Chemical Structures and Hepatoprotective Effects of Constituents from the Leaves of *Salacia chinensis*

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The methanolic extract from the leaves of *Salacia chinensis* collected in Thailand was found to show a protective effect on D-galactosamine-induced cytotoxicity in primary cultured mouse hepatocytes. From the methanolic extract, eight new glycosides, named foliachinenosides E, F, G, H, and I, and foliasalaciosides J, K and L, were isolated together with 26 known constituents. The structures of new glycosides were determined on the basis of physicochemical and chemical evidence. In addition, the hepatoprotective effects of the isolated compounds on D-galactosamine-induced cytotoxicity were examined. Among them, lignans, eleutheroside E_2 and 7*R*,8*S*-dihydrodehydrodiconiferyl alcohol 4-*O*-β-D-glucopyranoside, were found to show the protective effects [inhibition (%) 41.4±3.6 ($p<0.01$), 45.5±2.7 ($p<0.01$) at 100 μM, respectively].

Key words *Salacia chinensis*; Hippocrateaceae; foliachinenoside; foliasalacioside; glycoside; hepatoprotective effect

In the course of our characterization studies on bioactive constituents from *Salacia* species (Hippocrateaceae),[1—6] we have reported the isolation and absolute stereostructure elucidation of 13 megastigmane glycosides, 7 phenolic glycosides, and 11 triterpenes from the leaves of *Salacia chinensis* collected in Thailand together with 40 known constituents.[7—11] As a continuning study on the leaves of *Salacia chinensis*, the methanolic (MeOH) extract was found to show a protective effect on D-galactosamine-induced cytotoxicity in primary cultured mouse hepatocytes. From the MeOH extract, eight new glycosides, named foliachinenosides E, F, G, H, and I, and foliasalaciosides J, K, and L, were isolated together with 26 known constituents. Furthermore, we examined the hepatoprotective effects of the isolated compounds on D-galactosamine-induced cytotoxicity. In this paper, we describe the isolation and structure elucidation of the new constituents (**1**—**8**) and the hepatoprotective effects of isolated compounds from the leaves of *Salacia chinensis*.

The dried leaves of *S. chinensis*, which were collected at Nakhon Si Thammarat province, Thailand, were finely cut and extracted with MeOH to furnish a MeOH extract (13.0%). The MeOH extract was partitioned into an EtOAc–H_2O (1 : 1, v/v) mixture to furnish an EtOAc-soluble fraction (4.1%) and an aqueous phase. The aqueous phase was further extracted with *n*-BuOH to give an *n*-BuOH-soluble fraction (2.4%) and a H_2O-soluble fraction (6.6%). The *n*-BuOH-soluble fraction was subjected to Diaion HP-20 column chromatography (H_2O→MeOH) to give the water- and MeOH-eluted fractions as previously reported.[7] The EtOAc-soluble fraction and the MeOH-eluted fraction were respectively subjected to normal- and reversed-phase silica gel column chromatographies, and finally HPLC to give eight new compounds, foliachinenosides E (**1**, 0.00009%), F (**2**, 0.00013%), G (**3**, 0.00017%), H (**4**, 0.00048%), and I (**5**, 0.0018%), and foliasalaciosides J (**6**, 0.00017%), K (**7**, 0.00016%), and L (**8**, 0.00007%), together with 26 known compounds, 3-methyl-2-but-2-en-1-ol 6-*O*-α-L-arabinopyranosyl-β-D-glucopyranoside (**9**, 0.0017%),[12] (3*Z*)-3-hexen-1-ol 6-*O*-α-L-arabinopyranosyl-β-D-glucopyranoside (**10**, 0.0014%),[13] 2,4,6-trimethoxyphenol 1-*O*-β-D-glucopyranoside (**11**, 0.00016%),[14] benzyl alcohol β-D-glucopyranoside (**12**, 0.00003%),[15] benzyl alcohol 6-*O*-α-L-arabinopyranosyl-β-D-glucopyranoside (**13**, 0.0026%),[16] benzyl β-primeveroside (**14**, 0.00014%),[17] violutoside (**15**, 0.00039%),[18] 2-phenethyl alcohol 6-*O*-α-L-arabinopyranosyl-β-glucopyranoside (**16**, 0.00033%),[19] 2,6-dimethoxy-4-(2-hydroxyethyl)phenol 1-*O*-β-D-glucopyrano-

