Indian Journal of Chemistry
Vol. 36B, February 1997, pp. 150-153

Phenylpropanoid, neolignan and iridoid glycosides from *Pedicularis semitorta*

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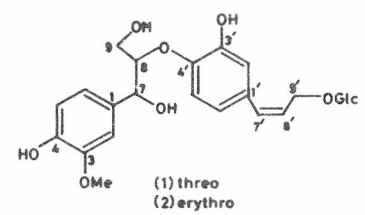
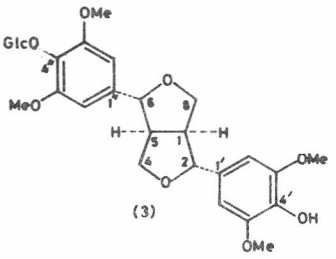
Received 24 August 1995; revised and accepted 7 May 1996

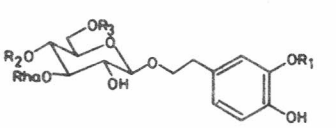
From the ethanolic extract of the whole plants of *Pedicularis semitorta*, nine known glycosides, syringaresinol-4″-O-β-D-monoglucopyranoside, cistanoside D, cistanoside C, verbascoside, isoverbascoside, mussaenoside, shanzhiside methyl ester, euphroside and aucubin along with one new phenylpropanoid, *cis*-isoverbascoside and a mixture of *erythro*- and *threo*-neolignans, named semitortoside A and semitortoside B, respectively, have been isolated. Their structures have been elucidated mainly by spectral evidence.

In continuation of our studies on the glycosidic constituents of the genus *Pedicularis*, we now report the isolation and structural elucidation of *cis*-isoverbascoside **8**, and a mixture of *erythro*- and *threo*-neolignans: semitortoside A **1** and semitortoside B **2** from the whole plants of *P. semitorta*[1] along with nine known glycosides, syringaresinol-4″-*O*-β-D-monoglucopyranoside **3**[2], cistanoside D **4**, cistanoside C **5**[3,4], verbascoside **6**[4,5], isoverbascoside **7**[6], mussaenoside **9**[7,8], shanzhiside methyl ester **10**[9], euphroside **11**[10,11] and aucubin **12**[11,12], which were identified by comparison of their spectral data (FABMS, ^{1}H and ^{13}C NMR) with those reported in the literature and authentic samples.

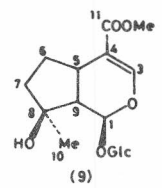
cis-Isoverbascoside **8**, $[\alpha]_D^{15}$-28.5° (MeOH; *c* 0.20), was obtained as a white amorphous powder after separation from isoverbascoside **7** by HPLC (ODS-C_{18}) eluting with 38% MeOH-H_2O. It gave a positive colouration with ferric chloride and Molish reagents indicating glycosidic nature of the compound containing a phenolic hydroxyl group. Its UV spectrum showed λ_{max}^{MeOH} at 330, 292 and 220 nm. The FAB mass spectrum gave ion peaks at m/z 631 $[M+Li]^2$ and 647 $[M+Na]^+$, suggesting the molecular formula to be $C_{29}H_{36}O_{15}$. Acid hydrolysis of **8** showed the presence of caffeoyl, 3, 4-dihydroxyphenylethyl, D-glucose and L-rhamnose moieties. The signals in its ^{1}H NMR spectrum at δ 4.32 (1H, d, J=8.0 Hz, Glc. H-1′) and 5.17 (1H, s, Rha. H-1) showed that the D-glucose and L-rhamnose residues were having β- and α-configurations, respectively. Comparison of the chemical shifts of inner glucose in its ^{13}C NMR [δ 104.3 (C-1′), 75.4 (C-2′), 84.0 (C-3′), 70.7 (C-4′), 75.7 (C-5′) and 64.6 (C-6′)] (cf. Table I) with those of methyl-β-D-glucoside showed that the L-rhamnose was linked to C-3′ [+7.2 (C-3′), −0.6 (C-4′)] and caffeoyl group was connected at C-6′ [+2.8 (C-6′) and −0.9 (C-5′)]. The structure of **8** was therefore very similar to isoverbascoside **7**[6], but in their ^{1}H NMR spectra the signals of H-α′, β′ in isoverbascoside appeared at δ 6.28,

