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Iridoid, Phenylethanoid and Monoterpene Glycosides from *Phlomis sieheana*

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From the aerial parts of *Phlomis sieheana*, an iridoid glucoside, ipolamiide (**1**), six phenylethanoid glycosides, acteoside (= verbascoside) (**2**), *cis*-acteoside (**3**), β-hydroxyacteoside (**4**), leucosceptoside A (**5**), martynoside (**6**), forsythoside B (**7**), and a monoterpene glycoside, betulalbuside A (**8**) were isolated and characterized. The structure elucidations of the isolated compounds were established on the basis of spectroscopic evidence.

Key Words: *Phlomis sieheana*, Lamiaceae, iridoid glucoside, ipolamiide, phenylethanoid glycosides, acteoside, *cis*-acteoside, β-hydroxyacteoside, leucosceptoside A, martynoside, forsythoside B, monoterpene glycoside, betulalbuside A.

Introduction

The genus *Phlomis* is represented by 34 species in the flora of Turkey[1]. Some *Phlomis* species are used as tonics and stimulants in Anatolian folk medicine[2]. Investigations on *P. linearis*[3−5], *P. armeniaca*[6], *P. pungens* var. *pungens* and var. *hirta*[7−9], *P. bourgaei*[10], *P. longifolia* var. *longifolia*[11] and *P. lycia*[12] in our laboratory led to the isolation of several iridoid glucosides, phenylethanoid glycosides and monoterpene glucosides. In addition, Japanese-Turkish research groups have also reported some iridoid and phenylethanoid glycosides from *P. grandiflora* var. *grandiflora*[13] and *P. rigida*[14] of Turkish origin. In a continuation of the systematic studies on Turkish *Phlomis* species, we studied *P. sieheana*, an endemic Turkish species[1]. The present paper deals with the isolation and structure elucidation of the iridoid glucoside, ipolamiide (**1**), in addition to the phenylethanoid glycosides, acteoside (= verbascoside) (**2**), *cis*-acteoside (**3**), β-hydroxyacteoside (**4**), leucosceptoside A (**5**), martynoside (**6**), and forsythoside B (**7**), as well as the monoterpene glycoside, betulalbuside A (**8**).

Experimental

General Experimental Procedures: The UV ($\lambda_{max.}$) spectrum was recorded on a Hitachi HP 8452 A spectrophotometer. The FTIR (cm^{-1}) spectrum was determined on a Perkin-Elmer 2000 FTIR spectrometer, in KBr pellets. ESIMS were performed in positive and negative ion modes on a Finnigan TSQ 7000 spectrometer. NMR measurements in CD_3OD at room temperature were measured using a Varian Unity 500 spectrometer operating at 500 MHz for ^1H and 125 MHz for ^{13}C. ^1H-^{13}C HSQC, and HMBC experiments were recorded by employing conventional pulse sequences. Polyamide (Macherey Nagel MN SC-6) and silica gel 60 (0.063-0.200 mm, Merck) were used for open column chromatographies. MPLC separations were performed on a Labomatic glass column (1.8x35.2 cm, i.d.), packed with LiChroprep RP-18, using a Lewa M5 peristaltic pump. TLC analyses were carried out on pre-coated silica gel 60 F_{254} aluminum sheets (Merck). Compounds were detected by UV fluorescence and spraying 1% vanillin/H_2SO_4, followed by heating at 100°C for 1-2 min.

Plant Material. *Phlomis sieheana* Rech. fil (Lamiaceae) was collected at florescence from Konya, Sultanhanı, in July 1999. Voucher specimens have been deposited at the Herbarium of the Pharmacognosy Department, Faculty of Pharmacy, Hacettepe University, Ankara, Turkey (HUEF 99-031).

