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SECOIRIDOID GLUCOSIDES ESTERIFIED WITH A PHENOLIC GLUCOSIDE FROM *ALSTONIA MACROPHYLLA*

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Abstract – Eleven novel secoiridoid glucosides, *O*-methylfrachinoside (**1**) and alstomacrosides A–J (**2**–**11**) were isolated, together with seventeen known compounds, from the dried twigs of *Alstonia macrophylla*. The structures of the new compounds were established on the basis of 1D and 2D NMR spectroscopic data. These compounds were commonly characterized as esters of secoxyloganin with a phenolic glucoside.

INTRODUCTION

The genus *Alstonia* (Apocynaceae), which is widely distributed over tropical regions of Central America and Asia, is well known to be rich in unique alkaloidal constituents.[1] *A. macrophylla* Wall. ex G. Don of this genus has been used in conventional medicines in Thailand as a general tonic, aphrodisiac, anticholeric, antidysenteric, antipyretic, emmenagogue and vulnerary agents.[2] Previous studies on this plant led to the discovery of diverse types of indole alkaloids with interesting biological activities.[3–5] In the course of our studies on glucoalkaloids from indole or ipecac alkaloids-producing plants,[6–9] we investigated the polar fraction of *A. macrophylla* to isolate new secoiridoid glucosides along with seventeen known compounds including two glucoalkaloids. We report here the isolation and structural elucidation of eleven novel secoiridoid glucosides (**1**–**11**) (Figure 1).

RESULTS AND DISCUSSION

The *n*-BuOH soluble fraction of a methanolic extract of the twigs of *A. macrophylla* was separated using a combination of chromatographic procedures to afford eleven new compounds, *O*-methylfrachinoside (**1**) and alstomacrosides A–J (**2**–**11**) along with seventeen known compounds: sweroside,[10] secoxyloganin

(**12**),[11] naresuanoside (**13**),[3] strictosamide (**14**),[12] (5*S*)-5-carboxystrictosidine (**15**),[13] 10-hydroxystrictamine,[14] blumenol C 9-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside,[15] acantrifoside F,[16] (+)-lyoniresinol 3α-*O*-β-D-glucopyranoside,[17,18] (−)-lyoniresinol 3α-*O*-β-D-glucopyranosids,[17,18] dehydrodiconiferyl alcohol 9-*O*-β-D-glucopyranoside,[19] (+)-isolariciresinol-9'-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside,[20] [(2*S*,3*R*)-2,3-dihydro-2-(4-hydroxy-3,5-dimethoxyphenyl)-5-[(1*E*)-3-hydroxy-1-propenyl]-7-methoxy-3-benzofuranyl]methyl-β-D-glucopyranoside,[19] [(2*R*,3*S*)-2,3-dihydro-2-(4-hydroxy-3,5-dimethoxyphenyl)-5-[(1*E*)-3-hydroxy-1-propenyl]-7-methoxy-3-benzofuranyl]methyl-β-D-glucopyranoside,[19] arjunolic acid,[21] and asteryunnanoside B.[21]

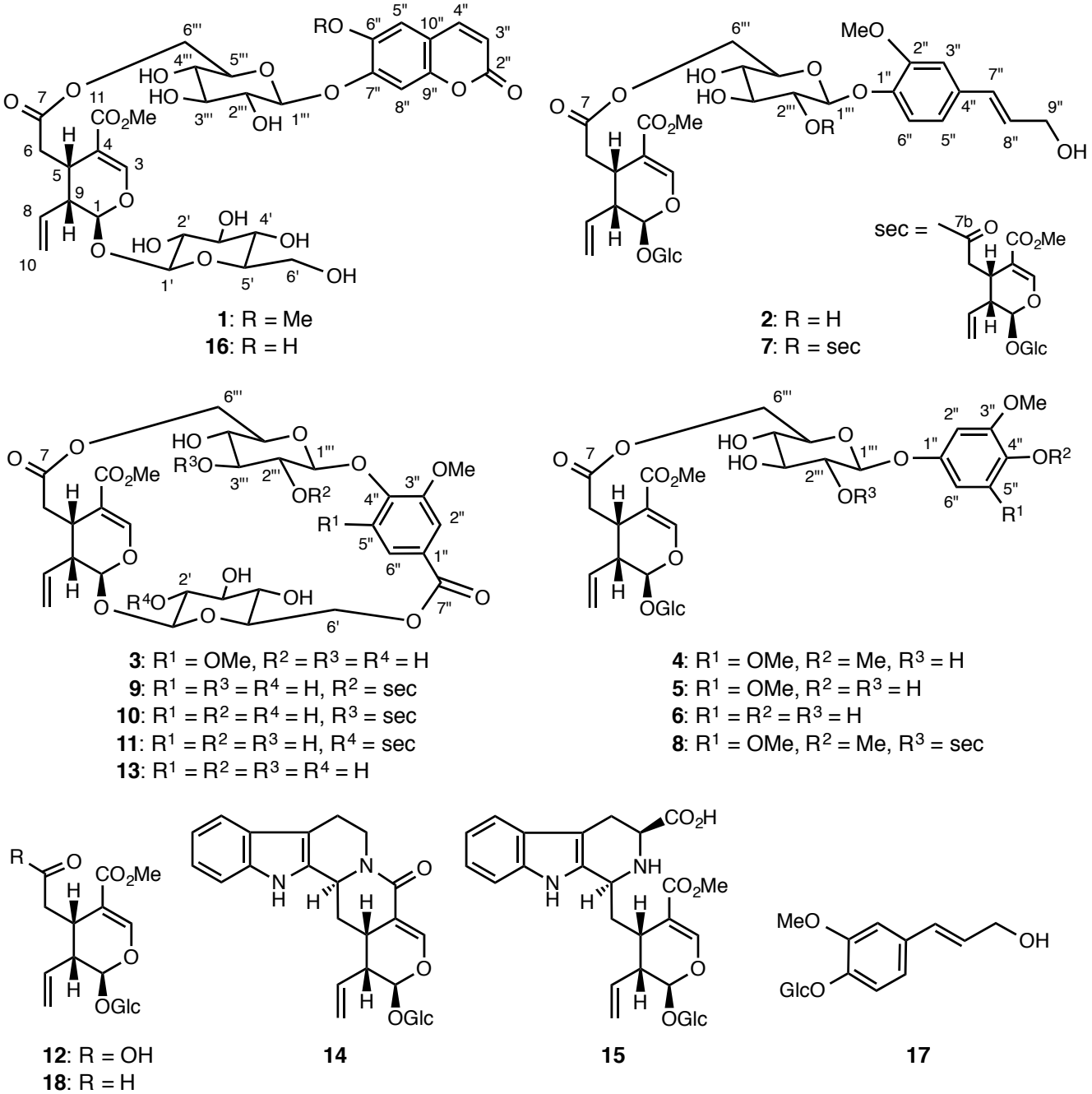

Figure 1. Structures of isolated glucosides **1**–**15** and their related compounds