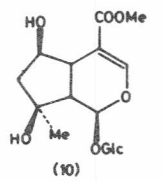


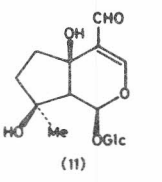




	R_1	R_2	R_3
(4)	Me	Feruloyl	H
(5)	Me	Caffeoyl	H
(6)	H	Caffeoyl	H
(7)	H	H	Caffeoyl
(8)	H	H	cis-Caffeoyl







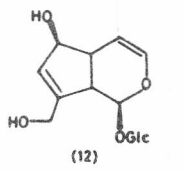


Table I—^{13}C NMR chemical shifts of compounds **7** and **8** (100 MHz; δ, ppm)*

C	7	8	C	7	8
Aglycone			Acyl moiety		
1	131.4 (s)	131.4 (s)	1	127.7 (s)	127.7 (s)
2	117.1 (d)	117.6 (d)	2	115.1 (d)	115.1 (d)
3	146.0 (s)	146.1 (s)	3	146.7 (s)	146.8 (s)
4	144.6 (s)	144.6 (s)	4	149.5 (s)	149.6 (s)
5	116.3 (d)	116.3 (d)	5	116.5 (d)	116.7 (d)
6	121.3 (d)	121.3 (d)	6	123.1 (d)	123.0 (d)
α	72.3 (t)	72.3 (t)	α	114.9 (d)	115.0 (d)
β	36.6 (t)	36.6 (t)	β	147.2 (d)	146.0 (d)
			CO	169.1 (s)	167.7 (s)
Glc.			Rha		
1′	104.3 (d)	104.4 (d)	1	102.7 (d)	102.7 (d)
2′	75.4 (d)	75.4 (d)	2	72.3 (d)	72.3 (d)
3′	84.0 (d)	84.0 (d)	3	72.3 (d)	72.3 (d)
4′	70.0 (d)	70.0 (d)	4	74.0 (d)	74.0 (d)
5′	75.6 (D)	75.7 (d)	5	70.4 (d)	70.4 (d)
6′	64.6 (t)	64.6 (t)	6	17.8 (q)	17.9 (q)

*CD_3OD as solvent; TMS as internal standard

7.55 (each 1H, d, J=15.9 Hz), respectively, while in **8** both H-α′,β′ were upfield at δ 5.76, 6.94 (each 1H, d, J=13.0 Hz). Thus, the caffeoyl group in **8** has *cis*-configuration[13]. From the above results, compound **8** was chracterized as *cis*-isoverbascoside.

Semitortoside A (**1**) and B (**2**) were obtained as a 1:1 mixture. The IR spectrum showed ν_{max}^{KBr} at 3400 (OH), 1652 (double bond), 1600, 1512 and 1481 cm^{-1} (phenyl). The molecular formula, $C_{25}H_{32}O_{12}$, was deduced from the FAB mass spectrum showing peaks at m/z 531 $[M+Li]^+$ and 547 $[M+Na]^+$. Most of the NMR signals of the mixture were doubled. It was evident from the ^1H NMR spectrum that both **1** and **2** exhibited six aromatic proton signals at δ7.26 (dd, J=8.0, 1.5 Hz, H-6), 7.16 (d, J=1.5 Hz, H-2), 7.10 (d, J=1.5 Hz, H-2′), 7.07 (dd, J=8.0, 1.5 Hz, H-6′) and 6.97 (d, J=8.0 Hz, H-5,5′), the coupling constants of which pointed to the substitution pattern shown in their structural formula; one methoxy group at δ 3.82 (s), (*Z*)-cafesterol side chain at 6.05 (d, J=12.5 Hz, H-7′), 5.83 (dt, J=12.5, 5.1 Hz, H-8′) and 4.45 (dd, J=5.1, 1.5 Hz, H-9′); 1-phenyl-2-phenoxylpropane-1,3-diol[14] moiety at δ 5.23 (d, J=6.9 Hz, H-7 of **1**), 5.18 (d, J=4.1 Hz, H-7 of **2**), 4.54 (m, H-8 of **1**), 4.30 (m, H-8 of **2**) and the anomeric proton of sugar moiety at 4.61 (d, J=7.6 Hz). The EIMS showed strong peaks at m/z 137 and 151; this showed that the methoxyl group was connected at ring-A of **1** and **2**. The NMR spectra showed that both **1** and **2** were glucopyranosides very similar to cirtusin A[15]. Thus, a comparison of the NMR data of **1** and **2** with those of cirtusin A, both H-7′ and H-8′ showed significant upfield shifts and the $J_{7',8'}$ was 12.5 Hz, a characteristic of *cis*-double band at C-7′ and C-8′. This was supported by the downfield shifts of C-9′ and C-7′ signals by 8.7 and 1.7 ppm respectively (cf. Table II) and an upfield shift of C-8′ signal by 3.0 ppm also proving the position of the β- glucose moiety at C-9′ oxygen. The signals at δ 5.23 (d, J=6.9 Hz) and 75.3 due to H-7 and C-7 of compound **1**, and 5.18 (d, J=4.1 Hz) and 71.7 due to H-7 and C-7 of compound **2** were in close agreement with those of cirtusin A[15] and alashanioside[16]. The coupling constant between H-7 and H-8 in the *threo*-isomer is larger (6-8 Hz) than that in the *erythro*- isomer (2-4 Hz)[17-20]. Hence, a difference of +3.6 ppm for C-7 between the ^{13}C NMR spectra of **1** and **2** and the value of the coupling constant of H-7 and H-8 showed that **1** and **2** were *threo*- and *erythro*-isomers, respectively. From the above results, the structures of semitortoside A(**1**) and B(**2**) were established as *threo*- and *erythro*-1-(4-hydroxy-3-methoxyphenyl)-2-{2-hydroxy-4- [(*Z*)-3-glucosyl-prop-1-enyl]phenoxy}propane-1,3-diol, respectively.