Extraction and Isolation. The air-dried and powdered aerial parts of *P. sieheana* (490 g) were extracted twice with MeOH (2x3000 ml) at 40°C. The combined extracts were evaporated under reduced pressure. The resultant crude extract (70 g) was dissolved in H_2O (300 ml) and partitioned with petroleum-ether (5x200 ml). The petroleum-ether layer was then rejected and 53 g of H_2O extract was obtained. An aliquot of the H_2O extract (25 g) was fractionated on polyamide employing H_2O and gradient MeOH-H_2O mixtures (25-100%). This yielded seven main fractions (A-G). [Fr. A (16.96 g), Fr. B (1.82 g), Fr. C (413 mg), Fr. D (250 mg), Fr. E (993 mg), Fr. F (672 mg), Fr. G (965 mg)]. Fr. A was subjected to Si gel column chromatography, eluting with CH_2Cl_2-MeOH-H_2O (80:20:1→60:40:4) to yield seven fractions (frs. A_1-A_7). Fraction A_5 (572 mg) was rechromatographed over silica gel and eluted with CH_2Cl_2-MeOH-H_2O (80:20:1→80:20:2) to afford five fractions (frs. A_{5a}-A_{5e}). Fr. A_{5e} was pure **1** (40 mg). Fr. A_{5b} (97 mg) was subjected to polyamide CC, and elution with H_2O afforded two fractions (frs. A_{5b-1}-A_{5b-2}). Fr. A_{5b-1} (50 mg) was fractionated over Si gel using CH_2Cl_2-MeOH (90:10) and CH_2Cl_2-MeOH-H_2O (90:10:0.5) mixtures as eluent to yield **8** (10 mg). Fraction E was subjected to C_{18}-medium-pressure liquid chromatography (MPLC) using gradient MeOH-H_2O mixtures (20-50%) to afford **2** (17 mg), **3** (9.8 mg), **4** (3.2 mg), **5** (384 mg) and **6** (62.8 mg). Fraction D was subjected to C_{18}-medium-pressure liquid chromatography. Elution with MeOH-H_2O mixtures (5-65%) gave **7** (32.5 mg) and additional amounts of **6** (22.9 mg).

Acetylation of 4: 0.8 mg of compound **4** was dissolved in pyridine (1 ml) and acetic anhydride (1 ml) and the solution was left at room temperature overnight. The reaction mixture was diluted with cold water and filtered through an RP-18 cartridge. The cartridge was then washed with cold water (10 ml). The acetylated product in the cartridge was eluted with $CHCl_3$ (20 ml). The $CHCl_3$ extract was concentrated *in vacuo* to give the decaacetate (**4a**) (0.9 mg).

Ipolamiide (1): ^1H NMR (500 MHz, CD_3OD): δ_H 7.44 (3H, s, H-3), 5.81 (1H, s, H-1), 4.58 (1H, d, J = 7.9 Hz, H-1′), 3.90 (1H, dd, J = 12.0/1.8 Hz, H-6′$_b$), 3.73 (3H, s, COOC$\underline{H}_3$), 3.71 (1H, dd, J = 12.0/5.8 Hz, H-6′$_a$), 3.50 (1H, m, H-5′), 3.46 (1H, t, J = 9.2 Hz, H-3′), 3.42 (1H, t, J = 9.0 Hz, H-4′), 3.20 (1H, dd, J = 7.9/9.5 Hz, H-2′), 2.48 (1H, s, H-9), 2.26 (1H, m, H-6$_b$), 2.10 (1H, m, H-7$_b$), 1.92 (1H, m, H-6$_a$), 1.59 (1H,

m, H-7_a), 1.15 (3H, s, H_3-10); ^{13}C NMR (125 MHz, CD_3OD): δ_C 168.0 (s, C-11), 152.6 (d, C-3), 115.1 (s, C-4), 99.5 (d, C-1′), 94.1 (d, C-1), 78.9 (s, C-8), 78.3 (d, C-5′), 77.3 (d, C-3′), 74.3 (d, C-2′), 71.6 (s, C-5), 71.4 (d, C-4′), 62.8 (t, C-6′), 61.6 (d, C-9), 51.7 (q, COO$\underline{C}H_3$), 40.3 (t, C-7), 38.8 (t, C-6), 23.2 (q, C-10).

Acteoside (2): ^{1}H NMR (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD) data (Table) superimposable with those reported in the literature[15].

***Cis*-acteoside (3):** ^{1}H NMR (500 MHz, CD_3OD): aglycon moiety: δ_H 6.68 (1H, d, J = 2.0 Hz, H-2), 6.66 (1H, d, J = 8.1 Hz, H-5), 6.55 (1H, dd, J = 8.1/2.0 Hz, H-6), 4.05 (1H, m, H-α), 3.72 (1H, m, H-α), 2.79 (2H, t, J = 7.3 Hz, H-β), acyl moiety: δ_H 7.51 (1H, d, J = 2.0 Hz, H-2‴), 7.10 (1H, dd, J = 8.3/2.0 Hz, H-6‴), 6.72 (1H, d, J = 8.3 Hz, H-5‴), 6.86 (1H, d, J = 13.0 Hz, H-β'), 5.76 (1H, d, J = 13.0 Hz, H-α'), glucose moiety: δ_H 4.34 (1H, d, J = 7.8 Hz, H-1′), 4.93 (1H, t, J = 9.4 Hz, H-4′), rhamnose moiety: δ_H 5.17 (1H, d, J = 1.4 Hz, H-1″), 1.15 (3H, d, J = 6.1 Hz, H-6″).

