Iridoid Glucosides from *Eremostachys moluccelloides* BUNGE

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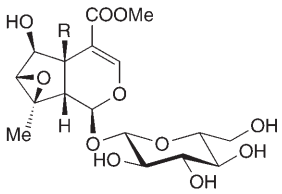
From the aerial parts of *Eremostachys moluccelloides* BUNGE, a new iridoid glucoside, lamalbidic acid (**7**), was isolated as its choline salt **7a** together with six known iridoid glucosides, 5-deoxysesamoside (**1**), 6β-hydroxy-7-epiloganin (**2**), lamalbide (**3**), shanzhiside methyl ester (**4**), sesamoside (**5**), and 5-deoxypulchelloside I (**6**). The structures of **7a** and **7** (obtained from **7a**) were elucidated by spectroscopic (UV, IR, 1D- and 2D-NMR, and ESI-MS) methods.

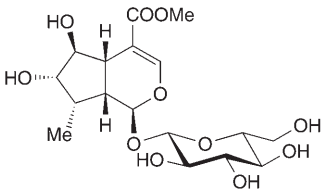
Introduction. – The genus *Eremostachys* BUNGE (Lamiaceae), closely related to the genus *Phlomis* L., comprises about 60 species occurring mainly in the Irano-Turanian region in West and Central Asia [1]. *Eremostachys* is represented by three species in Turkey [2], namely *E. moluccelloides* BUNGE, *E. laciniata* (L.) BUNGE and *E. glabra* BOISS. *ex* BENTH. Previous work on iridoid glucosides of this genus revealed the presence of harpagide in *E. labiosiformis* [3], while harpagide and acetylharpagide were found in *E. fetissovii* [4]. More recently, three iridoid glucosides with unusual configuration were reported from *E. glabra* [5]. However, these were later shown to be in fact identical to barlerin, penstemoside, and 7,8-didehydropenstemoside [6]. As a part of our ongoing phytochemical study on the members of the Lamiaceae growing in Turkey, we now investigated *E. moluccelloides*. We describe here the isolation and structure elucidation of the iridoid glucosides contained in the aerial parts.

Results and Discussion. – The aerial parts of *E. moluccelloides* were extracted with MeOH. Fractionation of the H_2O-soluble part of the MeOH extract by vacuum and medium-pressure liquid chromatography (*LiChroprep C_{18}*) and open-column chromatography (silica gel) afforded the seven iridoid glucosides **1**–**6** and **7a**. Compound **7a** was the choline salt of the acid **7**.

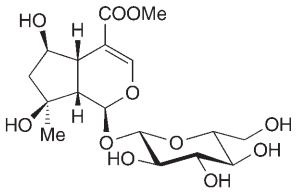
The known compounds **1**–**6** were identified on the basis of their optical-rotation values, UV, IR, NMR, and MS data as 5-deoxysesamoside (= phlorogidoside C; **1**) [7][8], 6β-hydroxy-7-epiloganin (**2**) [9], lamalbide (**3**) [10–12], shanzhiside methyl ester (**4**) [13][14], sesamoside (**5**) [7][15–17], and 5-deoxypulchelloside I (**6**) [12][18–21].



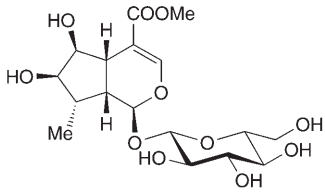
5-Deoxysesamoside (**1**) R = H
Sesamoside (**5**) R = OH



6β-Hydroxy-7-*epi*-loganin (**2**)



Shanzhiside methyl ester (**4**)



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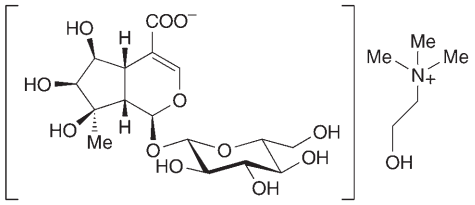
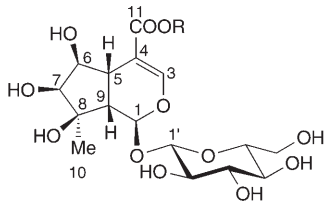


