Secoiridoid Glucosides from *Strychnos spinosa*

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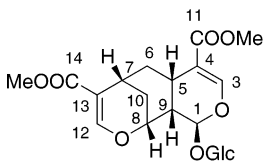
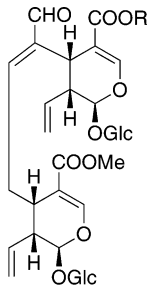
Three new secoiridoid glucosides, stryspinoside (**1**) and strychosides A (**2**) and B (**3**), were isolated, together with 23 known compounds, from the dried branches of *Strychnos spinosa*. The structures of the new compounds were determined by spectroscopic means.

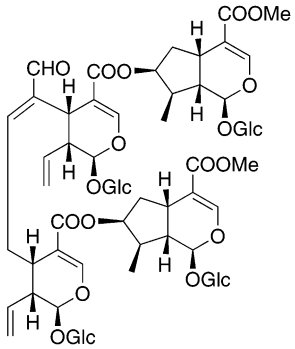
The genus *Strychnos* (Loganiaceae) is well known to contain various bioactive indole alkaloids represented by strychnine.[1] From our interest in indole alkaloids and related glycosides,[2] we examined the glycosidal fraction of *Strychnos spinosa* Lam. cultivated in Kyoto, Japan. *S. spinosa* is a thorny shrub or small tree distributed in Africa. The ripe fruits, called monkey oranges, are eaten in Malawi. Various parts of the plant have been used in African traditional medicine for earache, dropsy, fever, and snakebite.[3] Previous phytochemical studies on this plant reported the isolation of some indole alkaloids, pyridine derivatives, a lignan, monoterpenoids, triterpenoids, and fatty acids.[4−9] In this paper we describe the isolation and characterization of three new secoiridiod glucosides.



1



2: R=H
4: R=Me



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Dried branches of *S. spinosa* were extracted with MeOH under reflux. The extract was successively partitioned between H_2O and $CHCl_3$ and between H_2O and *n*-BuOH. The *n*-BuOH-soluble fraction was separated by a combination of chromatographic procedures to afford three new compounds, **1**−**3**, along with 23 known compounds: loganin,[10] secologanin,[11] sweroside,[10] secoxyloganin,[11] secologanin dimethyl acetal,[10] secologanoside,[11] secologanoside 7-methyl ester,[12] secologanoside dimethyl ester,[11] secologanic acid,[13] vogeloside,[14] *epi*-vogeloside,[14] (5*S*)-5-carboxystrictosidine,[15] cantleyoside,[16] triploside A,[17] (*E*)-aldosecologanin (**4**),[18] 2,4,6-trimethoxyphenol 1-*O*-*β*-D-glucopyranoside,[19] benzyl alcohol *O*-α-L-arabinopyranosyl-(1→6)-*β*-D-glucopyranoside,[20] trifolin,[21] geraldol,[22] hyperin,[23] astragalin,[23] hirsutrin,[23] and nicotiflorin.[23] All compounds were isolated for the first time from this species. The new glucosides were named stryspinoside (**1**), strychoside A (**2**), and strychoside B (**3**).

Stryspinoside (**1**) was isolated as an amorphous powder. Its molecular formula was deduced as $C_{21}H_{28}O_{12}$ by HRSIMS. It showed a UV maximum at 232 nm and IR bands at 3415, 1701, and 1636 cm^{-1}. Its ^1H NMR spectrum exhibited signals for an olefinic proton at δ 7.15 (d, J = 2.5 Hz), a carbomethoxyl group at δ 3.59 (s), and two acetal protons at δ 4.63 (d, J = 8.0 Hz) and 5.74 (brs), suggesting an iridoid or a secoiridoid glucoside. Additional signals for a carbomethoxyl group at δ 3.66 (s) and an olefinic proton at δ 7.37 (s) were observed. These signals, together with ^{13}C NMR signals at δ 109.7, 159.6, and 169.2, indicated another *β*-alkoxy-α,*β*-unsaturated carboxylate system. COSY correlations of H-1−H-9−H-5−H_2-6−H-7−H_2-10−H-8−H-9 revealed a cyclohexane ring with substituted groups at C-7 and C-8. HMBC correlation peaks between H-6/C-13, H-10/C-13, H-8/C-12, and H-12/C-7, -8, -13, and -14 suggested the planar structure **1**. The relative configuration was based on $^3J_{H,H}$ values and NOE correlations. The coupling constants between H-5 and H_2-6 ($J_{5,6\alpha}$ = 3.5 Hz and $J_{5,6\beta}$ = 6.5 Hz) and between H-5 and H-9 ($J_{5,9}$ = 6.5 Hz) and 1,3-diaxial NOESY correlations between H-6*β* and H-9 and between H-9 and H-10 established a chair conformation for the cyclohexane ring with H-6*β* and H-9 at axial orientations and H-5 at an equatorial position. The absolute configurations of **1** were assumed to be 1*S*, 5*S*, 7*R*, 8*R*, and 9*S* from biogenetic consideration that stryspinoside (**1**) could be derived from secologanin and a C_3-unit from malonic acid. An analogous bridged compound has been chemically synthesized from secologanin through a tandem-Knoevenagel−hetero-Diels−Alder reaction.[24] This is the first example of the isolation of this type of secoiridoid glucoside.

