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PHENYLETHANOID GLYCOSIDES FROM *STACHYS OFFICINALIS*

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Key Word Index—*Stachys officinalis*; Labiatae; betonyosides; phenylethanoid glycosides.

Abstract—From the aerial parts of *Stachys officinalis*, six new phenylethanoid glycosides, named betonyosides A–F, and six known phenylethanoid glycosides, acetoside, acetoside isomer, campneosides II, forsythoside B and leucosceptoside B, were isolated and their structures were elucidated from spectroscopic and chemical evidence. Campneosides II were separated into two epimers. Copyright © 1996 Published by Elsevier Science Ltd

INTRODUCTION

In our previous paper, we reported on the isolation of phenylethanoid glycosides and oleanane-type triterpene saponins from *Stachys sieboldii* Miq. [1] and *S. riederi* Chamisso [2, 3]. In this paper, we wish to report on the isolation of six new and six known phenylethanoid glycosides from the aerial parts of *S. officinalis* Trevisan. As constituents of *S. officinalis*, phenylethanoid glycosides [4], iridoid glycosides [5] and diterpenoid [6] have been reported.

RESULTS AND DISCUSSION

A water extract of the aerial parts of *S. officinalis* gave 12 phenylethanoid glycosides (**1**–**12**) after separation by porous polymer gel column, silica gel column chromatography and reversed-phase prep HPLC.

Compounds **1**–**4**, **8** and **9** were identified by ^{1}H and ^{13}C NMR spectra as acteoside (**1**) [7], acteoside isomer (**2**) [7], campneoside II (**3**, **4**) [2, 8], forsythoside B (**8**) [9] and leucosceptoside B (**9**) [7].

Betonyosides A-C (**5**–**7**) were obtained as amorphous powders, $[\alpha]_D$ −74.2°, −57.0° and −42.0°. FAB-mass spectroscopy gave the same quasi-molecular ion peak at *m/z* 677 $[M + Na]^+$ and the elemental analysis data gave the molecular formula $C_{30}H_{38}O_{16}$. The ^{1}H NMR spectra of these three compounds suggested that they were also phenylethanoid glycosides. Acid hydrolysis gave the same degradation products, ferulic acid, 2-(3,4-dihydroxyphenyl)-2-hydroxyethane-1-ol, L-rhamnose and D-glucose. The ^{1}H and ^{13}C NMR data of **5** were similar to those of acteoside (**1**) for the sugar moiety, suggesting that rhamnose was attached to C-3 of glucose and ferulic acid was attached to C-4 of glucose. These data led us to conclude that the structure of **5** was as shown in formula **5**. Because the carbinyl carbon in the aglycone moiety was observed at δ 73.5 as one carbon signal, this compound was not an epimeric mixture. The ^{1}H and ^{13}C NMR spectra of **6** and **7** were similar to those of acteoside isomer (**2**) for the sugar moiety, suggesting that rhamnose was attached to C-3 of glucose and ferulic acid was attached to C-6 of glucose. The structures of **6** and **7** were deduced to be as shown in formulae **6** and **7** without the assignment of absolute configuration of the carbinyl carbon in the aglycone moiety.

Betonyoside D (**10**) was obtained as an amorphous powder, $[\alpha]_D$ −60.9°. The FAB-mass spectrum and the elemental analysis data gave the molecular formula $C_{36}H_{48}O_{19}$. Acid hydrolysis gave *cis*-ferulic acid, 3-hydroxy-4-methoxyphenethyl alcohol, D-apiose, L-rhamnose and D-glucose. The ^{1}H and ^{13}C NMR data were superimposable to those of leucosceptoside B (**9**) except for the ester moiety. In the ^{1}H NMR spectrum, two olefinic protons in the ester moiety were observed at δ 5.80 (*d*, J = 12.5 Hz) and 6.94 (*d*, J = 12.5 Hz). Thus, *cis*-ferulic acid was attached to C-4 of glucose. Sasaki *et al.* reported that jionoside A_1 having a *trans*-feruloyl residue and jionoside A_2 having a *cis*-feruloyl residue readily interchanged in daylight. This compound might be an artefact formed from compound **9** during extraction and isolation [10].

