Iridoid Glycoside Constituents of *Stachys lanata*

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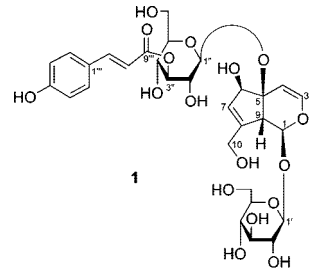
From the aerial parts and roots of *Stachys lanata*, four new iridoid glucosides, stachysosides E−H (**1**−**4**), were isolated together with 30 known compounds. The structures and the stereo configurations of these new compounds were elucidated on the basis of the results of spectroscopic analysis. Compounds **1**−**4** are esters of monomelittoside.

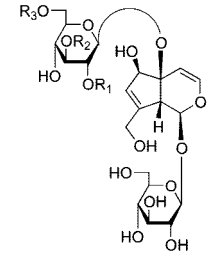
Stachys lanata Crantz. belongs to the plant family Labiatae and is known as "Lamb's ear". This species is used as a ground cover, and the dried flowers are valued decoratively. Previous studies on the chemical constituents of *S. lanata* have resulted in the isolation of three diterpenes.[1] In the present research work, four new iridoid glucosides, stachysosides E−H (**1**−**4**), chlorogenic acid,[2] 11 known phenylethanoid glycosides (verbasoside,[3] darendoside B,[4] verbascoside,[5] isoacteoside,[5] martynoside,[6] stachysoside B,[7] leonoside B,[8] campneoside II,[9] campneoside I,[9] rhodioloside,[10] and 2-phenylethyl-*β*-D-xylopyranosyl-(1→6)-*β*-D-glucopyranoside[11]), nine known flavone glycosides (echinacin,[12] apigenin 7-*O*-[6-*O*-*p*-(*Z*)-coumaroyl]-*β*-D-glucopyranoside,[13] apigenin 7-*O*-*β*-D-glucopyranoside,[14] apigenin 7-*O*-[3-*O*-*p*-(*Z*)-coumaroyl]-*β*-D-glucopyranoside,[15] anisofolin A,[16] stachysetin,[15] isoscutellarein 7-*O*-(6-*O*-acetyl)-*β*-D-allopyranosyl-(1→2)-*β*-D-glucopyranoside,[17] 4-*O*-methylhypolaetin 7-*O*-(6-*O*-acetyl)-*β*-D-allopyranosyl-(1→2)-*β*- D-glucopyranoside,[18] and isoscutellarein 4-methyl ether 7-*O*-(6-*O*-acetyl)-*β*-D-allopyranosyl-(1→2)-*β*-D-glucopyranoside[17]), two known phenylpropanoid glycosides (coniferin[19] and syringin[20]), a sugar ester (cistanoside F[21]), three known acetophenone glycosides (androsin,[22] glucoacetosyringone,[23] and neolloydosin[24]), and three known megastigmanes (vomifoliol,[25] dehydrovomifoliol,[26] and citroside A[27]) were isolated from the water layer of the methanol extract of the aerial parts and roots of *S. lanata*. The structures of compounds **1**−**4** were elucidated on the basis of spectroscopic evidence and by chemical transformation.

Stachysoside E (**1**) was isolated as a colorless amorphous powder with the ^{1}H NMR and ^{13}C NMR data assigned as shown in Table 1. On the basis of its HRFABMS and ^{13}C NMR data, the molecular formula, $C_{30}H_{38}O_{17}$, was deduced (*m*/*z* 671.2166, calcd for $C_{30}H_{39}O_{17}$, 671.2187). The ^{1}H NMR and ^{13}C NMR spectra of **1** were in part almost superimposable with those of melittoside except for signals arising from a (*E*)-*p*-coumaroyl unit in the former.[28] The H-3″ resonance at *δ* 5.08 (dd, *J* = 9.5, 9.5 Hz) proton signal of **1** is shifted downfield relative to the H-3″ signal of the other glucose moiety. In the HMBC spectrum, the H-3″ signal was long-range coupled with the carbonyl carbon at *δ* 169.1 (C-9‴) and the H-1″ signal was long-range coupled with C-5. These data suggested that **1** is the 3″-*O*-*p*-(*E*)-coumaroyl ester of melittoside. Therefore, the structure of **1** was formulated as shown.