Experimental Section

General. ^1H and ^{13}CNMR spectra were recorded

Table II—^{13}C NMR chemical shifts* of compounds **1**, **2** and cirtusin A [100 MHz; δ, ppm]*

C	1	2	cirtusin A	C	1	2	cirtusin A
1	138.1	138.1	139.5 (s)	1′	135.2	135.1	133.7 (s)
2	113.0	113.0	112.8 (d)	2′	113.1	113.1	114.1 (d)
3	151.3	151.3	151.8 (s)	3′	145.8	145.8	151.5 (s)
4	147.7	147.3	148.1 (s)	4′	150.0	150.0	149.8 (s)
5	117.8	117.8	118.2 (d)	5′	118.5	118.5	119.0 (d)
6	121.7	121.7	122.3 (d)	6′	121.4	121.4	122.4 (d)
7	75.3	71.7	75.0 (d)	7′	135.0	135.0	133.3 (d)
8	88.2	87.9	85.9 (d)	8′	126.7	126.7	129.7 (d)
9	63.3	63.2	63.3 (t)	9′	73.8	73.6	65.1 (t)
3-OMe	58.3	58.3	58.5 (q)	3′-OMe			58.6 (q)
Glc.							
1	103.0[a]	103.1[b]	103.9 (d)	4	72.1	72.1	72.1 (d)
2	75.8[a]	75.7[b]	75.7 (d)	5	78.3[a]	78.0[b]	78.9 (d)
3	78.5[a]	78.4[b]	78.4 (d)	6	64.0[a]	63.8[b]	63.6 (t)

*D_2O as solvent; DSS as internal standard.

[a,b]Assignments may be interchanged.

on a Bruker AM400 spectrometer at 400 MHz and 100 MHz, respectively, in FT-mode. FAB and EI mass spectra were obtained on a VG ZAB-HS instrument. IR spectra were taken on a Nicolet 170-SX spectrometer and UV spectra on a Shimadzu UV-260 visible recording spectrometer.

Collection of plant material. *Pedicularis semitorta* Maxim was collected in Zhang County, Gansu Province of China in August 1989. It was identified by Prof. Zhang Guo-Liang of Lanzhou University. A voucher specimen (933102) has been preserved at the Herbarium of our Institute.