Compound **1** was isolated as an amorphous powder. The HRSIMS of **1** established an elemental composition of $C_{30}H_{40}O_{19}$. It showed UV maxima at 201, 227, 288 and 340 nm and IR bands at 3421, 1717, 1700, 1635, 1623, and 1508 cm^{-1}. Its distinctive ^{1}H-NMR spectral features [H-3 at δ_H 7.44 (d, J = 2.0 Hz), OMe at δ_H 3.59 (s), H-8 at δ_H 5.53 (dt, J = 17.0, 10.0 Hz), H_2-10 at δ_H 4.94 (dd, J = 0.0, 2.0 Hz) and 5.04 (br dd, J = 17.0, 2.0 Hz), H-1 at δ_H 5.43 (d, J = 4.0 Hz), H-1' at δ_H 4.66 (d, J = 8.0 Hz)] indicated that **1** possessed a secoxyloganin (**12**)[11] moiety in its structure. The ^{1}H-NMR spectrum displayed additional signals for a methoxy group at δ_H 3.90 (br s), two aromatic protons at δ_H 7.15 and 7.21 (each s), a pair of *cis*-olefinic protons at δ_H 6.29 and 7.89 (each d, J = 9.5 Hz), and an anomeric proton at δ_H 5.08 (d, J = 8.0 Hz). These features as well as its ^{13}C-NMR spectroscopic data (Table 1) indicated the similarity of **1** to frachinoside (**16**)[22] except for the presence of an additional methoxy signal. The structure was deduced from a combination of ^{1}H-^{1}H COSY, HMQC, HMBC and NOESY experiments. The HMBC correlations between H_2-6/C-7 and H-3/C-11 allowed assignment of the signals of the carbonyls C-7 and C-11. Further HMBC interactions from H_2-6''' to C-7 suggested that the C-7 carboxyl group of its secoxyloganin moiety was esterified with the hydroxy group at C-6'' of a glucose unit. Linkage of the β-glucose to C-7'' of coumarin skeleton as in frachinoside (**16**) was indicated by HMBC interaction from H-1''' at δ_H 5.08 (d, J = 8.0 Hz) to C-7'' (δ_C 151.5) and NOESY correlation between H-1''' and H-8'' (δ_H 7.15). The location of the methoxy group at C-6'' was substantiated by a NOESY interaction from H-5'' at δ_H 7.21 to the methoxy signal at δ_H 3.90 and an olefinic proton H-4'' at δ_H 7.89. Consequently, compound **1** was designated as *O*-methylfrachinoside.

Compound **2**, named alstomacroside A, was determined as $C_{33}H_{44}O_{18}$ from its HRSIMS. Its ^{1}H- and ^{13}C-NMR spectra (Table 1) demonstrated that **2** possessed a secoxyloganin moiety esterified with a different glucoside from **1**. The ^{1}H-NMR spectrum of **2** demonstrated, besides the signals due to the secoxyloganin moiety, the signals of a methoxy group (δ_H 3.87), a 1,3,4-trisubstituted benzene ring [δ_H 7.06 (d, J = 2.0 Hz), 7.06 (d, J = 8.0 Hz) and 6.94 (dd, J = 8.0, 2.0 Hz)], *trans*-olefinic protons [δ_H 6.54 (dt, J = 16.0, 1.5 Hz) and 6.28 (dt, J = 16.0, 6.0 Hz)] adjacent to an oxygenated methylene group [δ_H 4.21 (2H, dd, J = 6.0, 1.5 Hz)], and a glucose unit. It was evident from the coupling constant (J = 8.0 Hz) of the anomeric proton H-1''' at δ_H 4.90, an HMBC correlation between H-1''' and the aromatic carbon at δ_C 147.4 and NOESY cross-peak between H-1''' and the aromatic proton H-6'' at δ_H 7.06 that an additional glucose was connected to the hydroxy group of the aromatic ring with a β-linkage. Furthermore, NOESY interactions of MeO/H-3'', H-3''/H-7'', 8'' and H-5''/H-7'', 8'' determined the substitution pattern of the benzene ring. These findings suggested the additional glucoside unit in **2** to be coniferin (**17**).[23] Comparison of the NMR chemical shifts of H_2-6''' and C-6''' of **2** and **17** and HMBC experiments with **2**, which showed ^3J interactions between H_2-6''' and C-7 (δ_C 173.9), indicated that the C-7 carboxyl group of

the secoxyloganin unit was esterified with a hydroxy group at C-6''' of a coniferin unit. Accordingly, the structure of alstomacroside A (**2**) was elucidated as shown.