β-Hydroxyacteoside (4): UV (MeOH) $\lambda_{max.}$ 331, 289, 231 and 218; IR (KBr) $\upsilon_{max.}$ 3500 (OH), 1685 (α,β-unsaturated ester), 1630 (olefinic C=C) and 1600, 1518 cm^{-1} (aromatic ring); ^{1}H (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD): Table. Positive ESIMS m/z 663 [M+Na]$^+$, negative ESIMS m/z 639 [M-H]$^-$.

β-Hydroxyacteosidedecaacetate (4a): ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.89, 1.96, 2.09, 2.105, 2.109, 2.12 (each 3H, s, alcoholic OAc), 2.29, 2.30, 2.31, 2.32 (each 3H, s, aromatic OAc), 7.65 (1H, d, J = 15.9 Hz, H-β'), 6.36 (1H, d, J = 15.9 Hz, H-α'), 5.93 (1H, dd, J = 7.7/3.0 Hz, H-β), 1.05 (3H, d, J = 5.9 Hz, H-6″).

Leucosceptoside A (5): ^{1}H NMR (500 MHz, CD_3OD) data superimposable with those reported in the literature[15].

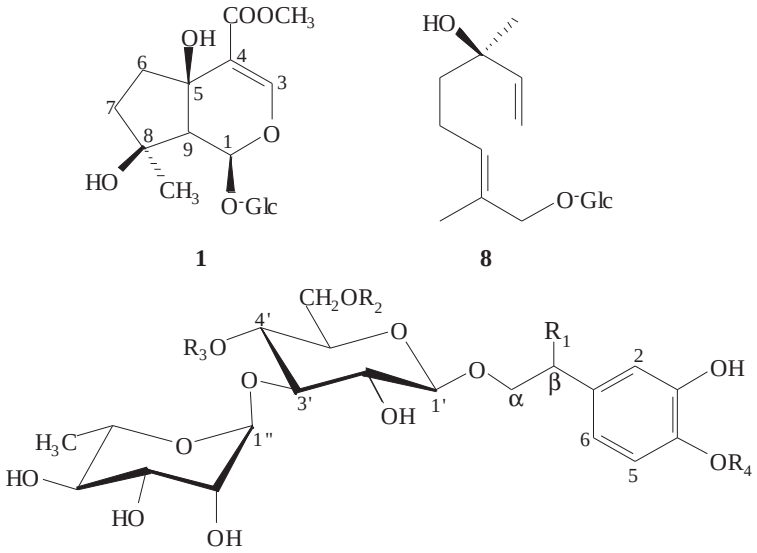
Martynoside (6): ^{1}H NMR (500 MHz, CD_3OD) data superimposable with those reported in the literature[16].

Forsythoside B (7): ^{1}H NMR (500 MHz, CD_3OD) data superimposable with those reported in the literature[17].

Betulalbuside (8): ^{1}H NMR (500 MHz, CD_3OD) data superimposable with those reported in the literature[18].

Results and Discussion

The water-soluble extract obtained from the methanolic extract of the aerial parts of *P. sieheana* was fractionated by polyamide column chromatography, followed by open CC on silica gel and C_{18}-medium-pressure liquid chromatography (MPLC) to yield compounds **1-8**.



1 **8**

2 R_1 = H, R_2 = H, R_3 = caffeoyl, R_4 = H
3 R_1 = H, R_2 = H, R_3 = caffeoyl, R_4 = H
4 R_1 = OH, R_2 = H, R_3 = caffeoyl, R_4 = H
5 R_1 = H, R_2 = H, R_3 = feruloyl, R_4 = H
6 R_1 = H, R_2 = H, R_3 = feruloyl, R_4 = CH_3
7 R_1 = H, R_2 = apiose, R_3 = caffeoyl, R_4 = H

Figure 1. Iridoid, phenylethanoid and monoterpene glycosides isolated from *P. sieheana*.