Strychoside A (**2**), $C_{33}H_{44}O_{19}$, was also isolated as an amorphous powder. Its ^1H NMR spectrum showed two olefinic proton signals for H-3 [δ 7.46 (J = 1.5 Hz), 7.54 (brs)], two sets of signals for terminal vinyl groups [δ 5.02 (J = 10.0 Hz), 5.06 (J = 17.0 Hz), 5.28 (J = 10.0 Hz), 5.34 (J = 17.0 Hz), 5.62 (J = 17.0, 10.0 Hz), 5.77 (m)], two acetal proton signals for H-1 [δ 5.47 (d, J = 3.5 Hz), 5.56 (brd, J

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Table 1. ^{1}H NMR Data of **1**–**3** in CD_3OD at 500 MHz

	1	**2**[a]				**3**[a]							
H		a part		b part		a part		b part		c part		d part	
1	5.74 brs	5.56	brd (5.5)	5.47	d (3.5)	5.56	d (4.5)	5.48	d (2.0)	5.26	d (5.0)	5.18	d (6.0)
3	7.15 d (2.5)	7.54	brs	7.46	d (1.5)	7.54	s	7.47	s	7.43	s	7.44	s
5	3.09 tdd (6.5, 3.5, 2.5)	3.04–3.15 m		4.04	m	3.01	m	4.10	brd (5.0)	3.11	brq (8.0)	3.01	m
6	1.72 ddd (14.5, 6.5, 3.5)	2.44	brdq (15.0, 7.5)			2.38	m			1.76	ddd (14.0, 8.0, 5.0)	1.60	ddd (14.0, 9.0, 5.0)
6	2.93 brd (14.5)	3.04–3.15 m				3.16	m			2.32	dd (14.0, 7.0)	2.14	m
7	2.72 brs	6.68	brt (7.0)	9.23	s	6.76	brt (7.0)	9.32	s	5.25	brt (5.0)	5.15	brt (5.0)
8	4.74 brs	5.77	m	5.62	dt (17.0, 10.0)	5.77	dt (17.0, 10.0)	5.63	dt (17.0, 10.0)	2.18	m	2.14	m
9	2.30 brd (6.5)	2.76	brdt (8.5, 5.5)	2.60	m	2.81	m	2.57	m	2.06	td (9.0, 5.0)	1.96	brq (7.0)
10	1.78 dtd (13.0, 3.5, 2.0)	5.28	brd (10.0)	5.02	brd (10.0)	5.30	brd (10.0)	5.01	brd (10.0)	1.08	d (7.0)	1.00	d (7.0)
10	1.91 ddd (13.0, 2.5, 1.5)	5.34	brd (17.0)	5.06	brd (17.0)	5.37	brd (17.0)	5.05	brd (17.0)				
12	7.37 s									3.71[c]	s	3.69[c]	s
11-OMe	3.59 s	3.72	s										
14-OMe	3.66 s												
1′	4.63 d (8.0)	4.68	d (8.0)	4.68	d (8.0)	4.68	d (8.0)	4.67	d (8.0)	4.66	d (8.0)	4.64	d (8.0)
2′	3.15 dd (9.0, 8.0)	3.19[b]	dd (9.0, 8.0)	3.25[b]	d (9.0, 8.0)	3.21	brt (8.5)	3.21	brt (8.5)	3.21	brt (8.5)	3.21	brt (8.5)
3′	3.34 t (9.0)	3.25–3.39 m		3.25–3.39 m		3.26–3.38 m		3.26–3.38 m		3.26–3.38 m		3.26–3.38 m	
4′	3.24 t (9.0)	3.25–3.39 m		3.25–3.39 m		3.26–3.38 m		3.26–3.38 m		3.26–3.38 m		3.26–3.38 m	
5′	3.32 m	3.25–3.39 m		3.25–3.39 m		3.26–3.38 m		3.26–3.38 m		3.26–3.38 m		3.26–3.38 m	
6′	3.65 dd (12.0, 6.5)	3.68	brd (12.0)	3.68	brd (12.0)	3.63–3.70 m		3.63–3.70 m		3.63–3.70 m		3.63–3.70 m	
6′	3.91 dd (12.0, 2.5)	3.88	brd (12.0)	3.88	brd (12.0)	3.86–3.91 m		3.86–3.91 m		3.86–3.91 m		3.86–3.91 m	