Table 1. ^{1}H- and ^{13}C-NMR spectral data of **1**, **2** and **3** in CD_3OD

	1		**2**		**3**	
C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	5.43 d (4.0)	97.7	5.46 d (3.5)	97.6	5.17 d (9.5)	98.0
3	7.44 d (2.0)	153.8	7.47 d (2.0)	153.8	7.43 s	154.1
4		109.9		109.9		110.9
5	3.33–3.38 m	28.6	3.33–3.38 m	28.6	3.03 ddd (11.0, 5.0, 3.0)	34.4
6	2.29 dd (16.5, 8.5)	35.6	2.26 dd (16.0, 9.0)	35.6	1.51 br t (12.0)	38.0
	3.03 dd (16.5, 5.5)		3.01 dd (16.0, 5.5)		2.19 dd (12.5, 3.0)	
7		174.0		173.9		173.3
8	5.53 dt (17.0, 10.0)	134.4	5.54 dt (17.0, 10.0)	134.1	5.71 ddd (17.5, 11.0, 7.0)	135.5
9	2.83 ddd (10.0, 5.5, 4.0)	45.1	2.84 ddd (10.0, 5.5, 3.5)	45.0	2.54 br ddd (9.0, 7.0, 5.0)	44.8
10	4.94 dd (10.0, 2.0)	120.6	5.06 dd (10.0, 1.5)	121.0	5.28 dt (17.5, 1.0)	119.6
	5.04 br dd (17.0, 2.0)		5.09 dd (17.0, 1.5)		5.31 dt (11.0, 1.0)	
11		168.8		168.9		168.8
11-OMe	3.59 s	51.6	3.64 s	51.8	3.61 s	51.8
1'	4.66 d (8.0)	100.1	4.67 d (8.0)	100.0	4.68 d (8.0)	101.5
2'	3.26–3.33 m	74.4	3.27–3.32 m	74.6	3.25 dd (9.0, 8.0)	74.6
3'	3.33–3.38 m	78.0	3.33–3.38 m	78.1	3.42 t (9.0)	78.2
4'	3.33–3.38 m	71.3	3.33–3.38 m	71.3	3.29 br t (9.5)	72.7
5'	3.26–3.33 m	78.2	3.27–3.32 m	78.3	3.72 td (10.0, 2.0)	75.7
6'	3.71 dd (12.0, 5.5)	62.5	3.72 dd (12.0, 5.0)	62.5	4.51 dd (12.0, 2.0)	64.9
	3.89 dd (12.0, 2.0)		3.90 dd (12.0, 2.0)		4.76 dd (12.0, 10.0)	
1''				147.4		127.0
2''		163.3		150.9	7.32 d (2.0)	108.1
3''	6.29 d (9.5)	114.6	7.06 d (2.0)	111.7		153.9
4''	7.89 d (9.5)	145.5		133.7		139.4
5''	7.21 s	110.8	6.94 dd (8.0, 2.0)	120.7		155.5
6''		148.2	7.06 d (8.0)	117.9	7.37 d (2.0)	108.0
7''		151.5	6.54 dt (16.0, 1.5)	131.3		167.1
8''	7.15 s	105.2	6.28 dt (16.0, 5.5)	129.0		
9''		150.7	4.21 dd (5.5, 1.5)	63.8		
10''		114.5				
OMe	3.90 s	57.1	3.87 s	56.8	3.80 s	56.9
					3.91 s	56.9
1'''	5.08 d (8.0)	101.6	4.90 d (8.0)	102.4	5.07 d (8.0)	102.9
2'''	3.66 dd (9.0, 8.0)	74.5	3.59–3.63 m	74.7	3.50 dd (9.0, 8.0)	75.2
3'''	3.51 t (9.0)	77.7	3.43–3.49 m	77.7	3.40 dd (9.5, 9.0)	77.9
4'''	3.43 dd (10.0, 9.0)	71.5	3.43–3.49 m	71.4	3.20 dd (9.5, 8.5)	73.0
5'''	3.78 ddd (10.0, 6.5, 2.0)	75.6	3.59–3.63 m	75.4	3.29 m	75.4
6'''	4.09 dd (12.0, 6.5)	64.4	4.14 dd (12.0, 5.5)	64.2	3.86 dd (11.5, 2.0)	65.4
	4.63 dd (12.0, 2.0)		4.57 dd (12.0, 2.0)		4.39 dd (11.5, 10.5)	

Values in parentheses are coupling constants in Hz.

The HRSIMS measurement of compound **3** revealed a molecular formula of $C_{32}H_{40}O_{19}$. Its ^{1}H- and ^{13}C-NMR spectra (Table 1) showed the signals corresponding to a secoxyloganin moiety together with signals of a substituted benzoyl group and β-glucose unit. However, the chemical shifts and coupling constants of

H-1, H_2-6, H-8, H_2-10 and H_2-6' of the secoxyloganin moiety in the ^{1}H-NMR spectrum of **3** were remarkably different from those of **1** and **2**. These characteristic features suggested that **3** possessed a cyclized structure through two ester linkages as in naresuanoside (**13**),[3] which was also isolated in this study.

Table 2. ^{1}H- and ^{13}C-NMR spectral data of **4**, **5** and **6** in CD_3OD

	4		**5**		**6**	
C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	5.44 d (3.5)	97.6	5.45 d (4.0)	97.6	5.46 d (4.0)	97.6
3	7.46 d (2.0)	153.7	7.46 d (1.5)	153.8	7.47 d (1.5)	153.8
4		109.7		109.8		109.9
5	3.32–3.38 m	28.4	3.33–3.38 m	28.5	3.33–3.38 m	28.6
6	2.25 dd (16.0, 9.0)	35.4	2.26 dd (16.0, 9.0)	35.5	2.28 dd (16.0, 9.0)	35.6
	3.04 dd (16.0, 5.5)		3.02 dd (16.0, 5.5)		3.01 dd (16.0, 5.5)	
7		173.8		173.9		173.9
8	5.54 dt (17.0, 10.0)	134.0	5.55 dt (17.0, 10.0)	134.1	5.57 dt (17.0, 10.0)	134.1
9	2.88 ddd (10.0, 5.5, 3.5)	44.8	2.88 ddd (10.0, 5.5, 4.0)	44.9	2.87 ddd (10.0, 5.5, 4.0)	45.0
10	5.10 dd (10.0, 1.5)	121.1	5.12 br d (10.0)	121.1	5.12 br d (10.0)	121.1
	5.16 dd (17.0, 1.5)		5.18 br d (17.0)		5.18 br d (17.0)	
11		168.8		168.8		168.8
11-OMe	3.65 s	51.7	3.65 s	51.7	3.65 s	51.7
1'	4.66 d (7.5)	100.0	4.66 d (7.5)	100.0	4.67 d (7.5)	100.0
2'	3.30 dd (9.0, 7.5)	74.4	3.28–3.32 m	74.5	3.28–3.32 m	74.5
3'	3.32–3.38 m	78.1	3.33–3.38 m	78.1	3.33–3.38 m	78.1
4'	3.32–3.38 m	71.2	3.33–3.38 m	71.3	3.33–3.38 m	71.3
5'	3.29–3.32 m	78.3	3.28–3.32 m	78.3	3.28–3.32 m	78.3
6'	3.73 dd (12.0, 5.5)	62.5	3.72 dd (12.0, 5.5)	62.5	3.72 dd (12.0, 5.5)	62.5
	3.90 dd (12.0, 2.0)		3.90 dd (12.0, 2.0)		3.90 dd (12.0, 2.0)	
1"		155.8		152.1		152.6
2"	6.44 s	96.6	6.47 s	97.3	6.74 d (2.5)	104.3
3"		154.8		149.2		149.2
4"		134.7		132.4		143.2
5"		154.8		149.2	6.69 d (8.5)	116.0
6"	6.44 s	96.6	6.47 s	97.3	6.57 dd (8.5, 2.5)	110.3
3"-OMe	3.81 s	56.7	3.81 s	56.9	3.82 s	56.5
4"-OMe	3.70 s	61.3				
5"-OMe	3.81 s	56.7	3.81 s	56.9		
1"'	4.83 d (7.5)	103.1	4.75 d (8.0)	103.9	4.73 d (8.0)	103.8
2"'	3.54 dd (9.0, 7.5)	74.6	3.50 m	74.7	3.50 m	74.7
3"'	3.43–3.48 m	77.7	3.42–3.46 m	77.8	3.42–3.46 m	77.8
4"'	3.43–3.48 m	71.3	3.42–3.46 m	71.4	3.42–3.46 m	71.4
5"'	3.63 ddd (9.5, 5.5, 2.0)	75.4	3.57 m	75.5	3.57 m	75.4
6"'	4.12 dd (12.0, 5.5)	64.1	4.13 dd (12.0, 5.5)	64.1	4.14 dd (12.0, 5.5)	64.1
	4.66 dd (12.0, 2.0)		4.65 dd (12.0, 2.0)		4.61 dd (12.0, 2.0)	