Stachysoside F (**2**), a colorless amorphous powder, was assigned with the molecular formula $C_{30}H_{38}O_{17}$ by HRFABMS (*m*/*z* 671.2211, calcd for $C_{30}H_{39}O_{17}$, 671.2187) and from the ^{13}C NMR data. The ^{1}H NMR and ^{13}C NMR spectra of **2** were similar to those of **1**, except for the olefinic signals. The ^{1}H NMR spectrum of the olefinic signals at *δ* 5.85 (d, *J* = 13 Hz) and 6.86 (d, *J* = 13 Hz) suggested the presence of a (*Z*)-*p*-coumaroyl unit. From these data, the structure of **2** was deduced as shown.



1



2 R_1 = H, R_2 = *O*-*p*-(*Z*)-coumaroyl, R_3 = H
3 R_1 = H, R_2 = H, R_3 = *O*-*p*-(*E*)-coumaroyl
4 R_1 = *O*-*p*-(*E*)-coumaroyl, R_2 = H, R_3 = H

Stachysoside G (**3**), a colorless amorphous powder, was assigned with the molecular formula $C_{30}H_{38}O_{17}$ by HRFABMS (*m*/*z* 671.2166, calcd for $C_{30}H_{39}O_{17}$, 671.2187) and from the ^{13}C NMR data. The ^{1}H NMR and ^{13}C NMR spectra of **3** were similar to those of **1**. The H-6″ proton signals at *δ* 4.23 (dd, *J* = 12, 5 Hz) and 4.53 (dd, *J* = 12, 2 Hz) were shifted downfield relative to those of **1**. In the HMBC spectrum, signals for H-6″ were long-range coupled with the carbonyl carbon at *δ* 169.4 (C-9‴). These data suggested that **3** is the 6″-*O*-*p*-(*E*)-coumaroyl ester of melittoside. Hence, the structure of **3** was formulated as shown.

Stachysoside H (**4**), a colorless amorphous powder, was assigned with the molecular formula $C_{30}H_{38}O_{17}$ by HRFABMS (*m*/*z* 693.1991, calcd for $C_{30}H_{38}O_{17}Na$, 693.2005) and from the ^{13}C NMR data. The ^{1}H NMR and ^{13} C NMR spectra of **4** were similar to those of **1**. The ^{1}H−^{1}H COSY spectrum correlated the anomeric proton at *δ* 4.82 (d, *J* = 8 Hz, *β*-D-glucose) with H-2″ at *δ* 4.79 (dd, *J* = 9, 8 Hz). The H-2″ proton signal was shifted downfield relative to that of **1**. In the HMBC spectrum, the signal for H-2″ was long-range coupled with the carbonyl carbon at *δ* 168.9 (C-9‴). These data suggested that **1** is the 2″-*O*-*p*-(*E*)-coumaroyl ester of melittoside. Therefore, the structure of **4** was formulated as shown.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a JASCO DIP-360 polarimeter. CD spectra were recorded on a JASCO J-600 or J-700 spectropolarimeter. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL JNM-AL400 FT-NMR spectrometer, ^{1}H NMR (270 MHz) and ^{13}C NMR (67 MHz) spectra were recorded on a JEOL JNM-EX270 FT-NMR spectrometer, and chemical shifts were given as *δ* values with TMS as an internal standard at 30°C. Inverse-detected heteronuclear correlations were measured using HMQC (optimized for $^1J_{C-H}$ = 145 Hz) and HMBC (optimized for $^nJ_{C-H}$ = 8 Hz) pulse sequences with a pulsed field gradient. HRFABMS and EIMS data were obtained on a JEOL JMS700 mass spectrometer, using a *m*-nitrobenzyl alchol or a glycerol matrix. Preparative HPLC was performed on a JASCO 2089 instrument.