[a] Structural parts a, b, c, and d are indicated in Figure 1. [b,c] Values with the same superscript are interchangeable.

Table 2. ^{13}C NMR Data of **1**–**3** in CD_3OD at 125 MHz

	1	**2**[a]		**3**[a]			
C		a part	b part	a part	b part	c part	d part
1	97.0	97.6	97.3	97.9[h]	97.2	97.7[h]	98.3
3	152.2	154.2	151.9	154.1	151.9	152.7	153.2
4	111.6	110.5	109.9	111.1	109.8	113.1	112.6
5	24.4	33.8	31.2	33.0	30.7	32.9	33.6
6	30.3	29.6	143.3	29.6	143.7	40.4[i]	40.3[i]
7	25.4	156.2	196.9	156.1	197.2	78.4[j]	78.0[j]
8	74.3	135.8[b]	135.5[b]	135.6	135.4	41.1	41.1
9	44.0	45.4	46.5	45.3	46.6	47.1	46.9
10	30.7	120.3	119.2	120.6	119.4	14.2	14.3
11	169.0	169.0	171.0	168.2[k]	168.3[k]	169.5	169.5
12	159.6						
13	109.7						
14	169.2						
OMe	51.5	52.0				51.8	51.8
OMe	51.6						
1′	99.6	99.8[c]	100.1[c]	100.2	99.6	100.2	100.4
2′	74.7	74.6[d]	74.7[d]	74.5[l]	74.6[l]	74.8[l]	74.7[l]
3′	78.0	77.9[e]	78.0[e]	77.8[m]	77.8[m]	78.0[m]	77.9[m]
4′	71.7	71.5[f]	71.6[f]	71.5[n]	71.6[n]	71.6[n]	71.6[n]
5′	78.3	78.3	78.3	78.2[o]	78.3[o]	78.6[o]	78.4[o]
6′	62.9	62.6[g]	62.7[g]	62.7[p]	62.8 [p]	62.9[p]	62.8[p]

[a] Structural parts a, b, c, and d are indicated in Figure 1. [b–p] Values with the same superscript are interchangeable.

Figure 1.

= 5.5 Hz)], and two sets of signals for β-glucopyranosyl units [δ 3.19–4.68], indicating the presence of two secoiridoid glucoside units in the molecule. In addition, signals for an aldehyde [δ_H 9.23 (s), δ_C 196.9] and a trisubstituted olefin [δ_H 6.68 (brt, J = 7.0 Hz), δ_C 143.3 and 156.2] were observed in its ^{1}H and ^{13}C NMR spectra. The NOESY interactions between the olefinic proton at δ 6.68 and the aldehyde proton at δ 9.23 and between H-6a and H-5b and the HMBC correlations between the olefinic proton at δ 6.68 and C-5b and the aldehyde carbon and between the aldehyde proton and C-5b and C-6b suggested a structural resemblance to (*E*)-aldosecologanin (**4**)[18] except for the absence of one methoxyl group in **2**. A carbomethoxyl group was placed at C-4a by the HMBC correlation between a methoxyl signal at δ 3.72 and C-11a (δ 169.0), which was discriminated from C-11b (δ 171.0) by 2D NMR studies. Accordingly, the structure of strychoside A was deduced to be **2**.