Values in parentheses are coupling constants in Hz.

This was supported by HMBC correlations of H_2-6'/C-7" and H_2-6"'/C-7. The marked differences between **3** and **13** were that compound **3** showed two aromatic methoxy singlets at δ_H 3.80 and 3.91 and two doublets of *meta*-coupled aromatic protons at δ_H 7.32 and 7.37 (each d, J = 2.0 Hz) instead of one methoxy and three aromatic proton signals in **13**. These findings demonstrated that C-5" of the benzene ring of **13** was substituted by another methoxy group in **3**. The proposed structure was confirmed by HMBC experiments and NOESY interactions of H-2"/3"-OMe and H-6"/5"-OMe. Thus, compound **3** was designated as alstomacroside B.

Compound **4** was obtained as an amorphous powder with molecular formula $C_{32}H_{44}O_{19}$. The ^{1}H- and ^{13}C-NMR spectra (Table 2) showed the signals assignable to a secoxyloganin moiety as in **1** and **2**, and the signals of a 1,3,4,5-substituted benzene ring and three methoxy groups [δ_H 6.44 (2H, s), 3.81 (6H, s), 3.70 (3H, s); δ_C 155.8 (C), 154.8 (2C), 134.7 (C), 96.6 (2CH), 61.7 (CH_3), 56.7 ($2CH_3$)], and another β-glucose unit. The HMBC connectivities between H-1"'/C-1", H-2"/C-1", 3", 4" and H-6"/C-1", 4", 5" and NOESY correlations of H-1"'/H-2", 6", H-2"/3"-OMe, and H-6"/5"-OMe indicated the location of methoxy groups and glucosyl unit on the benzene ring. Acid hydrolysis of **4** liberated D-glucose, which was identified using GLC analysis of its thiazolidine derivative.[24] These findings suggested the additional glucoside in **4** to be 3,4,5-trimethoxyphenyl β-D-glucopyranoside.[25] The ester linkage of C-7 in the secoxyloganin moiety with a hydroxy group at C-6"' was confirmed by the lower shift of H_2-6"' in the ^{1}H-NMR spectrum and HMBC correlation from H_2-6"' to C-7. Accordingly, compound **4** was formulated as shown and designated as alstomacroside C.

Alstomacrosides D (**5**) and E (**6**) were obtained as an inseparable mixture in a ratio of 1:2. Their structural determination was performed in the form of a mixture. HRSIMS established the elemental compositions of **5** and **6** as $C_{31}H_{42}O_{19}$ and $C_{30}H_{40}O_{18}$, respectively. Their NMR spectra were similar to those of **4**, except for the signals arising from the aromatic unit (Table 2). Compound **5** showed signals deducible as a 4-hydroxy-3,5-dimethoxyphenyl group [δ_H 6.47 (2H, s), 3.81 (6H, s); δ_C 152.1 (C), 149.2 (2C), 132.4 (C), 97.3 (2CH), 56.9 ($2CH_3$)], whereas **6** showed the signals assignable to a 4-hydroxy-3-methoxyphenyl group [δ_H 6.74 (d, J = 2.5 Hz), 6.69 (d, J = 8.5 Hz), 6.57 (dd, J = 8.5, 2.5 Hz), 3.82 (3H, s); δ_C 152.6 (C), 149.2 (C), 143.2 (C), 116.0 (CH), 110.3 (CH), 104.3 (CH), 56.5 (CH_3)]. The substitution pattern on the benzene ring was confirmed using NOESY cross peaks of the anomeric proton H-1"'/H-2" (H-6") and H-2"/aromatic methoxy signal in each case. Thus, compounds **5** and **6** were characterized as shown.

The ^{1}H- and ^{13}C-NMR spectral features of compounds **7**, $C_{50}H_{66}O_{28}$ and **8**, $C_{49}H_{66}O_{29}$ were closely comparable to those of **2** and **4**, respectively, except for the presence of an additional signals assignable to a secoxyloganin unit (Table 3). Compounds **7** and **8** were, therefore, assumed to be esters of **2** and **4** (a unit) with secoxyloganin (b unit). Esterification of the hydroxy group at C-2"' of the glucose unit with the carboxyl group of the second secoxyloganin unit was elucidated by NMR chemical shift of H-2"' (**7**: δ_H

5.01, **8**: δ_H 4.96) and HMBC correlations between H-2''' and C-7b (**7**: δ_C 173.3, **8**: δ_C 173.3). Accordingly, the structures of **7** and **8** were assigned to alstomacrosides F and G, respectively.

