound. The molecular mass of **3** was 2 mass units (two hydrogens) less than that of **2**. The ^{1}H and ^{13}C NMR spectra (Table 1) of **3** were similar to those of **3**, with the exception that instead of the signals for the C-7 methylene, C-8 methine, and a methyl doublet (C-10, vicinal coupling J = 7.0 Hz), there were signals for an

olefinic methine (C-7, δ_H 5.53, δ_C 129.1), an olefinic quaternary carbon (C-8, 143.6), and a deshielded methyl doublet (C-10, long-range coupling J = 1.0, δ_H 1.81, δ_C 15.9). The $^1H-^1H$ COSY spectrum exhibited all expected $^1H-^1H$ correlations including some long-range couplings as well. The olefinic methine (H-7) showed vicinal coupling to oxymethine H-6 and long-range coupling (*zigzag*) to H-9 and C-10 methyl protons. Long-range couplings were also evident between the H-6 and C-10 methyl, which was also correlated (long-range) to H-1. In the $^1H-^{13}C$ HMBC spectrum (Table S1, Supporting Information), the CH_3-10 showed ^3J correlations to C-7 and C-9, and ^2J to C-8. The olefinic proton H-7 displayed ^3J correlations to C-5, C-9, and C-10, and ^2J to C-6. Thus the position of the double bond at C-7 was confirmed. The MS and ^1H and ^{13}C NMR data were similar to those published for dehydropenstemoside.[15] However, the ^1H NMR signal assigned to H-1 (δ_H 5.83) appeared as a clear doublet (J = 3.0 Hz) in **1**, as opposed to a singlet in the reported ^1H NMR data for dehydropenstemoside.[15] Detailed analysis of the NOE interactions using a $^1H-^1H$ NOSEY experiment (Table S2, Supporting Information) revealed that the compound **3** was actually an epimer of dehydropenstemoside, and the relative stereochemistry at C-1, C-5, C-9, and C-6 was exactly the same as that found in **2**. The deshielded nature of the H-9 chemical shift (δ_H 3.11) confirmed that the OH at C-5 must be on the same face as H-9. As H-9 has been depicted as α, the C-5 hydroxyl group should also be α. The introduction of the double bond between C-7 and C-8 rendered extra rigidity and less flexibility in the cyclopentanopyran ring system, and therefore the NOE interactions observed in the NOESY were regarded as conclusive. Thus, compound **3** was identified as 5,9-*epi*-7,8-didehydropenstemoside.

Iridoid glycosides similar to **1**−**3** are of common occurrence in several species of the genus *Phlomis*.[16,17] Both the genera *Eremostachys* and *Phlomis* belong to the subtribe Lamieae of the family Lamiaceae.[1] Morphologically, the genera *Eremostachys* and *Phlomis* are similar.[1,2] Anatomical and cytological studies on the species of these genera also established this close affinity between these two genera.[1] During the preliminary chemotaxonomic studies on the family Lamiaceae using flavonoids as the markers, some degree of similarities between these genera were also identified.[1,18] Iridoids can be considered as valuable chemotaxonomic markers,[19] and in fact, they have been employed successfully to describe chemotaxonomic relationships among the taxa within various families, e.g., Acanthaceae,[20] Bigoniaceae,[21] Cornaceae,[22] Oleaceae,[23] and Rubiaceae.[24] Within the family Lamiaceae, iridoid glycosides have recently been employed as chemotaxonomic markers for the species of the genus *Lamium*.[25] Therefore, the co-occurrence of iridoid glycosides in the closely related genera *Eremostachys* and *Phlomis* could be significant chemotaxonomically.

All three iridoid glycosides (**1**−**3**) showed a low level of free-radical scavenging activity (antioxidant activity) in the DPPH assay.[26,27] The RC_{50} values of **1**−**3** were found to be 1.10×10^{-1}, 4.90×10^{-1}, and 4.10×10^{-1} mg/mL, respectively, compared to 2.88×10^{-5} mg/mL for quercetin, a well-known natural antioxidant.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Bellingham Stanley ADP220 polarimeter. UV spectra were obtained using a Hewlett-Packard 8453 UV/vis spectrophotometer in MeOH. IR spectra were obtained using a Nicolet Avatar 360 FT-IR spectrometer. NMR spectra were recorded in D_2O on a Bruker DRX 500 MHz NMR spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C). HMBC spectra were optimized for a long-range J_{H-C} of 9 Hz, and a NOESY experiment was carried out with a mixing time of 0.8 s. MS analyses were performed on a Finnigan MAT95 spectrometer. An analytical JASCO HPLC gradient system (LG 1580-02) coupled with a UV detector (model No. JASCO-UV 1575) was used for developing solvent systems for isolation and also for checking purity of the isolated compounds. A Discovery C_{18} analytical column (250 × 4.6 mm; particle size 5 μm) was used for analytical purposes. Preparative HPLC separation was performed in a Dionex prep-HPLC system coupled with a Gynkotek GINA50 autosampler and a Dionex UVD340S photodiode array detector. A Luna C_{18} preparative HPLC column (10 μm, 250 mm × 21.2 mm) was used. A Supelco Sep-Pak DSC-18 10 g cartridge was used for pre-HPLC fractionation. RC_{50} stands for the concentration that causes 50% reduction of absorbance of DPPH at 517 nm (lower RC_{50} value = higher antioxidant activity).