Lamalbidic acid choline salt (**7a**)



Lamalbide (**3**) R = Me
Lamalbidic acid (**7**) R = H

Compound **7a** was obtained as a hygroscopic powder. The UV spectrum showed an absorption maximum at 235 nm, indicating the presence of an α,β-unsaturated C=O moiety. The structure of **7a** as lamalbidic acid choline salt, was deduced from 1D- (^{1}H- and ^{13}C-NMR, and DEPT) and 2D-NMR (COSY, HSQC, HMBC, and NOESY) and ESI-MS data and by comparison with the data of lamalbide (**3**).

The ^{1}H- and ^{13}C-NMR spectra (*Tables 1* and *2*) of compound **7a** were very similar to those of lamalbide (**3**), except for the lack of a methyl ester signal present in the latter. This suggested **7a** to be the corresponding carboxylic acid, for which we propose the name lamalbidic acid. However, the unusually upfield positions of the signals of H–C(3)[1]) (δ(H) 7.02) and C(3) (δ(C) 147.0) as well as the downfield positions of the signals of C(4) (δ(C) 116.9) and C(11) (δ(C) 174.2) seen for **7a** when compared to those for **3**, indicated that the former was a salt [21]. Beside the signals for the iridoid-anion moiety, the ^{1}H-NMR spectrum displayed a spin system consisting of signals at δ(H) 3.99 (*m*, CH_2O) and 3.45 (*m*, CH_2N) together with a nine-proton *s* at δ(H) 3.13 (Me_3N), which were assigned to a choline (=2-hydroxy-*N*,*N*,*N*-trimethylethanaminium) unit. This was corroborated by the corresponding resonances at δ(C) 56.4 (*t*), 68.2 (*t*), and 54.6 (*q*), respectively, assigned by HSQC and HMBC experiments. To

[1]) Trivial atom numbering; for the systematic name, see *Exper. Part.*

Table 1. *^{1}H-NMR Data of* **3**, **7**, *and* **7a**. δ in ppm, J in Hz.

	3[a])	**7**[b])	**7**[a])	**7a**[a])
H−C(1)	5.61 (br. *s*)	5.61 (*d*, *J* = 1.3)	5.66 (*d*, *J* = 0.8)	5.53 (br. *s*)
H−C(3)	7.43 (*s*)	7.41 (*s*)	7.47 (*s*)	7.02 (*s*)
H−C(5)	2.90 (*dd*, *J* = 11.0, 3.8)	2.91 (*dd*, *J* = 10.9, 3.7)	2.94 (*dd*, *J* = 11.0, 3.4)	2.86 (*dd*, *J* = 11.2, 4.0)
H−C(6)	4.02 (*dd*, *J* = 4.4, 3.8)	3.97 (*dd*, *J* = 4.1, 4.0)	4.08 (*dd*, *J* = 4.4, 3.4)	3.88 (*dd*, *J* = 4.1, 4.0)
H−C(7)	3.63 (*d*, *J* = 4.4)	3.57 (*d*, *J* = 4.3)	3.70 (*d*, *J* = 4.4)	3.64 (*d*, *J* = 4.1)
H−C(9)	2.79 (br. *d*, *J* = 11.0)	2.80 (*dd*, *J* = 10.9, 1.3)	2.84 (*dd*, *J* = 11.0, 0.8)	2.73 (br. *d*, *J* = 11.0)
Me(10)	1.18 (*s*)	1.21 (*s*)	1.23 (*s*)	1.17 (*s*)
H−C(1′)	4.72 (*d*, *J* = 8.0)	4.61 (*d*, *J* = 7.9)	4.78 (*d*, *J* = 8.1)	4.70 (*d*, *J* = 8.1)
H−C(2′)	3.21 (*dd*, *J* = 9.1, 8.0)	3.17 (*dd*, *J* = 9.0, 7.9)	3.27 (*dd*, *J* = 9.3, 8.1)	3.22 (*dd*, *J* = 9.2, 8.1)
H−C(3′)	3.44[c])	3.36 (*t*, *J* = 9.0)	3.50 (*t*, *J* = 9.3)	3.45[c])
H−C(4′)	3.34 (*t*, *J* = 9.4)	3.26 (*t*, *J* = 9.5)	3.40 (*t*, *J* = 9.5)	3.31 (*t*, *J* = 9.5)
H−C(5′)	3.44[c])	3.31[c])	3.52[c])	3.45[c])
CH_2(6′)	3.88 (*dd*, *J* = 12.2, 2.0), 3.68 (*dd*, *J* = 12.2, 6.0)	3.89 (*dd*, *J* = 12.0, 2.0), 3.65 (*dd*, *J* = 12.0, 5.9)	3.93 (*dd*, *J* = 12.4, 2.1), 3.72 (*dd*, *J* = 12.4, 6.1)	3.87 (*dd*, *J* = 12.2, 2.0), 3.66 (*dd*, *J* = 12.2, 6.1)
Choline:				
CH_2O				3.99[c])
CH_2N				3.45[c])
Me_3N				3.13 (*s*)