Table 3. ^{1}H-NMR spectral data of **7** and **8** in CD_3OD

	7		**8**	
C	a part	b part	a part	b part
1	5.49 d (4.5)	5.47 d (3.5)	5.47[c] d (4.0)	5.48[c] d (4.0)
3	7.48[a] d (1.5)	7.47[a] d (1.5)	7.47 d (1.5)	7.47 d (1.5)
5	3.24–3.38 m	3.24–3.38 m	3.32–3.40 m	3.32–3.40 m
6	2.36 dd (16.0, 5.5)	2.34 dd (16.0, 8.0)	2.33 dd (16.5, 8.5)	2.42 dd (16.5, 9.5)
	2.88 dd (16.0, 5.5)	3.24–3.38 m	2.91 dd (16.5, 6.0)	3.17 dd (16.5, 4.0)
8	5.60 dt (17.0, 10.0)	5.61 dt (17.0, 10.0)	5.58 dt (17.0, 10.0)	5.61 dd (17.0, 10.0)
9	2.75 ddd (10.0, 5.5, 4.0)	2.91 ddd (10.0, 6.0, 3.5)	2.78 ddd (10.0, 5.5, 4.0)	2.85 ddd (10.0, 5.5, 4.0)
10	5.15 dd (10.0, 1.5)	5.21 dd (10.0, 1.5)	5.13 ddd (10.0, 1.5)	5.21 dd (10.0, 1.5)
	5.20 br d (17.0)	5.30 dd (17.0, 1.5)	5.21 dd (17.0, 1.5)	5.30 dd (17.0, 1.5)
11-OMe	3.64[b] s	3.65[b] s	3.63[d] s	3.65[d] s
1'	4.66 d (8.0)	4.61 d (8.0)	4.62[e] d (8.0)	4.65[e] d (8.0)
2'	3.24 br t (9.0)	3.09 dd (9.0, 8.0)	3.16[f] dd (9.0, 8.0)	3.24[f] dd (9.0, 8.0)
3'	3.24–3.38 m	3.24–3.38 m	3.32–3.40 m	3.32–3.40 m
4'	3.24–3.38 m	3.24–3.38 m	3.28 t (10.0)	3.28 t (10.0)
5'	3.24–3.38 m	3.24–3.38 m	3.27–3.32 m	3.27–3.32 m
6'	3.64–3.70 m	3.64–3.70 m	3.60–3.70 m	3.60–3.70 m
	3.89 br d (12.0)	3.89 br d (12.0)	3.88 br d (12.0)	3.88 br d (12.0)
2''	7.04 d (1.5)		6.35 s	
5''	7.06 d (8.0)			
6''	6.92 dd (8.0, 1.5)		6.35 s	
7''	6.54 br d (16.0)			
8''	6.28 dt (16.0, 5.5)			
9''	4.21 dd (5.5, 1.0)			
OMe	3.84 s		3.81 s	
OMe			3.71 s	
OMe			3.81 s	
1'''	4.97 d (8.0)		5.06 d (8.0)	
2'''	5.01 br t (8.5)		4.96 dd (9.5, 8.0)	
3'''	3.60 br t (9.0)		3.63 t (9.5)	
4'''	3.46 br t (9.5)		3.46 t (9.5)	
5'''	3.62 ddd (10.0, 6.5, 2.0)		3.71 ddd (9.5, 6.0, 2.0)	
6'''	4.19 dd (12.0, 6.5)		4.17 dd (12.0, 6.0)	
	4.49 dd (12.0, 2.0)		4.57 dd (12.0, 2.0)	

Values in parentheses are coupling constants in Hz.
[a–f)]Assignments with the same superscript may be interchanged.

Compounds **9**, **10**, and **11** were recognized as isomers, $C_{48}H_{60}O_{28}$, from their HRSIMS. The ^{1}H- and ^{13}C-NMR spectra (Tables 4 and 5) of each glucoside exhibited signals ascribable to a naresuanoside unit as well as additional signals due to a secoxyloganin moiety. Comparative studies of the ^{1}H- and ^{13}C-NMR spectra of **9**, **10**, and **11** with those of **13**, together with HMBC experiments, suggested these compounds were esters of naresuanoside (**13**) with secoxyloganin (**12**). The structural differences among the three

compounds were accounted for only by the point of ester linkage of the additional secoxyloganin unit (b unit) to the naresuanoside moiety (a unit). In each glucoside, H-1'a was assigned using HMBC correlation with C-1a, on the other hand H-1''' was assigned using HMBC correlation with C-4'' and ROESY interaction with H-5''. The COSY and TOCSY correlations from H-1'a and H-1''' led to assigning the other proton signals of the glucose units. In HMBC experiments with **9**, downfield shifted H-2''' (δ_H 5.07)

Table 4. ^{1}H-NMR spectral data of **9**, **10**, **11** and **13** in CD_3OD

	9		**10**	
C	a part	b part	a part	b part
1	5.54 d (9.5)	5.44 d (3.0)	5.54 d (9.5)	5.49 d (3.5)
3	7.58 s	7.44 d (1.5)	7.59 s	7.50 d (2.0)
5	3.15 ddd (11.5, 5.0, 2.5)	3.30–3.36 m	3.14 ddd (11.5, 4.5, 2.5)	3.37 m
6	2.08 br t (12.0)	2.28 dd (16.5, 12.0)	2.09 dd (12.5, 11.5)	2.42 dd (16.5, 9.0)
	2.52 dd (12.5, 2.5)	3.30–3.36 m	2.48 dd (12.5, 2.5)	3.11 dd (16.5, 5.0)
8	5.73 ddd (17.5, 11.0, 7.0)	5.59 dt (17.0, 10.0)	5.71 ddd (17.5, 11.0, 6.5)	5.64 dt (17.0, 10.0)
9	2.66 dddt (10.0, 6.5, 5.0, 1.0)	2.93 ddd (10.0, 5.0, 3.0)	2.66 dddt (9.5, 6.5, 4.5, 1.0)	2.85 ddd (10.0, 5.5, 3.5)
10	5.22 dt (11.0, 1.0)	5.25 dd (10.0, 1.5)	5.19 dt (11.0, 1.0)	5.25 dd (10.0, 1.5)
	5.30 dt (17.5, 1.0)	5.34 dd (17.0, 1.5)	5.29 dt (17.5, 1.0)	5.33 dd (17.0, 1.5)
11-OMe	3.68[a] s	3.64[a] s	3.68[b] s	3.69[b] s
1'	4.83 d (8.0)	4.49 d (8.0)	4.83 d (8.0)	4.66 d (8.0)
2'	3.26–3.35 m	2.72 dd (9.0, 8.0)	3.25–3.36 m	3.21 dd (9.0, 8.0)
3'	3.44 t (9.0)	3.25 br t (9.5)	3.45 t (9.0)	3.25–3.36 m
4'	3.26–3.35 m	3.07 br t (9.5)	3.25–3.36 m	3.25–3.36 m
5'	3.73 td (10.0, 2.0)	3.23 ddd (9.5, 7.0, 2.0)	3.74 td (10.5, 2.0)	3.25–3.36 m
6'	4.14 dd (11.5, 10.0)	3.63–3.69 m	4.18 dd (11.0, 10.5)	3.66 dd (12.0, 6.0)
	4.73 dd (11.5, 2.0)	3.88 dd (12.0, 2.0)	4.67 dd (11.0, 2.0)	3.89 dd (12.0, 2.0)
2''	7.59 (overlapped)		7.62 d (2.0)	
5''	7.05 d (8.5)		7.08 d (8.5)	
6''	7.60 dd (8.5, 1.5)		7.64 dd (8.5, 2.0)	
3''-OMe	3.86 s		3.91 s	
1'''	5.22 d (8.0)		5.09 d (7.5)	
2'''	5.07 dd (9.5, 8.0)		3.68 dd (9.5, 7.5)	
3'''	3.63–3.69 m		5.11 t (9.5)	
4'''	3.37 br t (9.0)		3.47 br t (9.5)	
5'''	3.63–3.69 m		3.76 td (10.0, 2.5)	
6'''	4.12 dd (11.5, 2.0)		4.10 dd (11.5, 2.5)	
	4.32 br t (11.0)		4.34 br t (11.0)	

Values in parentheses are coupling constants in Hz.
[a, b]Assignments with the same superscript may be interchanged.

correlated with C-7b (δ_C 172.9), indicating the site of esterification of the second secoxyloganin unit to be at C-2'''.