Compounds **2** and **5**-**8** were obtained as amorphous compounds. Their structures were identified as acteoside (**2**)[15], leucosceptoside A (**5**)[15], martynoside (**6**)[16], forsythoside B (**7**)[17] and betulalbuside (**8**)[18] by comparing their ^{1}H NMR data with previously published data and by direct comparison with the authentic samples on a TLC plate.

Compound **1** was obtained as a colourless amorphous compound. The ^{13}C NMR spectrum of **1** (*see* Experimental) showed 17 carbon signals, six of which could be assigned to a β-glucopyranosyl moiety. The ^{1}H NMR spectrum of **1** (*see* Experimental) exhibited the characteristic signals for an iridoid structure and showed the existence of a methoxycarbonyl function (δ_H 3.73, s), and a tertiary methyl group (δ_H 1.15, s). In addition, resonances arising from two methylene groups were observed. The ^{1}H NMR signal at δ_H 4.58 (d, J = 7.9 Hz) was assigned to the anomeric proton of a β-glucopyranose unit. The H-1 signal (δ_H 5.81, s), which was shifted downfield due to glycosidation, indicated the attachment of the β-glucopyranose unit at the C-1 position of the iridoid aglycon. The chemical shift values and the splitting patterns of H-3 (δ_H 7.44, s) and H-9 (δ_H 2.48, s) were suggestive of C-4, C-5 and C-8 to be substituted. Thus, the methoxycarbonyl group was assigned to be positioned at C-4, due to the highly deshielded signal of the H-3 proton, and the quaternary carbon resonance at δ_C 71.6 was attributed to C-5. The complete analysis of the ^{1}H and ^{13}C NMR data of **1** allowed the assignments of the multiplet signals observed at δ_H 2.26/1.92 and δ_H 2.10/1.59 to the methylene protons at C-6 (δ_C 38.8, t) and C-7 (δ_C 40.3, t), respectively. The multiplicity of H-9 was also indicative of a totally substituted C-8. However, the chemical shift value of the tertiary methyl group (δ_H 1.15, s) suggested its attachment at C-8. On the other hand, the chemical shift values of both C-8 (δ_C 78.9, s) and H_3-10 also indicated the presence of a tertiary hydroxyl function at C-8 position. By the

complete analysis of the NMR data of **1**, and a comparison with the data given in the literature, compound **1** was determined to be ipolamiide[19,20].

Table $^{13}C^{\dagger}$ and $^{1}H^{\ddagger}$ NMR data of acteoside (**2**) and β-hydroxyacteoside (**4**)

		2[a]		**4**[b]		
C/H atom	DEPT135	δ_C	$\delta_H J$ (Hz)	δ_C	$\delta_H J$ (Hz)	HMBC (from C to H)
Aglycon						
1	C	131.5		133.6		H-2, H-5, H-6, H-β
2	CH	117.2	6.69 d (1.8)	115.7	6.76 d (2.0)	H-6
3	C	146.7		146.2		H-2, H-5
4	C	144.3		146.0		H-2, H-6
5	CH	116.4	6.67 d (8.2)	116.1	6.79 d (8.2)	
6	CH	121.3	6.56 dd (8.2/1.8)	118.9	6.74 dd (8.2/2.0)	
α	CH_2	72.4	4.05 m, 3.72 m	76.7	3.98 dd (10.6/3.2), 3.55[c]	H-1′
β	CH_2	36.6	2.79 t (7.2)	74.2[d]	4.75 dd (7.5/3.2)	
Glucose						
1′	CH	104.3	4.37 d (7.9)	104.6	4.41 d (7.8)	
2′	CH	76.3	3.39 dd (9.1/7.2)	76.1	3.46 dd (9.2/7.8)	
3′	CH	81.7	3.81 t (9.1)	81.4	3.84 t (9.2)	H-1″
4′	CH	70.7	4.95 t (9.4)	70.4	4.95 t (9.4)	
5′	CH	76.1	3.55 m	76.1	3.55 m	
6′	CH_2	62.4	3.61 dd (12.2/2.0)			
			3.53 dd (12.2/6.4)	62.3	3.63[c], 3.53[c]	
Rhamnose						
1″	CH	103.1	5.18 d (1.8)	102.9	5.20 d (1.7)	
2″	CH	72.3	3.91 dd (3.4/1.8)	72.4	3.93 dd (1.7/3.2)	
3″	CH	72.1	3.57 dd (9.7/3.4)	72.0	3.58[c]	
4″	CH	73.9	3.28 t (9.7)	73.8	3.28 t (10.0)	H-2″, H-5″, H_3-6″
5″	CH	70.5	3.54 m	70.4	3.57 m	H-1″, H-4″, H_3-6″
6″	CH_3	18.5	1.09 d (6.1)	18.5	1.10 d (6.2)	
Acyl moiety						
1‴	C	127.7		127.6		H-5‴, H-α'
2‴	CH	115.3	7.05 d (1.4)	115.2	7.05 d (2.0)	
3‴	C	146.9		147.2		H-2‴, H-5‴
4‴	C	149.9		149.8		H-2‴, H-5‴, H-6‴
5‴	CH	116.6	6.77 d (8.2)	116.5	6.79 d (8.2)	
6‴	CH	123.2	6.96 dd (8.2/1.4)	123.2	6.96 dd (8.2/2.0)	H-β', H-2‴
α'	CH	114.8	6.28 d (15.9)	114.6	6.27 d (15.9)	H-β', H-6‴
β'	CH	148.1	7.59 d (15.9)	148.0	7.60 d (15.9)	
C=O	C	168.3		168.2		H-α', H-β', H-4′