[a]) Recorded in D_2O. [b]) Recorded in CD_3OD. [c]) Signal pattern unclear due to overlapping.

Table 2. *^{13}C-NMR and DEPT Data* (D_2O) *of* **7** *and* **7a** *and ^{13}C,^{1}H-HMBC correlations for* **7a**. δ in ppm.

	7	**7a**[a])	**7a**: Significant ^{13}C,^{1}H-HMBC correlations
C(1)	94.5 (*d*)	94.2 (*d*)	H−C(1′), H−C(3), H−C(9)
C(3)	152.4 (*d*)	147.0 (*d*)	H−C(1), H−C(5)
C(4)	111.4 (*s*)	116.9 (*s*)	H−C(3), H−C(5), H−C(6), H−C(9)
C(5)	36.1 (*d*)	36.9 (*d*)	H−C(1), H−C(3), H−C(7), H−C(9)
C(6)	76.6 (*d*)	77.5 (*d*)	
C(7)	78.8 (*d*)	78.7 (*d*)	H−C(6), H−C(9), H−C(10)
C(8)	78.5 (*s*)	78.4 (*s*)	H−C(7)
C(9)	47.9 (*d*)	48.4 (*d*)	H−C(6), H−C(7), H−C(10)
C(10)	21.3 (*q*)	21.8 (*q*)	H−C(7), H−C(9)
C(11)	171.7 (*s*)	174.2 (*s*)	H−C(3)
C(1′)	98.8 (*d*)	98.7 (*d*)	H−C(1), H−C(2′)
C(2′)	73.3 (*d*)	73.4 (*d*)	
C(3′)	76.7 (*d*)	76.3 (*d*)	
C(4′)	70.2 (*d*)	70.4 (*d*)	
C(5′)	77.1 (*d*)	77.0 (*d*)	
C(6′)	61.5 (*t*)	61.5 (*t*)	
Choline:			
CH_2O		56.4 (*t*)	CH_2N
CH_2N		68.2 (*t*)	Me_3N
Me_3N		54.6 (*q*)	CH_2N

[a]) Spectra are aligned by setting δ(C(6′)) to 61.5 [22].

establish the relative configuration of the chiral centers in **7a**, a 2D-NOESY experiment was performed. The NOE cross-peaks observed between Me–C(10), H–C(1), H–C(6), and H–C(7) indicated that these H-atoms were placed on the same side (α) of the molecule. Similarly, significant NOE cross-peaks were observed between H–C(5) and H–C(9). Thus, the cyclopentanopyran ring system of the iridoid moiety was determined to be β,β-*cis*-fused. The ESI-MS data of **7a** exhibited two main peaks at *m*/*z* 105 and 431 attributed to $[\text{choline} + \text{H}]^+$ and $[\text{lamalbidic acid} + \text{Na}]^+$, resp.