In a similar manner, the ester linkage was determined using the HMBC interaction of H-3''' (δ_H 5.11, t, *J* = 9.5 Hz) with C-7b (δ_C 174.0) in **10**, and HMBC correlation from H-2'a (δ_H 4.84, m) to C-7b (δ_C 172.9) in **11**. Consequently, the structures of new compounds are represented as **9**, **10**, and **11**, and these compounds were designated as alstomacrosides H, I and J, respectively.

Table 4. (continued)

	11		**13**
C	a part	b part	
1	5.49 d (9.5)	5.48 d (3.0)	5.54 d (9.5)
3	7.62 s	7.47 d (2.0)	7.58 s
5	3.15 ddd (11.0, 5.0, 3.0)	3.25–3.38 m	3.14 ddd (11.5, 5.0, 2.5)
6	2.11 dd (13.0, 11.0)	2.28 dd (16.0, 11.0)	2.09 dd (13.0, 11.5)
	2.49 dd (13.0, 3.0)	3.25–3.38 m	2.49 dd (13.0, 2.5)
8	5.68 ddd (17.5, 10.5, 6.5)	5.60 dt (17.0, 10.0)	5.71 ddd (17.5, 10.5, 6.5)
9	2.62 dddt (9.5, 6.5, 5.0, 1.0)	2.92 ddd (10.0, 5.5, 3.0)	2.66 br ddd (9.5, 6.5, 5.0)
10	5.16 dt (10.5, 1.0)	5.23 dd (10.0, 1.5)	5.19 dt (10.5, 1.0)
	5.28 dt (17.5, 1.0)	5.27 dd (17.0, 1.5)	5.29 dt (17.5, 1.0)
11-OMe	3.68[c] s	3.69[c] s	3.68 s
1'	5.04 d (8.0)	4.65 d (8.0)	4.84 d (8.0)
2'	4.84 m	3.20 dd (9.0, 8.0)	3.28 dd (9.0, 8.0)
3'	3.61 t (9.0)	3.25–3.38 m	3.45 t (9.0)
4'	3.25–3.38 m	3.61–3.70 m	3.26–3.32 m
5'	3.80 td (10.0, 2.0)	3.25–3.38 m	3.73 td (10.0, 2.0)
6'	4.21 dd (11.5, 10.0)	3.70 dd (12.0, 6.0)	4.16 dd (11.5, 10.0)
	4.68 dd (11.5, 2.0)	3.91 dd (12.0, 2.0)	4.68 dd (11.5, 2.0)
2''	7.62 (overlapped)		7.61 (overlapped)
5''	7.05 d (9.0)		7.05 d (9.0)
6''	7.63 dd (9.0, 2.0)		7.62 dd (9.0, 2.0)
3''-OMe	3.91 s		3.90 s
1'''	4.97 d (8.0)		4.98 d (7.5)
2'''	3.56 dd (9.0, 8.0)		3.57 dd (9.0, 7.5)
3'''	3.48 t (9.0)		3.49 t (9.0)
4'''	3.25–3.38 m		3.26–3.32 m
5'''	3.61–3.70 m		3.64 td (10.0, 2.5)
6'''	4.13 dd (11.5, 2.0)		4.10 dd (11.5, 2.5)
	4.28 dd (11.5, 10.5)		4.29 br t (11.0)

[c)]Assignments with the same superscript may be interchanged.

In the present study, eleven novel secoiridoid glucosides were isolated together with strictosamide (**14**), (5*S*)-5-carboxystrictosidine (**15**) and an indole alkaloid 10-hydroxystrictamine from *A. macrophylla*. Glucoalkaloids **14** and **15** were biosynthesized from an important intermediate secologanin (**18**) through condensation with tryptamine or tryptophane. Secologanin (**18**) is, on the other hand, oxidized to secoxyloganin (**12**), which could be esterified with a various phenolic glucoside to produce diverse glucosides in this species.