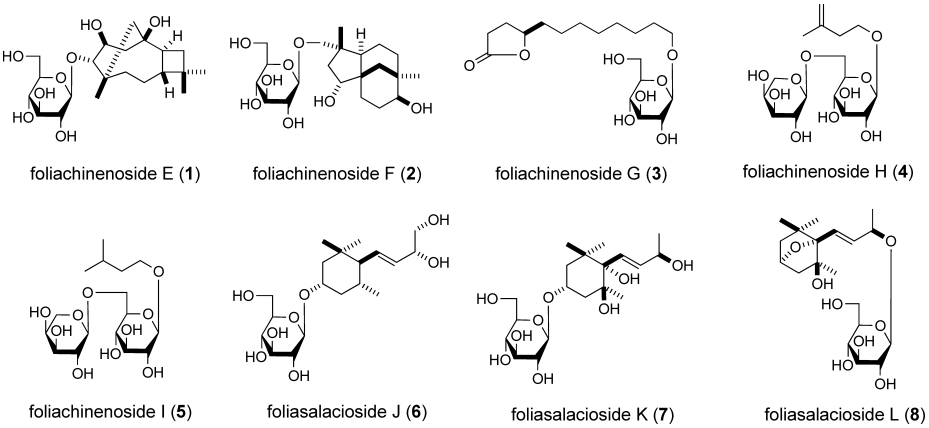

Chart 1

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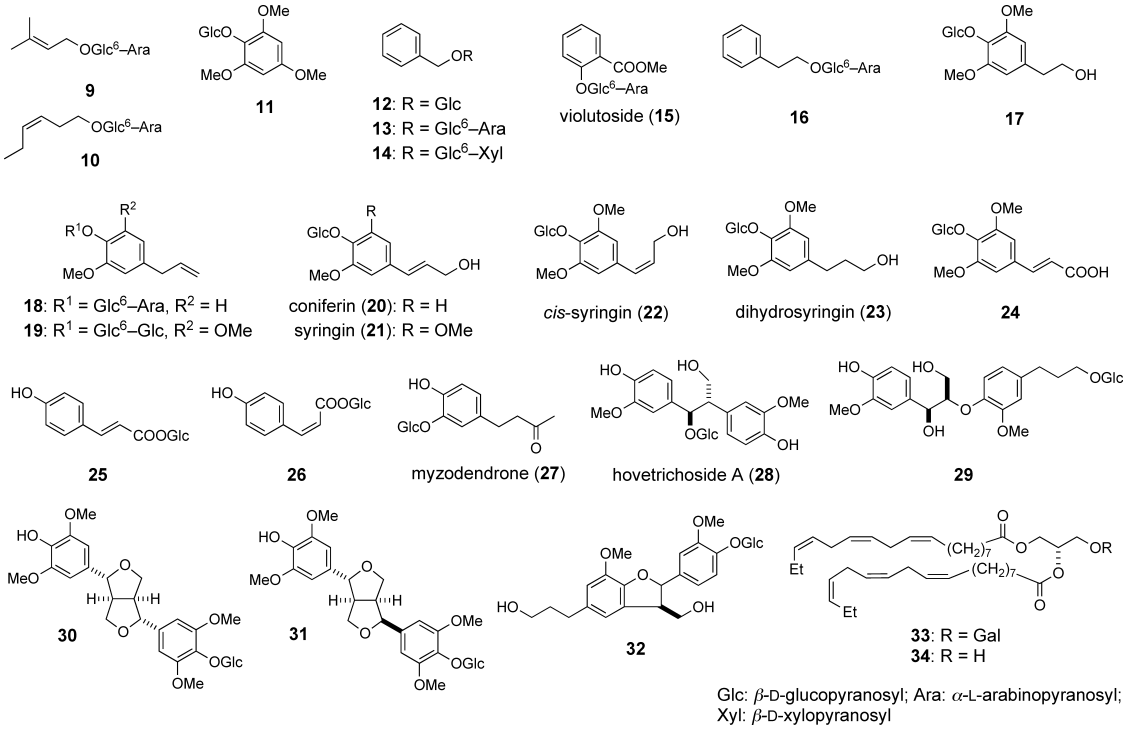