To verify the presence of lamalbidic acid as the anion part in compound **7a**, the latter was dissolved in H_2O containing oxalic acid. The solution was applied to reversed-phase column chromatography (*RP-18*, H_2O, then MeOH) to yield lamalbidic acid (**7**) as an amorphous colorless powder. The molecular formula was established as $C_{16}H_{24}O_{12}$ by ESI-MS (*m*/*z* 431 ($[M + \text{Na}]^+$, $C_{16}H_{24}NaO_{12}^+$)) and HR-TOF-ESI-MS (*m*/*z* 426.1595 ($[M + NH_4]^+$, $C_{16}H_{28}NO_{12}^+$)). The UV and IR absorptions of **7** and its NMR data (*Tables 1* and *2*) were very similar to those of lamalbide (**3**), except for the missing Me ester group in **7**. Thus, the structure of lamalbidic acid (**7**) was definitively established as (1α,4aα,5α,6α,7α,7aα)-1-(β-D-glucopyranosyloxy)-1,4a,5,6,7,7a-hexahydro-5,6,7-trihydroxy-7-methylcyclopenta[*c*]pyran-4-carboxylic acid.

Iridoid glycosides can be used as chemotaxonomic markers for the genera in the family Lamiaceae. The main compounds found in the present investigation are all C_{10} iridoids containing a 4-COOMe functional group. As an exception, compound **7** contains a carboxylic acid function and was isolated as the salt **7a** with choline as counterion. Choline and betaines like proline betaine, *trans*-4-hydroxyproline betaine, pipecolic acid betaine, *trans*-4-hydroxypipecolic acid betaine, and trigonelline and glycine betaine are widely distributed in the Lamiaceae. Betaines have been shown to have taxonomic significance since several taxa from the subfamilies of Ajugoideae, Lamioideae, Pogostemonoideae, Scutellaroideae, Teucrioideae, and Viticoideae contain these compounds [23]. Thus, all investigated species in the Lamioideae were found to have high betaine levels, which is in contrast to the other major subfamily, Nepetoideae, where the content of betaines is low or null. A similar distribution pattern has been found for iridoid glucosides, as already pointed out by *Kooiman* [3].

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Experimental Part

General. Medium-pressure liquid chromatography (MPLC): *Büchi* glass column (3 × 24 cm, i.d.) packed with *LiChroprep RP-18* (40–63 μm; *Merck*); *Büchi 681* chromatography pump. Vacuum liquid chromatography (VLC): glass column (5.2 × 10 cm, i.d.; vacuum by *Milipore* diaphragm pump) packed with *LiChroprep RP-18* (40–63 μm; *Merck*). Column chromatography (CC): silica gel *60* (0.063–0.200 mm; *Merck*, Darmstadt). TLC: precoated silica gel *60* F_{254} (*Merck*) aluminum plates; $CHCl_3$/MeOH/H_2O mixtures; visualization by spraying with 1% vanilin in conc. H_2SO_4 soln., followed by heating at 105° for 1–2 min. Optical rotations: *Rudolph Autopol-IV* automatic polarimeter. UV Spectra: *Agilent 8453* and *Shimadzu UV-1601* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Jasco FT/IR-420* spectrometer; KBr pellets: $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker Avance-400* spectrometer, at 400 (^{1}H) and 100 MHz (^{13}C)); δ in ppm, *J* in Hz; multiplicites for ^{13}C by DEPT experiments. ESI-MS: *Waters ZQ-Mass* spectrometer; positive-ion mode; in *m*/*z*. LC/HR-ESI-MS: *Agilent HP-1100* liquid chromatograph

equipped with a *BDS-C-18* reversed-phase column, coupled to a *LCT-TOF* mass spectrometer (*Waters*, Manchester, UK); electrospray negative-ion mode.

Plant Material. E. moluccelloides was collected in July 2004 between Hoşap and Başkale (Van), in the vicinities of the Güzeldere pass. Voucher specimens (VANF-6210) were deposited at the Herbarium of Yüzüncü Yıl University, Van, Turkey.