Betonyoside E (**11**) was obtained as an amorphous powder, $[\alpha]_D$ −76.6°. The FAB-mass spectrum and the elemental analysis data gave the molecular formula $C_{35}H_{46}O_{20}$. Acid hydrolysis afforded ferulic acid, 2-(3,4-dihydroxyphenyl)-2-hydroxy-ethan-1-ol, D-apiose, L-rhamnose and D-glucose. In the ^{13}C NMR spectrum, the carbinyl carbon signals of the sugar moiety were similar to those of **8** and the carbon signals of the aglycone moiety were similar to those of **3**–**7**. Because the β carbon was observed at δ 73.7 and 74.6, this compound was an epimeric mixture. The sugar se-

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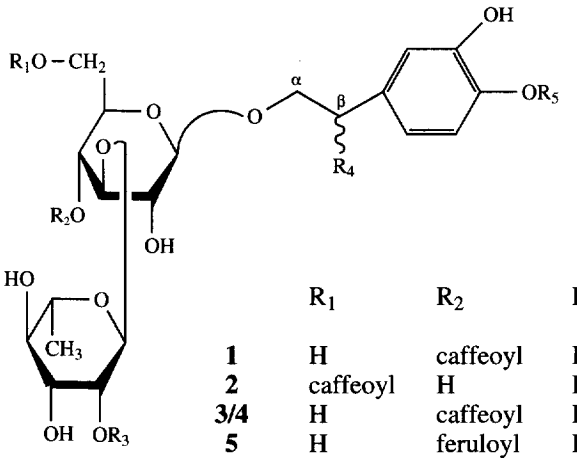

	R_1	R_2	R_3	R_4	R_5
1	H	caffeoyl	H	H	H
2	caffeoyl	H	H	H	H
3/4	H	caffeoyl	H	OH	H
5	H	feruloyl	H	OH	H
6/7	feruloyl	H	H	OH	H
8	Api	caffeoyl	H	H	H
9	Api	feruloyl	H	H	Me
10	Api	*cis*-feruloyl	H	H	Me
11	Api	feruloyl	H	OH	H
12	H	caffeoyl	Api	H	H

quence was confirmed by HMBC spectrum. The anomeric proton of glucose [δ 4.40/4.42 (*d*, $J = 8$ Hz)] was correlated to the α carbon of the aglycone (δ 76.3/76.8), the anomeric proton of rhamnose [δ 5.21 (*brs*)] was correlated to the C-3 of glucose (δ 81.2/81.1), and the anomeric proton of apiose [δ 4.91/4.89 (*d*, $J =$ 2 Hz)] was correlated to the C-6 of glucose (δ 68.5).

Betonyoside F (**12**), $C_{34}H_{44}O_{19}$, $[\alpha]_D$ −85.8°, afforded caffeic acid, 3,4-dihydroxyphenethyl alcohol, D-apiose, L-rhamnose and D-glucose on acid hydrolysis. To decide the binding site of the sugar, a NOE difference spectrum was employed after assignment of the sugar proton signals by detailed proton spin decoupling. On irradiation of the apiosyl anomeric proton at δ 5.11 (*d*, $J = 2$ Hz), the NOE was observed at the H-2 of rhamnose (δ 3.91). On irradiation of the rhamnosyl anomeric proton [δ 5.36 (*brs*)] and the glucosyl anomeric proton [δ 4.37 (*d*, $J = 8$ Hz)], the NOEs were observed at the H-3 of glucose [δ 3.78 (*dd*, $J = 9.5$, 8.5 Hz)] and the α proton of the aglycone (δ 3.71), respectively. The structure of **12** was, therefore, as shown in formula **12**.

EXPERIMENTAL

General procedure. FAB-MS: Jeol JMS-SX102 mass spectrometer, *m*-nitrobenzyl alcohol as a matrix, positive ion mode; ^1H and ^{13}C NMR; Jeol GSX-500. Chemical shifts are given on the δ scale with TMS as an int. standard.