Chart 2

side (**17**, 0.00008%),[20] eugenyl vicianoside (**18**,0.00096%),[21] 2,6-dimethoxy-4-(2-propenyl)phenol 6-*O*-*β*-D-glucopyranosyl-*β*-D-glucopyranoside (**19**, 0.00011%),[22] coniferin (**20**, 0.00024%),[23] syringin (**21**, 0.0032%),[24] *cis*-syringin (**22**, 0.00024%),[25] dihydrosyringin (**23**, 0.00024%),[26] *trans*-*p*-sinapoyl-*β*-D-glucopyranoside (**24**, 0.00068%),[27] (*E*)-coumaroyl-1-*O*-*β*-D-glucopyranoside (**25**, 0.00026%),[28] 1-[(2*Z*)-3-(4-hydroxyphenyl)-2-propenoate]-*β*-D-glucopyranoside (**26**, 0.00005%),[28] myzodendrone (**27**, 0.00024%),[29,30] hovetrichoside A (**28**, 0.00010%),[31] 4,7,9-trihydroxy-3,3′-dimethoxy-8-*O*-4′-neolignan-9′-*O*-*β*-D-glucopyranoside[7*S*, 8*R*-erythro form] (**29**, 0.00019%),[32] syringaresinol mono-*β*-D-glucopyranoside (**30**, 0.00049%),[33] eleutheroside E_2 (**31**, 0.00017%),[34] 7*R*,8*S*-dihydrodehydrodiconiferyl alcohol 4-*O*-*β*-D-glucopyranoside (**32**, 0.00028%),[35] (2*S*)-2,3-*O*-di-(9,12, 15-octadecatrienoyl)-glyceryl-*β*-D-galactopyranoside (**33**, 0.0066%),[36] and 1,2-di-9,12,15-octadecatrienoyl-*sn*-glycerol (**34**, 0.00023%).[37]

Structures of Foliachinenosides, E, F, G, H, and I, and Foliasalaciosides J, K, and L Foliachinenoside E (**1**) was obtained as a colorless amorphous powder with positive optical rotation ($[\alpha]_D^{27}$ +9.8° in MeOH). The IR spectrum showed absorption bands at 3400 and 1076 cm^{-1} assignable to hydroxyl and ether functions. The positive-ion fast atom bombardment (FAB) MS of **1** exhibited a quasimolecular ion peak at *m*/*z* 439 $(M+Na)^+$. The molecular formula $C_{21}H_{36}O_8$ of **1** was determined from the quasimolecular ion peak and by high-resolution (HR) FAB-MS measurement. Acid hydrolysis of **1** with aqueous HCl (1.0 m) liberated D-glucose, which was identified in HPLC analysis using an optical rotation detector.[38] The ^{1}H-NMR (pyridine-d_5) and ^{13}C-NMR (Table 1) spectra of **1**, which were assigned by various NMR experiments,[39] showed signals assignable to three methyls [δ 0.99, 1.02, 1.36 (3H each, all s, H_3-13, 12, 15)], two methines bearing an oxygen function [δ 3.61 (1H, d, J=8.9 Hz, H-5), 4.60 (1H, m, H-6)], a quaternary carbon bearing an oxygen function [δ_C 69.6 (C-8)] together with a *β*-D-glucopyranosyl part [δ 5.17 (1H, d, J=7.9 Hz, H-1′)]. The proton and carbon signals due to the aglycon part of **1** in the ^{1}H- and ^{13}C-NMR spectra were similar to those of (1*R*,4*R*, 5*R*,8*S*,9*S*)-4,11,11-trimethyltricyclo[6.3.1.0.^{1,9}]dodecane-5,8-diol 5-*O*-*β*-D-glucopyranoside[40] except for the 6-position. As shown in Fig. 1, the double quantum filter correlation spectroscopy (DQF COSY) experiment on **1** indicated the presence of partial structures written in bold lines (Fig. 1), and in the heteronuclear multiple bond connectivity spectroscopy (HMBC) experiment, long-range correlations were observed between the following protons and carbons: H-1 and C-8, 10; H-3 and C-15; H-5 and C-3, 15; H-7 and C-6; H-10 and C-1, 8, 13; H-12 and C-1, 10, 11, 13; H-13 and C-1, 10, 11, 12; H-14 and C-4, 5, 7, 9, 15; H-15 and C-3, 5, 14; H-1′ and C-5. In addition, the enzymatic hydrolysis of **1** afforded an aglycon, foliachinenol E (**1a**). Foliachinenol E (**1a**) was obtained as colorless oil with positive optical rotation ($[\alpha]_D^{23}$ +5.0° in MeOH). The molecular formula $C_{15}H_{26}O_3$ of **1a** was determined from a molecular ion peak [*m*/*z* 254 $(M)^+$] and by HR-electron ionization (EI)-MS measurement. The ^{1}H- (CD_3OD) and ^{13}C-NMR (Table 1) spectra[39] of **1a** showed signals assignable to three methyls [δ 1.00, 1.00, 0.99 (3H each, all s, H_3-12, 13, 15)], two methines bearing an oxygen function [δ 3.01 (1H, d, J=8.6 Hz, H-5), 3.80 (1H, m, H-6)]. Comparison of the ^{13}C-NMR data of **1** with those of **1a** indicated the presence of a glycosidation shift around the 5-position of **1**. Thus, the planar structures of **1** and **1a** were determined as shown. The relative stereostructure of **1** was elucidated by using the nuclear Overhauser enhancement spectroscopy (NOESY) experiment, which showed NOE correlations between the following proton pairs: H-1 and H-2*β*, H_3-12; H-3*α* and H-6, 9; H-5 and H-7*β*, H-14*β*, H_3-15; H-6 and H-9; H-7*α* and H-9; H-9 and H-10, H_3-13; H-10*α* and