Extraction and Isolation. The dry, powdered aerial parts of *E. molucelloides* (250 g) were extracted twice with MeOH (2×2.5 l, 4 h each) at 40°. Then the extracts were filtered, combined, and concentrated. The resultant residue was diluted with H_2O (100 ml) and filtered to remove lipophilic compounds. The filtrate was extracted with CH_2Cl_2 (2×100 ml), and the remaining H_2O phase was evaporated to yield 47 g of crude extract. An aliquot of the H_2O extract (35 g) was subjected to reversed-phase VLC (*LiChroprep RP-18*, 5×20 cm column; $0 \rightarrow 100$ MeOH/H_2O in steps of 5–10% of MeOH; TLC monitoring): *Fractions A–K*, *i.e.*, *Fr. A* (500 ml of H_2O; 20.390 g), *B* (250 ml of 5% MeOH; 0.67 g), *C* (200 ml of 10% and 100 ml of 20% MeOH; 2.24 g), *D* (200 ml of 30% MeOH; 2.89 g), *E* (100 ml of 40% MeOH; 0.93 g), *F* (100 ml of 50% MeOH; 0.4 g), *G* (100 ml of 60% MeOH; 0.39 g), *H* (100 ml of 70% MeOH; 0.90 g), *I* (100 ml of 80% MeOH; 1.07 g), *J* (100 ml of 90% MeOH; 0.56 g), and *K* (250 ml of MeOH; 0.21 g). *Fr. B* (0.67 g) was subjected to reversed-phase MPLC (*LiChroprep RP-18*, 26×260 mm column, H_2O (200 ml), 5% MeOH (200 ml), and finally MeOH (150 ml): *Fr.* B_1–B_{22} (25 ml/fraction). *Fr.* B_6–B_8 yielded lamalbidic acid choline salt (**7a**; 83 mg). *Fr. C* (2.24 g) was subjected to reversed-phase MPLC (*LiChroprep RP-18*, 26×260 mm column; MeOH/H_2O 0:1 → 25:75 in 5% steps, each 200 ml) to yield 48 fractions (30 ml/fraction) which were combined into five main groups: *Fr.* C_1 (fraction 6, 26 mg), C_2 (fractions 7 and 8; 40 mg), C_3 (fractions 9–12; 136 mg), C_4 (fractions 13–26; 970 mg), C_5 (fractions 27–30; 390 mg), C_6 (fractions 31–37; 338 mg), and C_7 (fractions 41–48; 385 mg). *Fr.* C_4 (970 mg) was subjected to CC (silica gel (65 g); CH_2Cl_2/MeOH/H_2O 90:10:1 (200 ml), 80:20:1 (200 ml), 80:20:2 (700 ml), and 70:30:3 (300 ml)): *Fr.* $C_{4.1}$–$C_{4.70}$. *Fr.* $C_{4.14}$–$C_{4.17}$ gave pure 5-deoxysesamoside (**1**; 20 mg), while *Fr.* $C_{4.22}$–$C_{4.26}$ yielded pure 6*β*-hydroxy-7-epiloganin (**2**; 192 mg). *Fr.* $C_{4.38}$–$C_{4.50}$ were found to be lamalbide (**3**; 401 mg) which was the major compound among the isolated compounds. *Fr. D* (2.89 g) was subjected to CC (silica gel (125 g); CH_2Cl_2/MeOH/H_2O 80:20:1 (500 ml), 80:20:2 (750 ml), 70:30:3 (250 ml), and 60:40:4 (250 ml); 20 ml/fraction) to yield 75 fractions which were combined into seven subfractions: *Fr.* D_1–D_7. *Fr.* D_1 (fractions 9–12) gave pure 5-deoxysesamoside (**1**; 56 mg), while *Fr.* D_2 (fractions 13–19) was a mixture of **1** and **2** (151 mg). *Fr.* D_3 (fractions 20–25; 134 mg) and D_4 (fractions 26–34; 150 mg) were rich in compounds **5** and **6**, resp. *Fr.* D_5 (fractions 35 and 36) was pure 5-deoxypulchelloside I (**6**; 12 mg). *Fr.* D_6 (fractions 37–52) and D_7 (fractions 53–60) gave almost pure 5-deoxysesamoside (**1**; 1455 and 252 mg, resp.). *Fr.* D_3 and D_4 were each subjected to CC (silica gel (30 g); CH_2Cl_2/MeOH/H_2O 80:15:1 (100 ml), 80:20:1 (100 ml), and 80:20:2 (200 ml); 15 ml/fraction): pure sesamoside (**5**; 32 mg) and 5-deoxypulchelloside I (**6**; 49 mg), resp. *Fr. F* (0.4 g) was subjected to reversed-phase MPLC (*LiChroprep RP-18*, 26×260 mm column; MeOH/H_2O 0:1 → 3:7 in 5% steps, each 200 ml): *Fr.* F_1–F_{40} (30 ml/fraction). *Fr.* F_{34}–F_{39} afforded shanzhiside methyl ester (**4**; 223 mg).