Plant material, extraction and isolation. Stachys officinalis Trevisan was cultivated in our botanical garden. A voucher specimen is deposited in the Herbarium, School of Pharmaceutical Sciences, University of Shizuoka. Dried aerial parts (2 kg) of *S. officinalis* were extracted twice with hot H_2O. The H_2O extract was passed through a porous polymer gel Diaion HP-20 column (9 × 37 cm). After the column was washed with H_2O, the adsorbed materials were eluted with MeOH–H_2O (3:2) and MeOH, successively. The MeOH–H_2O (3:2) eluate (83 g) was chromatographed on a silica gel column (1.2 kg) using $CHCl_3$–MeOH [(22:3) → (7:3)] to give 15 frs (Frs 1–15). From Frs 10–15, compounds **1–12** were isolated by prep. HPLC [Develosil Lop-ODS 5 × 50 cm × 2, MeCN–H_2O [(2:23) → (3:7)] linear gradient]. **1** (225 mg), **2** (60 mg), **3** (66 mg), **4** (50 mg), **5** (10 mg), **6** (6 mg), **7** (5 mg), **8** (210 mg), **9** (122 mg), **10** (12 mg), **11** (65 mg), **12** (60 mg).

Betonyoside A (**5**). Amorphous powder, $[\alpha]_D^{22}$ −74.2° (MeOH, *c* 0.99). UV λ_{max}^{MeOH} nm (log ε): 218 (4.30), 231 (sh 4.20), 243 (sh 4.04), 290 (4.08), 329 (4.24). (Found: C, 51.61; H, 6.34. $C_{30}H_{38}O_{16} \cdot 2.5\ H_2O$ requires: C, 51.50; H, 6.19%) FAB-MS *m/z*: 677 $[M + Na]^+$. ^1H and ^{13}C NMR: Tables 1 and 2.

Betonyoside B (**6**). Amorphous powder, $[\alpha]_D^{22}$ −57.0° (MeOH, *c* 0.50). UV λ_{max}^{MeOH} nm (log ε): 218 (4.40), 290 (4.12), 327 (4.25). (Found: C, 51.45; H, 6.25. $C_{30}H_{38}O_{16} \cdot 2.5\ H_2O$ requires C, 51.50; H, 6.19%) FAB-MS *m/z*: 677 $[M + Na]^+$. ^1H and ^{13}C NMR: Tables 1 and 2.

Betonyoside C (**7**). Amorphous powder, $[\alpha]_D^{22}$ −42.0° (MeOH, *c* 0.44). UV λ_{max}^{MeOH} nm (log ε): 218 (4.40), 290 (4.12), 327 (4.25). (Found: C, 51.67; H, 6.12. $C_{30}H_{38}O_{16} \cdot 2.5\ H_2O$ requires: C, 51.50; H, 6.19%) FAB-MS *m/z*: 677 $[M + Na]^+$. ^1H and ^{13}C NMr: Tables 1 and 2.

Betonyoside D (**10**). Amorphous powder, $[\alpha]_D^{22}$ −60.9° (MeOH, *c* 0.45). UV λ_{max}^{MeOH} nm (log ε): 218 (4.28), 230 (sh 4.20), 243 (sh 3.98), 288 (4.01), 329 (4.20). (Found: C, 52.22; H, 6.34. $C_{36}H_{48}O_{19} \cdot 2.5\ H_2O$ requires: C, 52.11; H, 6.44%) FAB-MS *m/z*: 807 $[M + Na]^+$. ^1H and ^{13}C NMR: Tables 1 and 2.