Plant Material. *Stachys lanata* was collected in June 2007. The plant's seeds were originally purchased from Chiltern Seeds (Ulverston, Cumbria, England), and they were cultivated in Shizuoka, Japan. The

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Table 1. NMR Spectroscopic Data for Compounds **1**−**4**

	1[a]		**2**[b]		**3**[a]		**4**[a]	
position	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1	5.61 (d, 3.5)	94.2	5.59 (d, 4)	94.4	5.46 (d, 5)	95.5	5.19 (d, 7.5)	97.7
3	6.38 (d, 6)	143.5	6.38 (d, 6.5)	143.7	6.33 (d, 6.5)	143.8	6.52 (d, 5.5)	145.7
4	5.13 (d, 6)	105.2	5.14 (d, 6.5)	105.3	5.10 (d, 6.5)	105.9	4.83 (overlapped)	106.3
5		80.2		80.4		81.1		83.3
6	4.39 (m)	80.0	4.40 (m)	80.1	4.42 (m)	81.2	4.45 (m)	83.9
7	5.80 (m)	128.2	5.79 (m)	128.2	5.77 (m)	128.0	5.72 (m)	129.7
8		147.4		147.3		147.2		145.5
9	3.35 (overlapped)	51.7	3.30 (overlapped)	51.7	3.30 (overlapped)	52.2	3.35 (overlapped)	52.2
10	4.20 (m)	61.0	4.19 (m)	61.0	4.12 (dd, 15, 1)	61.2	4.22 (m)	61.5
					4.24 (m)			
1′	4.62 (d, 8)	98.3	4.61 (d, 7.6)	98.3	4.58 (d, 7.5)	99.2	4.65 (d, 7.5)	99.7
2′	3.28 (overlapped)	75.0	3.28 (overlapped)	74.9	3.23 (overlapped)	74.9	3.23 (dd, 9, 7.5)	74.8
3′	3.2−3.4 (overlapped)	78.5	3.2−3.4 (overlapped)	78.5	3.2−3.4 (overlapped)	78.1	3.37 (overlapped)	78.5
4′	3.2−3.4 (overlapped)	71.7	3.2−3.4(overlapped)	71.7	3.2−3.4 (overlapped)	71.5	3.2−3.4 (overlapped)	71.6
5′	3.31 (overlapped)	77.3	3.31 (overlapped)	77.3	3.2−3.4 (overlapped)	77.6	3.26 (overlapped)	77.7
6′	3.66 (m)	62.8	3.66 (m)	62.8	3.61 (m)	62.8	3.62 (dd, 12.5, 5)	62.5
	3.88 (brd, 12)		3.88 (brd, 12)		3.85 (dd, 11.5, 1)		3.84 (dd, 12.5, 2)	
1″	4.81 (d, 8)	99.7	4.80 (d, 8)	99.7	4.67 (d, 8)	99.8	4.82 (d, 8)	97.9
2″	3.47 (dd, 9.5, 8)	73.5	3.42 (dd, 9.5, 8)	73.4	3.26 (overlapped)	75.1	4.79 (dd, 9, 8)	75.4
3″	5.08 (dd, 9.5, 9.5)	79.3	5.07 (dd, 9.5, 9.5)	78.7	3.2−3.4 (overlapped)	78.5	3.64 (dd, 9, 9)	76.0
4″	3.61 (dd, 9.5, 9.5)	69.2	3.55 (dd, 9.5, 9.5)	69.1	3.29 (overlapped)	71.8	3.42 (dd, 9.5, 9)	71.5
5″	3.43 (m)	78.0	3.40 (m)	78.0	3.59 (m)	75.4	3.32 (overlapped)	77.9
6″	3.75 (dd, 12.5, 5)	61.9	3.73 (dd, 12.5, 5)	61.9	4.23 (dd, 12, 5)	64.8	3.69 (dd, 12.5, 5)	62.7
	3.83 (dd, 12.5, 2)		3.82 (dd, 12.5, 2)		4.53 (dd, 12, 2)		3.84 (dd, 12.5, 2)	
1‴		127.4		127.6		127.2		127.2
2‴	7.47 (d, 8.5)	131.1	7.66 (d, 8.5)	133.8	7.47 (d, 9)	131.3	7.48 (d, 9)	131.3
3‴	6.89 (d, 8.5)	116.9	6.73 (d, 8.5)	115.9	6.82 (d, 9)	117.0	6.82 (d, 9)	116.9
4‴		161.2		160.2		161.5		161.4
5‴	6.89 (d, 8.5)	116.9	6.73 (d, 8.5)	115.9	6.82 (d, 9)	117.0	6.82 (d, 9)	116.9
6‴	7.47 (d, 8.5)	131.1	7.66 (d, 8.5)	133.8	7.47 (d, 9)	131.3	7.48 (d, 9)	131.3
7‴	7.66 (d, 16)	146.6	6.86 (d, 13)	144.8	7.65 (d, 16)	146.8	7.68 (d, 16)	147.4
8‴	6.40 (d, 16)	115.6	5.85 (d, 13)	116.9	6.37 (d, 16)	115.3	6.40 (d, 16)	115.1
9‴		169.1		168.1		169.4		168.9