Plant Material. The rhizomes of *Eremostachys glabra* Boiss. (syn: *E. pulvinaris*, family: Lamiaceae alt. Labiatae) were collected from Tabriz in Azarbaijan Province (Iran) during September−October 2003, and a voucher specimen (PHSH0008) representing this collection has been retained in the herbarium of the Plant and Soil Science Department, University of Aberdeen, Scotland (ABD).

Extraction and Isolation. The dried, ground rhizomes of *E. glabra* (100 g) were sequentially extracted with *n*-hexane, dichloromethane, and methanol (1.1 L each) using a Soxhlet apparatus. A portion of the MeOH extract (2 g) was subjected to Sep-Pak fractionation using a step gradient of a MeOH−water mixture (10:90, 20:80, 40:60, 60:40, 80:20, and 100:0). The preparative HPLC (mobile phase: 0−15 min, 10% ACN in water; 15−45 min, ACN from 10% to 27% in water; 45−55 min, 27% ACN in water, flow rate 20 mL/min) of the 40% MeOH Sep-Pak fraction resulted in the isolation of three iridoid glycosides, **1** (8.6 mg, t_R = 28.0 min), **2** (4.8 mg, t_R = 15.9 min), and **3** (3.5 mg, t_R = 13.0 min).

6,9-*epi*-8-*O*-Acetylshanziside methyl ester (1): pale yellow amorphous solid; $[\alpha]_D^{20}$ −84.8° (*c* 0.00236, MeOH); UV (MeOH) λ_{max} 236 nm (log ε 4.05); IR ν_{max} (KBr) 3555, 3420, 1739, 1732, 1692, 1638, 1089, 980 cm^{-1}; ^1H and ^{13}C NMR (Table 1); ESIMS (positive-ion mode) *m*/*z* 471 $[M + Na]^+$; ESIMS (negative-ion mode) *m*/*z* 447 $[M - H]^-$; HRESIMS *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{28}O_{12}Na$ 471.1478, found 471.1477.

5,9-*epi*-Penstemoside (2): pale yellow amorphous solid; $[\alpha]_D^{20}$ −90.9° (*c* 0.00044, MeOH); UV (MeOH) λ_{max} 234 nm (log ε 4.02); IR ν_{max} (KBr) 3550, 3440, 1728, 1692, 1630, 1120, 992 cm^{-1}; ^1H and ^{13}C NMR (Table 1); ESIMS (positive ion mode) *m*/*z* 429 $[M + Na]^+$; ESIMS (negative ion mode) *m*/*z* 405 $[M - H]^-$; HRESIMS *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{26}O_{11}Na$ 429.1372, found 429.1373.

5,9-*epi*-7,8-Didehydropenstemoside (3): pale yellow amorphous solid; $[\alpha]_D^{20}$ −92.6° (*c* 0.00054, MeOH); UV (MeOH) λ_{max} 237 nm (log ε 4.10); IR ν_{max} (KBr) 3460, 3300, 1710, 1695, 1102, 988 cm^{-1}; ^1H and ^{13}C NMR (Table 1); ESIMS (positive ion mode) *m*/*z* 427 $[M + Na]^+$; ESIMS (negative ion mode) *m*/*z* 403 $[M - H]^-$; HRESIMS *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{24}O_{11}$ 427.1216, found 427.1216.

Antioxidant Activity (DPPH Assay). 2,2-Diphenyl-1-picrylhydrazyl (DPPH), molecular formula $C_{18}H_{12}N_5O_6$, was obtained from Fluka Chemie AG, Bucks, UK. Quercetin was obtained from Avocado Research Chemicals Ltd., Heysham, Lancs., UK. The method used by Takao[26] was adopted with suitable modifications.[27] DPPH (4 mg) was dissolved in MeOH (50 mL) to obtain a concentration of 80 μg/mL.

Qualitative Assay. Test compounds (**1**−**3**) were applied on a TLC plate and sprayed with DPPH solution using an atomizer. It was allowed to develop for 30 min. The color changes (purple on white) were noted.

Quantitative Assay. Compounds **1**−**3** were dissolved in MeOH to obtain a concentration of 0.5 mg/mL. Dilutions were made to obtain concentrations of 5×10^{-2}, 5×10^{-3}, 5×10^{-4}, 5×10^{-5}, 5×10^{-6} 5×10^{-7}, 5×10^{-8}, 5×10^{-9}, and

5×10^{-10} mg/mL. Diluted solutions (1.00 mL each) were mixed with DPPH (1.00 mL) and allowed to stand for half an hour for any reaction to occur. The absorbance was recorded at 517 nm. The experiment was performed in triplicate, and the average absorption was noted for each concentration. The same procedure was followed for the standard (quercetin).

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Supporting Information Available: Tables S1 and S2, respectively, for HMBC and NOESY NMR data of compounds **1**–**3**. This information is available free of charge via the Internet at http://pubs.acs.org.

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