5-Deoxysesamoside (= *Phlorogidoside C*, **1**): $[\alpha]_D^{33} = -63$ ($c = 0.1$, MeOH). ^{1}H- and ^{13}C-NMR: as reported [7][8]. ESI-MS: 427 ($[M+Na]^+$, $C_{17}H_{24}NaO_{11}^+$).

6β-Hydroxy-7-epiloganin (**2**): $[\alpha]_D^{33} = -123$ ($c = 0.1$, MeOH). ^{1}H- and ^{13}C-NMR: as reported [9]. ESI-MS: 429 ($[M+Na]^+$, $C_{17}H_{26}NaO_{11}^+$).

Lamalbide (**3**): $[\alpha]_D^{33} = -123$ ($c = 0.1$, MeOH). ^{1}H- and ^{13}C-NMR: as reported [10–12]; *Tables 1* and *2*. ESI-MS: 445 ($[M+Na]^+$, $C_{17}H_{26}NaO_{12}^+$).

Shanzhiside Methyl Ester (**4**): $[\alpha]_D^{33} = -115$ ($c = 0.1$, MeOH). ^{1}H- and ^{13}C-NMR: as reported [13][14]. ESI-MS: 429 ($[M+Na]^+$, $C_{17}H_{26}NaO_{11}^+$).

Sesamoside (**5**): $[\alpha]_D^{33} = -76$ ($c = 0.1$, MeOH). ^{1}H- and ^{13}C-NMR: as reported [7][15–17]. ESI-MS: 443 ($[M+Na]^+$, $C_{17}H_{24}NaO_{12}^+$).

5-Deoxypulchelloside I (**6**): $[\alpha]_D^{33} = -104$ ($c = 0.1$, MeOH). ^{1}H- and ^{13}C-NMR: as reported [18–21]. ESI-MS: 429 ($[M+Na]^+$, $C_{17}H_{26}NaO_{11}^+$).

Lamalbidic Acid Choline Salt (= rel-*(1*R,*4a*R,*5*R,*6*R,*7*S,*7a*R*)-1-(β*-D-*Glucopyranosyloxy)-1,4a,5,6,7,7a-hexahydro-5,6,7-trihydroxy-7-methylcyclopenta[*c*]pyran-4-carboxylic Acid 2-Hydroxy-

N,N,N-*trimethylethanaminium Salt*; **7a**): Hygroscopic powder. ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS: 431 ([lamalbidic acid + Na]$^+$), 105 ([choline + H]$^+$).

Lamalbidic Acid (**7**). Compound **7a** (40 mg) was dissolved in a soln. of oxalic acid (10 mg/1 ml H_2O) and applied to CC (*LiChroprep C18*, 2 × 4 cm column), H_2O (10 ml), then MeOH (10 ml): **7** (30 mg). Amorphous colorless powder. $[\alpha]_D^{33} = -122$ ($c = 0.1$, MeOH). UV (MeOH): 232 (3.94). IR (KBr): 3420 (OH), 2921 (CH), 1684 (C=O), 1646 (C=C). ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. HR-TOF-ESI-MS: 426.1595 ($[M + NH_4]^+$, $C_{16}H_{28}NO_{12}^+$; calc. 426.1612). ESI-MS: 431 ($[M + Na]^+$, $C_{16}H_{24}NaO_{12}^+$).

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