Table 1. ^{1}H NMR chemical shifts of compounds **5–7** and **10–12** in CD_3OD

H	**5**	**6**	**7**	**10**	**11**	**12**
Aglycone moiety						
2	6.85 (d, J = 1.5 Hz)	6.84 (*brs*)	6.83 (*brs*)	6.73 (*d*, *J* = 1.5 Hz)	6.86; 6.84 (*d*, *J* = 1.5 Hz)	6.70 (*d*, *J* = 2 Hz)
5	6.74 (*d*, *J* = 8 Hz)	6.69 (*brs*)	6.67 (*brs*)	6.77 (*d*, *J* = 8 Hz)	6.77; 6.76 (*d*, *J* = 8 Hz)	6.68 (*d*, *J* = 8.5 Hz)
6	6.71 (*dd*, *J* = 8, 1.5 Hz)	6.69 (*brs*)	6.67 (*brs*)	6.69 (*dd*, *J* = 8, 1.5 Hz)	6.73*	6.57 (*dd*, *J* = 8.5, 2 Hz)
α	3.72 (*dd*, *J* = 11, 3Hz)	3.72*	3.72*	3.72*	3.60*	3.71*
	3.91*	3.81*	3.81*	4.01*	3.89*	4.04*
β	4.75 (*dd*, *J* = 8, 3.5 Hz)	4.74*	4.74*	2.82 (*m*)	4.76*	2.80 (*m*)
OMe				3.82 (*s*)		
Ester moiety						
2	7.20 (*d*, *J* = 1.5 Hz)	7.16 (*d*, *J* = 1.5 Hz)	7.14 (*d*, *J* = 1.5 Hz)	7.87 (*d*, *J* = 1.5 Hz)	7.20 (*d*, *J* = 1.5 Hz)	7.06 (*d*, *J* = 2 Hz)
5	6.81 (*d*, *J* = 8 Hz)	6.80 (*d*, *J* = 8 Hz)	6.80 (*d*, *J* = 8 Hz)	6.83 (*d*, *J* = 8 Hz)	6.82 (*d*, *J* = 8.5 Hz)	6.79 (*d*, *J* = 8.5 Hz)
6	7.08 (*dd*, *J* = 8, 1.5 Hz)	7.03 (*dd*, *J* = 8, 1.5 Hz)	6.98 (*dd*, *J* = 8, 1.5 Hz)	7.15 (*dd*, *J* = 8, 1.5 Hz)	7.09 (*dd*, *J* = 8.5, 1.5 Hz)	6.99 (*dd*, *J* = 8.5, 2 Hz)
β	6.38 (*d*, *J* = 16 Hz)	6.38 (*d*, *J* = 16 Hz)	6.36 (*d*, *J* = 16 Hz)	5.80 (*d*, *J* = 12.5 Hz)	6.38 (*d*, *J* = 16 Hz)	6.28 (*d*, *J* = 16 Hz)
γ	7.65 (*d*, *J* = 16 Hz)	7.63 (*d*, *J* = 16 Hz)	7.60 (*d*, *J* = 16 Hz)	6.94 (*d*, *J* = 12.5 Hz)	7.66 (*d*, *J* = 16 Hz)	7.59 (*d*, *J* = 16 Hz)
OMe	3.88 (*s*)	3.85 (*s*)	3.86 (*s*)	3.90 (*s*)	3.89 (*s*)	
Sugar moiety						
Glucose						
1	4.42 (*d*, *J* = 8 Hz)	4.39 (*d*, *J* = 8 Hz)	4.37 (*d*, *J* = 8 Hz)	4.35 (*d*, *J* = 8 Hz)	4.42; 4.40 (*d*, *J* = 8 Hz)	4.37 (*d*, *J* = 8 Hz)
2	3.46 (*t*, *J* = 8 Hz)	3.37 (*t*, *J* = 8 Hz)	3.37 (*t*, *J* = 8 Hz)	3.37 (*dd*, *J* = 8.5, 8 Hz)	3.45 (*t*, *J* = 8 Hz)	3.39 (*dd*, *J* = 8.5, 8 Hz)
3	3.84 (*dd*, *J* = 9.5, 8 Hz)	3.56*	3.56*	3.75 (*dd*, *J* = 9.5, 8 Hz)	3.85 (*dd*, *J* = 9.5, 8 Hz)	3.78 (*dd*, *J* = 9.5, 8.5 Hz)
4	4.93 (*t*, *J* = 9.5 Hz)	3.43 (*t*, *J* = 9.5 Hz)	3.42 (*t*, *J* = 9.5 Hz)	4.88 (*t*, *J* = 9.5 Hz)	4.95 (*t*, *J* = 9.5 Hz)	4.92 (*t*, *J* = 9.5 Hz)
5	3.56*	3.58 (*m*)	3.58 (*m*)	3.72*	3.73*	3.53*
6	3.53*	4.33*	4.33*	3.47 (*dd*, *J* = 11, 6 Hz)	3.49*	3.54*
	3.62*	4.54*	4.54*	3.86*	3.86*	3.63*
Rhamnose						
1	5.22 (*brs*)	5.19 (*brs*)	5.20 (*brs*)	5.15 (*d*, *J* = 1.5 Hz)	5.21 (*brs*)	5.36 (*brs*)
2	3.92*	3.95*	3.95*	3.92*	3.93*	3.90*
3	3.59 (*dd*, *J* = 9.5, 3 Hz)	3.72*	3.72*	3.57 (*dd*, *J* = 9.5, 3 Hz)	3.58*	3.66 (*dd*, *J* = 9.5, 3 Hz)
4	3.28*	3.40*	3.40*	3.33*	3.28 (*t*, *J* = 9.5 Hz)	3.25 (*t*, *J* = 9.5 Hz)
5	3.60*	4.00 (*m*)	4.00 (*m*)	3.60*	4.58*	3.54*
6	1.10 (*d*, *J* = 6.5 Hz)	1.25 (*d*, *J* = 6 Hz)	1.25 (*d*, *J* = 6 Hz)	1.15 (*d*, *J* = 6.5 Hz)	1.10 (*d*, *J* = 6.5 Hz)	1.08 (*d*, *J* = 6 Hz)
Apiose						
1				4.92 (*d*, *J* = 2 Hz)	4.91; 4.89 (*d*, *J* = 2 Hz)	5.11 (*d*, *J* = 2 Hz)
2				3.86 (*d*, *J* = 2 Hz)	3.87 (*d*, *J* = 2 Hz)	3.93 (*d*, *J* = 2 Hz)
4				3.72*	3.73*	3.73 (*d*, *J* = 9.5 Hz)
				3.92*	3.92*	3.95 (*d*, *J* = 9.5 hz)
5				3.52 (*s*)	3.52; 3.54 (*s*)	3.57 (*s*)