Table 5. ^{13}C-NMR spectral data of **7**–**11** and **13** in CD_3OD

	7		**8**		**9**		**10**		**11**		**13**
C	a part	b part	a part	b part	a part	b part	a part	b part	a part	b part	
1	97.4	97.4	97.4[e]	97.5[e]	97.5	96.7	97.8	97.7	98.2	97.4	96.7
3	153.8	153.8	153.8	153.8	154.2	153.6	154.3	154.1	154.3	153.7	154.3
4	110.0[a]	109.8[a]	109.9	109.8	111.3	109.5	111.3	109.7	111.5	109.9	111.3
5	29.1[b]	28.5[b]	28.7	28.5	34.6	28.4	34.6	28.8	30.8	28.1	34.6
6	35.8	34.9	35.5	34.9	38.5	35.0	38.4	35.2	38.5	35.0	38.5
7	174.1	173.3	174.1	173.3	173.4	172.9	173.5	174.0	173.5	172.9	173.5
8	133.9[c]	134.3[c]	134.2	134.1	135.1	133.9	135.1	134.1	134.0[r]	134.7[r]	135.1
9	45.4	44.6	45.4	45.0	44.7	44.2	44.7	45.3	44.6	44.4	44.7
10	120.8	121.4	120.9	121.3	119.6	121.5	119.7	121.2	119.9	121.4	119.7
11	168.9	168.9	168.8[f]	168.9[f]	168.8[k]	168.9[k]	168.9[n]	169.2[n]	168.9[s]	169.0[s]	168.9
11-OMe	51.7[d]	51.8[d]	51.7[g]	51.8[g]	52.0[l]	51.6[l]	52.0	51.8	51.8[t]	52.1[t]	52.0
1'	100.0	99.7	99.8[h]	99.9[h]	100.9	98.9	101.1	100.1	99.3	99.7	101.0
2'	74.6	74.6	74.6	74.6	74.3	74.5	74.6[o]	74.7[o]	74.5[u]	74.7[u]	74.6
3'	78.1	78.1	78.1	78.1	78.0	78.1	78.1[p]	78.2[p]	76.3	78.3[w]	78.2
4'	71.6	71.6	71.5[i]	71.6[i]	72.7[m]	71.8	72.8[q]	71.6	73.0	71.7	72.8
5'	78.5	78.5	78.5	78.5	75.4	78.5	75.5	78.4	75.3[v]	78.6	75.5
6'	62.8	62.8	62.8[j]	62.9[j]	66.2	63.0	66.4	62.8	66.2	62.9	66.4
1"	147.4		155.3		125.4		125.3		125.1		125.1
2"	151.8		96.4		114.6		114.1		114.1		114.0
3"	111.7		154.9		150.9		150.6		150.6		150.5
4"	134.4		135.0		151.3		151.5		151.7		151.6
5"	120.4		154.9		116.5		116.3		116.1		116.2
6"	119.7		96.4		123.7		124.1		124.2		124.1
7"	131.4				167.4		167.4		167.4		167.4
8"	129.3										
9"	63.8										
OMe	56.8		2×56.9		56.6		56.7		56.7		56.7
OMe			61.3								
1"'	101.4		100.8		98.8		100.8		100.9		100.9
2"'	75.0		75.1		74.5		72.9[q]		74.7[v]		74.6
3"'	76.0		75.8		76.6		78.7		78.1[w]		78.3
4"'	72.0		71.8		72.8[m]		71.0		72.6		72.6
5"'	75.6		75.6		75.4		75.0		75.6[v]		75.2
6"'	64.6		64.7		65.3		65.2		65.4		65.4

[a–w)]Assignments with the same superscript may be interchanged.

EXPERIMENTAL

General 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. GLC was carried out on a Shimadzu GC-18A equipped with FID. TLC was performed on precoated Kieselgel 60F_{254} plates (Merck).

Plant Material. The twigs of *Alstonia macrophylla* Wall. ex G. Don were collected at Nakhon Si Thammarat, Thailand in April 1985 and identified by Dr. T. Smitinand, The Forest Herbarium, Royal Forest Department, Bangkok, Thailand. A voucher specimen (No.1791) is deposited in the laboratory of the Nippon Shinyaku Institute for Botanical Research.

Extraction and Isolation. Dried twigs (1.81 kg) of *A. macrophylla* were extracted with MeOH under reflux. After concentration, the extract (74.4 g) was suspended in H_2O and extracted successively with $CHCl_3$ and *n*-BuOH. The residue (13.4 g) from the *n*-BuOH layer was fractionated using reversed-phase MPLC. Elution with H_2O-MeOH mixtures of the indicated MeOH content gave 14 fractions, 1 (0%, 0.69 g), 2 (5%, 0.64 g), 3 (10%, 0.75 g), 4 (10%, 0.42 g), 5 (10%, 0.22 g), 6 (20%, 0.57 g), 7 (20%, 0.65 g), 8 (30%, 0.18 g), 9 (30%, 0.49 g), 10 (30%, 0.61 g), 11 (40%, 0.29 g), 12 (40%, 1.32 g), 13 (60%, 3.21 g), and 14 (80%, 1.25 g). Fractions 4 and 5 were purified using preparative HPLC (μBondasphere 5μ C18-100 Å, MeOH-H_2O, 2:3) and preparative TLC ($CHCl_3$-MeOH, 3:2) to afford sweroside (13.3 mg) and **12** (62.3 mg), respectively. Fr. 7 was subjected to MPLC on Wakogel FC-40 eluting with $CHCl_3$-MeOH, followed by preparative HPLC (μBondasphere 5μ C18-100 Å, MeOH-H_2O, 2:3) to yield (+)-lyoniresinol 3-α-*O*-β-D-glucopyranoside (14.7 mg) and (−)-lyoniresinol 3-α-*O*-β-D-glucopyranoside (17.0 mg). The following fractions were also purified using a combination of MPLC (Wakosil 40C18 with MeOH-H_2O or Wakogel FC-40 with $CHCl_3$-MeOH), preparative HPLC (μBondasphere 5μ C18-100 Å, MeOH-H_2O, 2:3, 11:9, 3:2; MeCN-H_2O, 3:17, 1:4, 7:18, 3:7), and preparative TLC ($CHCl_3$-MeOH, 4:1; $CHCl_3$-MeOH-NH_4OH, 90:9: 1, 75:20:2). Fr. 8: 10-hydroxystrictamine (4.9 mg); Fr. 9: **15** (2.4 mg), (2*R*,3*R*,4*S*)-isolariciresinol 3a-*O*-α-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (28.6 mg); Fr. 10: **3** (4.8 mg), **7** (2.8 mg), blumenol C 9-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside (4.7 mg), dehydrodiconiferyl alcohol 9-*O*-β-D-glucopyranoside (4.8 mg), [(2*R*,3*S*)-2,3-dihydro-2-(4-hydroxy-3,5-dimethoxyphenyl)-5-[(1*E*)-3-hydroxy-1-propenyl]-7-methoxy-3-benzofuranyl]methyl-β-D-glucopyranoside (4.1 mg), [(2*S*,3*R*)-2,3-dihydro-2-(4-hydroxy-3,5-dimethoxyphenyl)-5-[(1*E*)-3-

hydroxy-1-propenyl]-7-methoxy-3-benzofuranyl]methyl-β-D-glucopyranoside (2.0 mg), acantrifoside F (2.3 mg); Fr. 11: a mixture of **5** and **6** (1.7 mg), blumenol C 9-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside (1.6 mg); Fr. 12: **1** (4.7 mg), **2** (4.0 mg), **4** (18.3 mg), **13** (17.6 mg), Fr. 13: **7** (4.9 mg), **8** (10.7 mg), **9** (9.9 mg), **10** (3.4 mg), **11** (5.0 mg), **14** (1.8 mg), asteryunnanoside B (2.7 mg); Fr. 14: arjunolic acid (1.0 mg).

***O*-Methylfrachinoside (1)**: Colorless amorphous powder, $[\alpha]_D^{27}$ −140 (*c*=0.40, MeOH); UV (MeOH) λ_{max} nm (log ε): 201 (4.57), 227 (4.41), 288 (3.79). 340 (3.91); IR (KBr) ν_{max} cm^{-1}: 3421, 1717, 1700, 1635, 1623, 1508; SIMS *m/z*: 739 $[M-H]^-$, 547, 403, 191; HRSIMS *m/z*: Calcd for $C_{30}H_{39}O_{19}$ $[M-H]^-$: 739.2087. Found: 739.2079.