[a] 400 MHz, in CD_3OD. [b] 270 MHz, in CD_3OD.

plant was identified by Prof. Yasuhisa Saiki, Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Kobe, Japan. A voucher specimen is deposited at the herbarium of Tohoku Pharmaceutical University, No. 20070604.

Extraction and Isolation. The powdered aerial parts (650 g) of *S. lanata* were extracted with 99% methanol (5 L) twice at room temperature for a month. The methanol extract was concentrated at reduced pressure and the extract was suspended in water (1.5 L) and extracted with ether (1.0 L) three times. The water layer (28.1 g) was obtained as a red-brown syrup. It was dissolved in water and the aqueous solution was passed through a porous polymer gel column (Mitsubishi Diaion HP-20, 70 × 100 mm) eluting with water, 10% and 80% MeOH, and MeOH. The 80% MeOH eluate (4.5 g) was chromatographed on a reversed-phase column using ODS (Cosmosil 140C_{18}-OPN, Nacalai Tesque, 150 g), eluting with 10%, 20%, 30%, 40%, 50%, and 80% MeOH to give six fractions (fractions 1A−1F). Fraction 1B (387 mg) was subjected to preparative LPLC [column, Yamazen, Ultra Pack ODS-SM-50C-M 37 × 100 mm; solvent, methanol−water (20:80)→(40:60); detector, UV 210 nm], to give 13 fractions (fractions 2A−2M). Fraction 2I (48.6 mg) was subjected to semipreparative HPLC [column, Tosoh, ODS-100V, 20 × 250 mm; solvent, acetonitrile−water (17.5:82.5); detector, UV 210 nm], to give five fractions: (fractions 3A−3E), fraction 3D (8.9 mg) was subjected to semipreparative HPLC [column, Nomura Chemical, Develosil C30-UG-5, 20 × 250 mm; solvent, acetonitrile-water (11.5:88.5); detector, UV 320 nm], to yield compounds **1** (5.0 mg) and **2** (1.6 mg). Fraction 1C (751 mg) was subjected to preparative LPLC [column, Yamazen, Ultra Pack ODS-SM-50C-M 37 × 100 mm; solvent, methanol−water (30:70)→(40:60); detector, UV 210 nm] to yield verbascoside (173.4 mg). Fraction 1D (386 mg) was subjected to preparative LPLC [column, Yamazen, Ultra Pack ODS-SM-50C-M 37 × 100 mm; solvent, methanol−water (40:60)→(50:50); detector, UV 210 nm] and HPLC [column, Tosoh, ODS-100V, 20 × 250 mm; solvent, acetonitrile-water (25:75); detector, UV 210 nm] to yield 2-phenylethyl-β-D-xylopyranosyl-(1→6)-β-D-glucopyranoside (2.7 mg), apigenin 7-*O*-β-D-glucopyranoside (19.0 mg), vomifoliol (2.7 mg), and dehydrovomifoliol (1.2 mg). Fraction 1E (330 mg) was subjected to preparative LPLC [column, Yamazen, Ultra Pack ODS-SM-50C-M 37 × 100 mm; solvent, methanol−water (50:50)→(60:40); detector, UV 210 nm] and HPLC [column, Tosoh, ODS-100V, 20 × 250 mm; solvent, acetonitrile−water (30:70); detector, UV 210 nm] to yield martynoside (10.1 mg), leonoside B (3.7 mg), isoscutellarein 7-*O*-(6-*O*-acetyl)-β-D-allopyranosyl-(1→2)-β-D-glucopyranoside (8.0 mg), and 4-*O*-methylhypolaetin 7-*O*-(6-*O*-acetyl)-β-D-allopyranosyl-(1→2)-β-D-glucopyranoside (11.9 mg). Fraction 1E (751 mg) was subjected to preparative HPLC [column, Tosoh, ODS-100V, 20 × 250 mm; solvent, acetonitrile−water (30:70); detector, UV 210 nm] to yield echinacin (25.7 mg), apigenin 7-*O*-[6-*O*-*p*-(*Z*)-coumaroyl]-β-D-glucopyranoside (12.9 mg), apigenin 7-*O*-[3-*O*-*p*-(*Z*)-coumaroyl]-β-D-glucopyranoside (4.0 mg), anisofolin A (1.0 mg), stachysetin (2.4 mg), and isoscutellarein 4′-methyl ether 7-*O*-(6-*O*-acetyl)-β-D-allopyranosyl-(1→2)-β-D-glucopyranoside (3.0 mg).