Strychoside B (**3**) was also isolated as an amorphous powder and showed the molecular formula $C_{66}H_{90}O_{37}$ from its HRSIMS. Its spectral features were closely similar to those of **2**. However, duplicated signals assignable to two 7-*O*-acylated loganin units[25] were additionally observed in its NMR spectra (Tables 1 and 2). The H-3 signals were assigned using COSY and TOCSY experiments, and HMBC correlations from H-3a, H-3c, and H-3d allowed assignments of C-11a, C-11c, and C-11d. Ester linkages of the 7-hydroxy groups in loganin units with carboxyl groups in

strychoside A (**2**) were revealed by the HMBC correlations between H-7c and C-11a and between H-7d and C-11b. Carbomethoxyl groups at C-11c and C-11d were demonstrated by HMBC correlations between a singlet at δ 3.71 and C-11c and between a singlet at δ 3.69 and C-11d. This suggestion was further supported by ROESY cross-peaks between H-3a and H_3-10c, between H-3b and H_3-10d, between H-3c and a methoxyl singlet at δ 3.71, and between H-3d and a methoxyl singlet at δ 3.69. Thus, strychoside B was characterized as **3**.

Experimental Section

General Experimental Procedures. UV spectra were recorded on a Shimadzu UV-2500PC spectrophotometer and IR spectra on a Shimadzu FTIR-8200 spectrophotometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Varian VXR-500 spectrometer with TMS as an internal standard. MS and HRMS were obtained with a Hitachi M-4100 mass spectrometer. Glycerol was used as the matrix for SIMS and HRSIMS. MPLC was carried out with Wakogel LP-40 C18. TLC was performed on precoated Kieselgel 60F_{254} plates (Merck).

Plant Material. The plant *Strychnos spinosa* Lam. was identified by one of us (T.A.) and cultivated in the Nippon Shinyaku Institute for Botanical Research. A voucher specimen (No. 2731) is deposited in the laboratory of the Nippon Shinyaku Institute for Botanical Research.

Extraction and Isolation. Dried branches (420 g) of *S. spinosa* were extracted with hot MeOH, extracts were concentrated in vacuo, and part (35.1 g) of the resulting residue (48.3 g) was resuspended in H_2O and extracted successively with $CHCl_3$ and *n*-BuOH. The residue (21.4 g) from the *n*-BuOH layer was fractionated using reversed-phase MPLC. Elution with H_2O−MeOH mixtures of the indicated MeOH content gave 10 fractions, 1 (5%, 2.21 g), 2 (5−15%, 3.53 g), 3 (15−20%, 1.85 g), 4 (25%, 0.54 g), 5 (30%, 0.42 g), 6 (30%, 0.34 g), 7 (35%, 0.43 g), 8 (35%, 0.39 g), 9 (40−45%, 1.17 g), and 10 (50%, 0.47 g). Fraction 1 was purified by preparative HPLC (μBondasphere 5μ C18−100 Å, MeOH−H_2O, 3:7, 1:3, MeCN−H_2O, 1:9, 3:17, 1:4) to afford secologanoside (262 mg), sweroside (363 mg), *epi*-vogeloside (10.4 mg), vogeloside (4.6 mg), secologanic acid (35.0 mg), loganin (9.0 mg), and 2,4,6-trimethoxyphenol 1-*O*-β-D-glucopyranoside (5.3 mg). In the same way, fractions 2−10 were purified by a combination of reversed-phase MPLC with MeOH−H_2O, preparative HPLC (μBondasphere 5μ C18−100 Å, MeOH−H_2O, 3:7−1:1; MeCN−H_2O, 33:7, 3:1), and preparative TLC ($CHCl_3$−MeOH, 4:1, 7:3; $CHCl_3$−MeOH−H_2O, 70:30:1.5, AcOEt−C_6H_6−EtOH, 4:1:2). Fraction 2 yielded loganin (70.8 mg), secologanin (8.3 mg), secologanic acid (220 mg), vogeloside (39.4 mg), *epi*-vogeloside (65.1 mg), secoxyloganin (442 mg), secologanoside 7-methyl ester (13.6 mg), sweroside (697 mg), and benzyl alcohol *O*-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside (5.4 mg); fraction 3 yielded secologanin (217 mg) and secologanin dimethyl acetal (22.5 mg); fraction 4 yielded **1** (24.1 mg); fraction 5 yielded secologanoside dimethyl ester (27.5 mg) and (5*S*)-5-carboxystrictosidine (5.8 mg); fraction 6 yielded **2** (14.7 mg), hirsutrin (7.9 mg), and hyperin (2.0 mg); fraction 7 yielded **4** (101 mg), astragalin (4.2 mg), trifolin (3.5 mg), and nicotiflorin (1.5 mg); fraction 8 yielded triploside A (22.7 mg), geraldol (5.3 mg), astragalin (5.8 mg), and nicotiflorin (4.9 mg); fraction 9 yielded sweroside (4.0 mg) and cantleyoside (225 mg); fraction 10 yielded **3** (5.1 mg). The known compounds were identified by comparison with literature data.