Alstomacroside A (2): Colorless amorphous powder, $[\alpha]_D^{26}$ −106 (*c*=0.30, MeOH); UV (MeOH) λ_{max} nm (log ε): 213 (4.34), 255 (4.12), 267sh (4.02), 297sh (3.60), 306sh (3.46); IR (KBr) ν_{max} cm^{-1}: 3421, 1734, 1697, 1636, 1508; SIMS *m/z*: 727 $[M-H]^-$, 547, 403, 179; HRSIMS *m/z*: Calcd for $C_{33}H_{43}O_{18}$ $[M-H]^-$: 727.2451. Found: 727.2463.

Alstomacroside B (3): Colorless amorphous powder, $[\alpha]_D^{27}$ −58 (*c*=0.23, MeOH); UV (MeOH) λ_{max} nm (log ε): 215 (4.51), 237 (4.09), 263sh (3.96); IR (KBr) ν_{max} cm^{-1}: 3437, 1717, 1636, 1595; SIMS *m/z*: 727 $[M-H]^-$, 255; HRSIMS *m/z*: Calcd for $C_{32}H_{39}O_{19}$ $[M-H]^-$: 727.2087. Found: 727.2092.

Alstomacroside C (4): Colorless amorphous powder, $[\alpha]_D^{27}$ −85 (*c*=1.00, MeOH); UV (MeOH) λ_{max} nm (log ε): 202 (4.64), 227 (4.25), 278 (3.33); IR (KBr) ν_{max} cm^{-1}: 3408, 1736sh, 1705, 1628, 1602, 1506; SIMS *m/z*: 731 $[M-H]^-$, 569, 499, 403; HRSIMS *m/z*: Calcd for $C_{32}H_{43}O_{19}$ $[M-H]^-$: 731.2400. Found: 731.2391.

Alstomacrosides D (5) and E (6): **5**: HRSIMS *m/z*: Calcd for $C_{31}H_{41}O_{19}$ $[M-H]^-$: 717.2243. Found: 717.2252. **6**: HRSIMS *m/z*: Calcd for $C_{30}H_{39}O_{18}$ $[M-H]^-$: 687.2138. Found: 687.2133.

Alstomacroside F (7): Colorless amorphous powder, $[\alpha]_D^{25}$ −118 (*c*=0.17, MeOH); UV (MeOH) λ_{max} nm (log ε): 224 (4.54), 254sh (4.28), 263sh (4.16). 292 (3.73); IR (KBr) λ_{max} cm^{-1}: 3400, 1716, 1699, 1635, 1508; SIMS *m/z*: 1113 $[M-H]^-$, 951, 547, 403, 223, 179; HRSIMS *m/z*: Calcd for $C_{50}H_{65}O_{28}$ $[M-H]^-$: 1113.3664. Found: 1113.3667.

Alstomacroside G (8): Colorless amorphous powder, $[\alpha]_D^{25}$ −102 (*c*=0.65, MeOH); UV (MeOH) λ_{max} nm (log ε): 205 (4.57), 232 (4.39), 279sh (3.10); IR (KBr) ν_{max} cm^{-1}: 3396, 1734, 1701, 1635, 1506; SIMS *m/z*: 1117 $[M-H]^-$, 955, 731, 403, 223; HRSIMS *m/z*: Calcd for $C_{49}H_{65}O_{29}$ $[M-H]^-$: 1117.3613. Found: 1117.3617.

Alstomacroside H (9): Colorless amorphous powder, $[\alpha]_D^{19}$ −99 (*c*=0.72, MeOH); UV (MeOH) λ_{max} nm (log ε): 220 (4.45), 233sh (4.34), 289 (3.66); IR (KBr) ν_{max} cm^{-1}: 3394, 2928, 1705, 1634, 1510; SIMS *m/z*: 1083 $[M-H]^-$, 693, 403; HRSIMS *m/z*: Calcd for $C_{48}H_{59}O_{28}$ $[M-H]^-$: 1083.3195. Found: 1083.3195.

Alstomacroside I (10): Colorless amorphous powder, $[\alpha]_D^{18}$ −102 (*c*=0.29, MeOH); UV (MeOH) λ_{max} nm

(log ε): 220 (4.43), 237 (4.33), 292 (3.63); IR (KBr) ν_{max} cm^{-1}: 3421, 1717, 1701, 1636, 1508; SIMS *m/z*: 1083 $[M-H]^-$, 697, 553, 403; HRSIMS *m/z*: Calcd for $C_{48}H_{59}O_{28}$ $[M-H]^-$: 1083.3195. Found: 1083.3195.
Alstomacroside J (11): Colorless amorphous powder, $[\alpha]_D^{25}$ −78 (*c*=0.23, MeOH); UV (MeOH) λ_{max} nm (log ε): 220 (4.39), 232sh (4.30), 289 (3.62); IR (KBr) ν_{max} cm^{-1}: 3421, 1734, 1698, 1635, 1508; SIMS *m/z*: 1083 $[M-H]^-$, 697, 403; HRSIMS *m/z*: Calcd for $C_{48}H_{59}O_{28}$ $[M-H]^-$: 1083.3195. Found: 1083.3200.

Acid hydrolysis of compounds 4, 9, 11, and 13. Each compound (1 mg) was heated at 95 °C with dioxane (0.5 mL) and 5% H_2SO_4 (0.5 mL) for 1 h. After neutralization with Amberlite IRA-400 (OH^- form), each reaction mixture was concentrated and the residue was passed through a Sep-Pak C_{18} cartridge with H_2O. The eluate was concentrated and the residue was treated with L-cysteine methyl ester hydrochloride (1 mg) in pyridine (0.125 mL) at 60 °C for 1 h. The solution was then treated with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (0.05 mL) at 60 °C for 1 h. The supernatant was applied to GLC; GLC conditions: column, Supelco SPB^{TM}-1, 30 m × 0.25 mm; column temperature, 230 °C; N_2 flow rate, 0.8 mL/min; t_R of derivatives, D-glucose 12.9 min, L-glucose 13.5 min. D-Glucose was detected from **4**, **9**, **11**, and **13**. Compounds **1**–**3**, **5**–**8** and **10** were not subjected to acid hydrolysis owing to the minute amount of the isolated compounds.

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