Extraction and isolation of compounds. The dried whole plants (4.5 kg) were refluxed with 95% EtOH (3 × 4L). The ethanolic extracts were concentrated to give a residue, which was diluted with H_2O and extracted with *n*-BuOH. The combined *n*-BuOH extracts were concentrated to give a crude syrup, which was chromatographed over polyamide column using H_2O as eluent to obtain part I and 50% MeOH-H_2O to obtain part II. Parts I and II were chromatographed separately on silica gel column eluting with gradients of $CHCl_3$-MeOH (9:1, 6:1, 4:1, and 3:1), Part I yield pure compounds **9** (80 mg), **10** (60 mg), **11** (45 mg) and **12** (100 mg) and part II gave pure **3** (28 mg), mixture of **1** and **2** (30 mg), pure **4** (66 mg), **5** (20 mg), **6** (600 mg), and a mixture of **7** and **8** (60 mg) in ascending order of polarity. Pure **7** (42 mg) and **8** (15 mg) were obtained by HPLC (column: ODS-C_{18}) using 38% MeOH-H_2O as eluent (Rt: **8**, 47 min; **7**, 52 min). Attempts to separate the mixture of **1** and **2**, however failed after using several HPLC solvent systems on an ODS-C_{18} column.

Semitortoside A(1) and B(2). Amorphous powder; IR ν_{max}^{KBr}: 3400, 2943, 1652, 1600, 1512, 1481, 1180-1000, 930 cm^{-1}; ^{1}H NMR (D_2O, DSS): δ 3.82 (s, 3-OMe), 4.30 (m, H-8 of **2**), 4.45 (dd, J=5.1, 1.5 Hz, H-9′), 4.54 (m, H-8 of **1**), 4.61 (d, J=7.6 Hz, Glc. H-1), 5.18 (d, J=4.1 Hz, H-7 of **2**), 5.23 (d, J=6.9 Hz, H-7 of **1**), 5.83 (dt, J=12.5, 5.1 Hz, H-8′), 6.05 (d, J=12.5 Hz, H-7′), 6.97 (d, J=8.0 Hz, H-5, 5′), 7.07 (dd, J=8.0, 1.5 Hz, H-6′), 7.10 (d, J=1.5 Hz, H-2′), 7.16 (d, J=1.5 Hz, H-2), 7.26 (dd, J=8.0, 1.5 Hz, H-6); ^{13}C NMR: see Table II; FAB-MS (S-Gly) m/z: 531 $[M+Li]^+$, 547 $[M+Na]^+$; EI-MS m/z: 362 $[M-162]^+$, 137, 151.

Isoverbascoside (7). Amorphous powder, $[\alpha]_D^{15}$ − 31.7° (MeOH; *c* 1.2); λ_{max}^{MeOH}: 329, 291, 219, 208 cm^{-1}; ^{1}H NMR (CD_3OD, TMS): δ 1.24 (3H, d, J=6.3 Hz, Rha. Me), 2.77 (2H, t, J=7.4 Hz, H-β), 3.30-4.02 (sugar protons), 4.32 (1H, d, J=8.0 Hz, Glc. H-1′), 4.49 (2H, d, J=10.7 Hz, Glc. H-6′), 5.17 (1 H, s, Rha. H-1), 6.28 (1H, d, J=15.9 Hz, H-α′), 6.53-7.03 (6H, m, aromatics H), 7.55 (1H, d, J=15.9 Hz, H-β′); ^{13}C NMR: see Table I; FAB-MS (S-Gly): m/z 631 $[M+Li]^+$, 647 $[M+Na]^+$.

cis-Isoverbascoside (8). Amorphous powder; $[\alpha]_D^{15} - 28.5°$ (MeOH; *c* 0.20); λ_{max}^{MeOH}: 330, 292, 220, 199 nm; ^1H NMR (CD_3OD, TMS): δ 1.24 (3H, d, J=6.0 Hz, Rha. Me), 2.77 (2H, t, J=7.1 Hz, H-β), 3.30-4.02 (sugar protons), 4.32 (1H, d, J=8.0 Hz, Glc. H-1′), 4.48 (2H, d, J=12.1 Hz, Glc. H-6′), 5.17 (1 H, s, Rha. H-1), 5.77 (1H, d, J=13.0 Hz, H-α′), 6.51-7.05 (6 H, m, aromatic H), 6.94 (1H, d, J=13.0 Hz, H-β′); ^{13}C NMR: see Table I; FAB-MS (S-Gly): m/z 631 $[M+Li]^+$ 647 $[M+Na]^+$.

Acknowledgement

This work was supported by the National Natural Science Foundation of China and the Foundation of the State Education Commission of China for Doctoral Progamme.

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