The powdered roots (620 g) of *S. lanata* were extracted with 99% methanol (3 L) twice at room temperature for a month. The methanol extract was concentrated at reduced pressure, and the extract was suspended in water (1.5 L) and extracted with ether (1.0 L) three times. The water layer (42.8 g) was obtained as a red-brown syrup. It was dissolved in water and the aqueous solution was passed through a porous polymer gel column (Mitsubishi Diaion HP-20, 70 mm × 100 mm) eluting with water, 10% and 80% MeOH, and MeOH. The 80% MeOH eluate (12.8 g) was chromatographed by reversed-phase chromatography using ODS (Cosmosil 140C_{18}-OPN, Nacalai Tesque, 100 g) eluting with 10%, 20%, 30%, 40%, 50%, and 80% MeOH (fractions 4A−4F). Fraction 4B (0.6 g) was subjected to preparative LPLC [column, Yamazen, Ultra Pack ODS-SM-50C-M 37 × 100 mm; solvent, methanol−water (30:70)→(60:40); detector, UV 210 nm], to yield verbascoside (180.2 mg) and isoacteoside (44.2 mg). Fraction 4A (1.8 g) was subjected to preparative LPLC [column, Yamazen, Ultra Pack ODS-SM-50C-M 37 × 100 mm; solvent, methanol−water (30:70)→(60:40); detector, UV 210 nm], to give seven fractions (fractions 5A-5G). Fraction 5E (201.1 mg) was subjected to semipreparative HPLC [column, Tosoh, ODS-100V, 20 × 250 mm; solvent, acetonitrile−water (17.5:82.5); detector, UV 210 nm and Nomura Chemical, Develosil C30-UG-5, 20 × 250 mm; solvent, acetonitrile−water (11.5:88.5); detector, UV 280 nm], to yield compounds **1** (10.6 mg), **2** (4.0