Recorded at 500 MHz.

*Overlapping with other signals.

Table 2. ^{13}C NMR chemical shifts of compounds **5–7** and **10–12** in CD_3OD

C	5	6	7	10	11	12
Aglycone moiety						
1	133.9	133.8	133.6	132.9	133.7; 133.6	131.5
2	114.8	114.8	114.6	112.9	114.8	117.1
3	146.0	146.0	146.0	147.4	146.0	146.0
4	146.2	146.3	146.3	147.6	146.2	144.6
5	116.1	116.1	116.1	117.1	116.2	116.5
6	119.1	119.1	119.0	121.2	119.1	121.3
α	76.1	76.6	77.0	72.2	76.3; 76.8	72.2
β	73.5	73.6	74.2	36.6	73.7; 74.6	36.5
OMe				56.5		
Ester moiety						
1	127.6	127.7	127.6	128.0	127.6	127.6
2	111.8	111.6	111.5	115.8	111.8	115.2
3	150.8	150.7	150.7	149.8	150.8	146.8
4	149.4	149.4	149.4	148.3	149.4	149.7
5	116.5	116.5	116.5	115.8	116.5	116.3
6	124.3	124.3	124.3	127.5	124.4	123.2
α	168.2	169.1	169.1	166.8	168.1	168.3
β	115.1	115.2	115.2	115.6	115.1	114.7
γ	147.9	147.2	147.2	147.8	148.0	148.0
OMe	56.5	56.4	56.4	56.5	56.5	
Sugar moiety						
Glucose						
1	104.1	104.4	104.8	104.3	104.3; 104.7	104.1
2	76.2	75.5	75.6	74.7	74.6	76.0
3	81.2	83.6	83.5	81.9	81.2; 81.1	81.9
4	70.4	70.0	70.0	70.5	70.4	70.6
5	76.1	75.9	75.9	76.1	76.0	75.9
6	62.3	64.6	64.6	68.4	68.5	62.3
Rhamnose						
1	102.9	102.6	102.6	103.3	102.9	101.9
2	72.3	72.3	72.3	72.3	72.3	79.9
3	72.1	72.4	72.4	72.2	72.0	71.6
4	73.7	74.0	74.0	73.8	73.7	74.1
5	70.5	70.3	70.3	70.8	70.8	70.3
6	18.4	17.9	17.9	18.3	18.4	18.5
Apiose						
1				110.9	111.1; 111.0	112.1
2				78.1	78.0	77.8
3				80.6	80.6	80.5
4				75.1	75.1	75.0
5				65.7	65.6	65.6

Recorded at 125.65 MHz.