†500 MHz, CD_3OD

‡125 MHz, CD_3OD

[a]Data from ref. 15

[b]Assignments confirmed by ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC and HMBC experiments

[c]Signal pattern unclear due to overlapping

[d]Multiplicity: CH

Compound **3** was obtained as an amorphous powder. The ^{1}H NMR data of compound **3** (*see* Experimental) revealed that **3** had most of the structural features of acteoside (**2**)[15]. However, the magnitude of the coupling constant value of a pair of olefinic proton signals that appeared at δ_H 6.86 and 5.76 (each 1H, d, J_{AX} = 13.0 Hz) was smaller than that of **2** (δ_H 7.59 and 6.28, each 1H, d, J_{AX} = 15.9 Hz, in

acteoside[15]). This fact clearly indicated that **3** was the *cis*-isomer of **2**. Since the ^{1}H NMR data of **3** was in good agreeement with the reported data, its structure was identified as *cis*-acteoside[21].

Compound **4** was obtained as an amorphous substance, with the molecular formula $C_{29}H_{36}O_{15}$ as determined by the ^{1}H and ^{13}C NMR data (Table) and ESIMS. The positive ESIMS showed a pseudomolecular ion $[M+Na]^+$ at m/z 663, while the negative ESIMS exhibited an ion $[M-H]^-$at m/z 639, which was 16 mass units higher than that of acteoside (**2**), suggesting the presence of an additional oxygen function in its structure. The UV spectrum ($\lambda_{max.}$ 218, 231, 289 and 331 nm) confirmed its polyphenolic nature, and IR bands (cm^{-1}) for hydroxyl groups (3500), an α,β-unsaturated ester (1685) and aromatic rings (1600 and 1518) were observed. In the ^{1}H NMR spectrum of **4,** two doublet signals that appeared at δ_H 4.41 (J = 7.8 Hz) and 5.20 (J = 1.7 Hz) were attributed to the anomeric protons of a β-glucose and α-rhamnose unit, respectively, indicating its disaccharide structure. Moreover, characteristic signals arising from six aromatic protons (2 ABX systems; δ_H 7.05-6.70 region), and two *trans*-olefinic protons (AB system; δ_H 7.60, d, J = 15.9 Hz and 6.27, d, J = 15.9 Hz) were consistent with a (E)-caffeic acid and a trisubstituted-phenyl moiety. All structural assignments were confirmed by the results obtained from the 2D shift-correlated ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC and HMBC (Fig. 2) experiments of **4**. The ^{13}C NMR spectroscopic data confirmed the diglycosidic structure, exhibiting two anomeric carbon resonances at δ_C 104.1 and 102.9, assigned to a glucose and a rhamnose unit, respectively. The HMBC correlation observed between the carbonyl carbon (δ_C 168.2) of the caffeoyl moiety and the H-4′ (δ_H 4.95) of the glucose revealed that the caffeoyl group occupied the C-4′ position of the glucose moiety as in **2**. A prominent HMBC coupling from C-3′ (δ_C 81.4) of the glucose to the H-1″ (δ_H 5.20) of the rhamnose unit indicated the linkage of the rhamnose unit at the C-3′ position of the glucose moiety. The ^{1}H and ^{13}C NMR data assigned to the acyl and sugar moieties as well as the benzyl unit within **4** and acteoside (**2**)[15] were superimposable. However, the ^{1}H and ^{13}C NMR signals due to the benzylic side-chain of **4** showed a remarkable difference from those of **2**. A characteristic ^{1}H NMR resonance assigned to the benzylic protons of the 3,4-dihydroxyphenethyl moiety in acteoside (**2**) (δ_H 2.79, 2H, t, J = 7.2 Hz, H_2-β[15]) disappeared in the ^{1}H NMR spectrum of **4**. Neverthless, the geminally coupled α-CH_2 methylene protons (δ_H 3.98, dd, J = 7.5/3.2; 3.92, overlapped) were mutually coupled to an oxymethine proton at δ_H 4.76 (1H, m), consistent with the secondary-hydroxyl group being affixed to C-β (δ_C 74.2). Further evidence for this assumption came from the heteronuclear coupling observed between the C-1 (δ_C 133.6) atom of the benzyl moiety and H-β. On the other hand, acetylation of **4** gave a decaacetate (**4a**). In the ^{1}H NMR spectrum of **4a** (*see* Experimental), six alcoholic (δ_H 1.89, 1.96, 2.09, 2.105, 2.109, 2.12) and four aromatic (δ_H 2.29, 2.30, 2.31, 2.32) acetyl signals were observed, supporting the proposed structure. In addition, in the ^{1}H NMR spectrum, the signal of H-β was shifted downfield (δ_H 5.93, 1H, dd, J = 7.7/3.0 Hz) due to acetylation. All these data suggested that the structure of **4** consisted of a β,3,4-trihydroxyphenethyl moiety as the aglycon. Finally, an HMBC correlation between H-1′ (δ_H 4.41) of the glucose unit and the C-α atom (δ_C 76.7) of the β,3,4-trihydroxyphenethyl unit showed the linkage of the glucose to be the C-α position of the β,3,4-trihydroxyphenethyl moiety. Consequently, the structure of compound **4** was established as β,3,4-trihydroxyphenethyl-*O*-α-L-rhamnopyranosyl-(1→3)-4-*O*-caffeoyl-β-D-glucopyranoside. Comparing its NMR data with those given in the literature, compound **4** was identified as β-hydroxyacteoside[22].

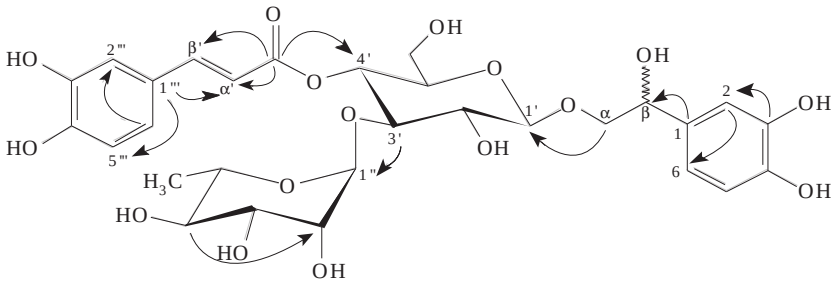


Figure 2. Selected heteronuclear multiple bond correlations (HMBC) for β-hydroxyacteoside (**4**). Arrows point from carbon to proton.

Conclusion

Concerning the iridoid and phenylethanoid glycosides of the genus *Phlomis* in the flora of Turkey, the isolation of the iridoid glucoside ipolamiide (**1**) and the phenylethanoid glycosides acteoside (**2**), leucosceptoside A (**5**), martynoside (**6**) and forsythoside B (**7**) from several Turkish *Phlomis* species[3−12] have been reported previously. *Cis*-acteoside (**3**) has been reported to be a constituent of *Stachys sieboldii* (Lamiaceae)[21] and *Osmanthus* sp. (Oleaceae)[23,24]. Kitagawa *et al.* have isolated and characterized β-hydroxyacteoside (**4**), from *Forsythia viridissima*[22] and *F. koreana* (Oleaceae)[25]. However, the isolation of these rare glycosides, *cis*-acteoside (**3**) and β-hydroxyacteoside (**4**), from *Phlomis* species is reported for the first time as well as for the family Lamiaceae. To our knowledge, the monoterpene glucoside betulalbuside (**8**) has been isolated from *Phlomis* species for the second time. This compound has only been reported from *P. armeniaca*[6], earlier.

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