mg), and **4** (4.0 mg), darendoside B (12.5 mg), and glucoacetosyringone (1.5 mg). Fraction 5F (90.7 mg) was subjected to semipreparative HPLC [column, Tosoh, ODS-100V, 20 × 250 mm; solvent, acetonitrile−water (20:80); detector, UV 210 nm and Kanto Chemical, Mightysil RP-18 GP, 10 × 250 mm; solvent, acetonitrile−water (15:85); detector, UV 210 nm], to yield compound **3** (5.3 mg), campneoside II (3.1 mg), campneoside I (2.0 mg), and citroside A (1.7 mg). Fraction 5B (193.4 mg) was subjected to semipreparative HPLC [column, Tosoh, ODS-100V, 20 × 250 mm; solvent, acetonitrile−0.2% TFA (trifluoroacetic acid) aq. (20:80); detector, UV 210 nm and Kanto Chemical, Mightysil RP-18 GP, 10 × 250 mm; solvent, methanol-0.2% TFA (25:75); detector, UV 210 nm, in darkness], to yield chlorogenic acid (5.9 mg). Fraction 5C (161.7 mg) was subjected to preparative HPLC [column, Tosoh, ODS-100V, 20 × 250 mm; solvent, acetonitrile−water (15:85); detector, UV 210 nm and column, Kanto Chemical, Mightysil RP-18 GP, 10 × 250 mm; solvent, methanol−water (10:90); detector, UV 210 nm] to yield verbasoside (13.2 mg), campneoside I (2.7 mg), rhodioloside (1.7 mg), coniferin (0.6 mg), cistanoside F (2.9 mg), and neolloydosin (3.2 mg). Fraction 5D (91.6 mg) was subjected to preparative HPLC [column, Tosoh, ODS-100V, 20 × 250 mm; solvent, acetonitrile-water (20:80); detector, UV 210 nm and Kanto Chemical, Mightysil RP-18 GP, 10 × 250 mm; solvent, methanol−water (15:85); detector, UV 210 nm] to yield syringin (3.7 mg) and androsin (2.4 mg). Fraction 5G (897.6 mg) was subjected to preparative LPLC [column, Yamazen, Ultra Pack ODS-SM-50C-M 37 × 100 mm; solvent, methanol−water (40:60); detector, UV 210 nm] and HPLC [column, Tosoh, ODS-100V, 20 × 250 mm; solvent, acetonitrile−water (25:75); detector, UV 210 nm] to yield stachysoside B (49.6 mg).

Stachysoside E (1): colorless, amorphous powder; $[\alpha]_D^{24}$ −23.6 (*c* 1.06, MeOH); ^{1}H NMR and ^{13}C NMR, Table 1; HRFABMS *m*/*z* 671.2188 (calcd for $C_{30}H_{39}O_{17}$, 671.2187).

Stachysoside F (2): colorless, amorphous powder; $[\alpha]_D^{24}$ −10.0 (*c* 0.30, MeOH); ^{1}H NMR and ^{13}C NMR, Table 1; HRFABMS *m*/*z* 671.2211 (calcd for $C_{30}H_{39}O_{17}$, 671.2187).

Stachysoside G (3): colorless, amorphous powder; $[\alpha]_D^{24}$ −7.9 (*c* 0.51, MeOH); ^{1}H NMR and ^{13}C NMR, Table 1; HRFABMS *m*/*z* 671.2166 (calcd for $C_{30}H_{39}O_{17}$, 671.2187).

Stachysoside H (4): colorless, amorphous powder; $[\alpha]_D^{24}$ +28.5 (*c* 0.40, MeOH); ^{1}H NMR and ^{13}C NMR, Table 1; HRFABMS *m*/*z* 693.1991 (calcd for $C_{30}H_{38}O_{17}Na$, 693.2005).

Sugar Identification. Each compound [**1** (1.2 mg), **2** (0.8 mg), **3** (1.1 mg), and **4** (0.8 mg)] was refluxed with 7% HCl (1 mL) for 2 h. After cooling, the reaction mixture passed through an Amberlite IRA400 column and the eluate was concentrated. The residues were dissolved in pyridine (0.5 mL) and stirred with L-cysteine methyl ester (5 mg) for 1.5 h at 60 °C, and then *o*-tolyl isothiocyanate (20 μL) was added to the mixture and heated at 60 °C for 1.5 h. The reaction mixtures were analyzed by HPLC and detected at 250 nm. Analytical HPLC was performed on a Shiseido Capcell Pak C_{18} column (4.6 × 250 mm) at 20 °C using as solvent CH_3CN−0.2% TFA in H_2O (25:75). Peaks were detected with a Tosoh UV8010 UV detector. D-Glucose (t_R, 16.7 min) was identified for **1**−**4** by comparing their retention times with those of the authentic samples, D-glucose (t_R, 16.7 min) and L-glucose (t_R, 14.8 min).[29]

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Supporting Information Available: Table of HMBC and NOE data of compounds **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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