Stryspinoside (1): amorphous powder; $[\alpha]^{20}_D$ −172° (*c* 1.1, MeOH); UV (MeOH) λ_{max} (log ϵ) 232 (4.28) nm; IR (KBr) ν_{max} 3415, 1701, 1636 cm^{-1}; ^{1}H NMR, Table 1; ^{13}C NMR, Table 2; NOESY, H-1 and H-8; H-6 (δ 1.72) and H-9; H-9 and H-10 (δ 1.91); HMBC, H-1 to C-3, 5, 8, 1′; H-3 to C-1, 4, 5, 11; H-5 to C-3, 4, 6, 7, 8, 9; H-6 to C-4, 7, 10, 13; H-8 to C-5, 12; H-9 to C-1, 4, 5; H-10 to C-7, 13; H-12 to C-7, 8, 13, 14; H-1′ to C-1, 3′, 5′; OMe (δ 3.59) to C-11; OMe (δ 3.66) to C-14; negative ion SIMS *m/z* 471 [M − H]$^-$, 309; negative ion HRSIMS *m/z* 471.1475 (calcd for $C_{21}H_{27}O_{12}$, 471.1503).

Strychoside A (2): amorphous powder; $[\alpha]^{21}_D$ −131° (*c* 1.0, MeOH); UV (MeOH) λ_{max} (log ϵ) 233 (4.35) nm; IR (KBr) ν_{max} 3379, 1690, 1636 cm^{-1}; ^{1}H NMR, Table 1; ^{13}C NMR, Table 2; NOESY, H-1a and H-1′a; H-6a and H-5b; H-7a and H-7b; H-9a and H-10a; H-1b and H-1′b; H-9b and H-10b; HMBC, H-6a to C-5a; H-7a to C-5b, 7b; H-9a to C-1a, 4a, 5a, 8a, 10a; H-10a to C-9a; H-1′a to C-1a; OMe to C-11a; H-1b to C-3b, 5b, 1′b; H-3b to C-1b, 4b, 5b, 11b; H-7b to C-5b, 6b; H-8b to C-1b; H-1′b to C-1b; negative ion HRSIMS *m/z* 743.2394 (calcd for $C_{33}H_{43}O_{19}$, 743.2400).

Strychoside B (3): amorphous powder; $[\alpha]^{21}_D$ −102° (*c* 0.33, MeOH); UV (MeOH) λ_{max} (log ϵ) 235 (4.68) nm; IR (KBr) ν_{max} 3442, 1695, 1636 cm^{-1}; ^{1}H NMR, Table 1; ^{13}C NMR, Table 2; ROESY, H-1a and H-1′a; H-3a and H-9a; H-3a and H_3-10c; H-5a and H-7b; H_2-6a and H-5b; H-7a and H-7b; H-9a and H-10a; H-9a and H-7b; H-1b and H-1′b; H-3b and H_3-10d; H-1c and H-1′c; H-3c and OMe (δ 3.71); H-3c and H-8c; H_3-10c and H-9c; H-1d and H-1′d; H-3d and OMe (δ 3.69); H-3d and H-5d; H_3-10d and H-9d; HMBC, H-1a to C-1′a; H-3a to C-1a, 4a, 5a, 11a; H-7a to C-5b; H-10a to C-9a; H-1′a to C-1a; H-3b to C-4b, 5b; H-7b to C-5b, 6b; H-1′b to C-1b; H-1c to C-3c, 1′c; H-3c to C-1c, 4c, 5c, 11c; H-5c to C-4c; H-6c to C-4c; H-7c to C-11a; H-8c to C-1c; H_3-10c to C-7c, 8c, 9c; H-1′c to C-1c; H-1d to C-3d, 5d, 8d, 1′d; H-3d to C-1d, 5d, 11d; H-6d to C-4d; H-7d, to C-5d, 11b; H-8d to C-1d, H_3-10d to C-7d, 8d, 9d; OMe (δ 3.69) to C-11d; H-1′d to C-1d; negative ion SIMS *m/z* 1473 [M − H]$^-$, 1311, 1101; negative ion HRSIMS *m/z* 1473.5102 (calcd for $C_{66}H_{89}O_{37}$, 1473.5085).

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