Betonyoside E (**11**). Amorphous powder, $[\alpha]_D^{22}$ −76.6° (MeOH, *c* 1.28). UV λ_{max}^{MeOH} nm (log ε): 219 (4.29), 230 (sh 4.20), 245 (sh 4.03), 291 (4.11), 328 (4.33). (Found: C, 50.09; H, 6.51. $C_{35}H_{46}O_{20} \cdot 3\ H_2O$ requires: C, 50.00; H, 6.23%) FAB-MS *m/z*: 809 $[M + Na]^+$. ^1H and ^{13}C NMR: Tables 1 and 2.

Betonyoside F (**12**). Amorphous powder, $[\alpha]_D^{22}$ −85.8° (MeOH, *c* 1.09). UV λ_{max}^{MeOH} nm (log ε): 219 (3.91), 228 (sh 3.75), 244 (3.62), 291 (3.73), 303 (sh 3.75), 333 (3.89). (Found: C, 51.36; H, 6.18. $C_{34}H_{44}O_{19} \cdot 2\ H_2O$ requires: C, 51.51; H, 6.10%) FAB-MS *m/z*: 779 $[M + Na]^+$. ^1H and ^{13}C NMR: Tables 1 and 2.

Acid hydrolysis of **5–7** *and* **10–12**. A soln of each glycoside (1 mg) in 5% H_2SO_4 aq. (3 drops) and dioxane (3 drops) was heated in the boiling water bath for 1 hr. The reaction mixture was diluted with H_2O and extracted with EtOAc ×3. The H_2O layer was passed through an Amberlite IRA-60E column. The eluate was concd and the residue was dissolved in H_2O (0.03 ml). After addition of D-cysteine [11] (0.05 mg) and pyridine (0.015 mg), the mixture was warmed at 60° for 1 hr. The solvent was blown off under an air stream. After dryness, the residue was trimethylsilylated and checked by GC. The GC conditions for the determination of the absolute configurations of the component monosaccharides were as follows: column, Supelco capillary column SPB™ − 1, 0.25 mm × 27 m; column temperature, 230° carrier gas, N_2; t_R, L-apiose (9.6 min), D-apiose (10.4 min), D-rhamnose (11.8 min), L-rhamnose (12.1 min), L-glucose (17.1 min), D-glucose (17.7 min). From **5–7**, L-rhamnose, D-glucose (1:1), from **10–12**, D-apiose, L-rhamnose, D-glucose (1:1:1) were detected. The EtOAc layer was concd to dryness

and was analysed by HPLC. HPLC conditions: column, YMC R-ODS-7, 4.6 mm × 25 cm; flow, 1 ml min^{-1}; solvent, MeCN–H_2O (7:33) containing 0.05% TFA; UV 280 nm; t_R, 3,4-dihydroxyphenethyl alcohol (4.8 min), 2-(3,4-dihydroxyphenyl)-2-hydroxyethan-1-ol (6.9 min), 3-hydroxy-4-methoxyphenethyl alcohol (8.6 min); MeCN–H_2O (1:4) containing 0.05% TFA; UV 320 nm; t_R, caffeic acid (6.0 min), *cis*-ferulic acid (9.9 min), ferulic acid (10.1 min). From **5–7** and **11**, ferulic acid and 2-(3,4-dihydroxyphenyl)-2-hydroxyethane-1-ol, from **10** *cis*-ferulic acid and 3-hydroxy-4-methoxyphenethyl alcohol, and from **12**, caffeic acid and 3,4-dihydroxyphenethyl alcohol were detected. The t_R for L-apiose and D-rhamnose were contained from their enantiomers (D-apiose + L-cysteine and L-rhamnose + L-cysteine, respectively).

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