H_3-13; H-14β and H_3-15. On the basis of this evidence, foliachinenoside E (**1**) was sesquiterpene glycoside possessing the rare tricyclo[6.3.1.0.^{1,9}]dodecane skeleton and the structure of **1** was determined to be 4,11,11-trimethyltricyclo[6.3.1.0.^{1,9}]dodecane-5α,6β,8β-triol 5-*O*-β-D-glucopyranoside.

Foliachinenoside F (**2**), obtained as a colorless amorphous powder with a negative optical rotation ($[\alpha]_D^{27}$ −22.0° in MeOH), showed the absorption bands at 3400 and 1075 cm^{-1} ascribable to hydroxyl and ether functions in the IR spectrum. The molecular formula $C_{21}H_{36}O_8$ of **2** was determined from the positive-ion FAB-MS at *m*/*z* 439 $(M+Na)^+$ and by HR-FAB-MS measurement. Acid hydrolysis of **2** with aqueous HCl (1.0 m) liberated D-glucose, which was identified in HPLC analysis using an optical rotation detector.[38] The ^{1}H-NMR (pyridine-d_5) and ^{13}C-NMR (Table 1) spectra of **2**,[39] showed signals assignable to two methyls [δ 1.16, 1.21 (3H each, both s, H_3-13, 15)], two methines and a methylene bearing an oxygen function [δ 3.56, 4.10 (1H each, both d, J=9.2 Hz, H_2-14), 3.58 (1H, m, H-9), 4.12 (1H, dd like, J=5.5, 7.9 Hz, H-2)] together with a β-D-glucopyranosyl part [δ 4.90 (1H, d, J=7.9 Hz, H-1′)]. The proton and carbon signals due to the aglycon part of **2** in the ^{1}H- and ^{13}C-NMR spectra were similar to those of clovane-2,9-diol,[41] except for the 14-position. As shown in Fig. 1, the DQF COSY experiment on **1** indicated the presence of partial structures written in bold lines, and in the HMBC experiment, long-range correlations were observed between the following protons and carbons: H-2 and C-1, 4, 11; H_2-6 and C-8; H-9 and C-11, 12; H_2-10 and C-1; H_2-12 and 5, 9, 11; H_3-13 and C-3, 5, 14; H_3-15 and C-7, 8, 9, 12; H-1′ and C-14. In addition, the enzymatic hydrolysis of **2** afforded an aglycon (**2a**), which was identified to be (1*S*,3*R*,3a*R*,6*S*,7*S*,9a*R*)-decahydro-1-(hydroxymethyl)-1,7-dimethyl-3a,7-methano-3a*H*-cyclopentacyclooctene[41,42] Comparison of the ^{13}C-NMR data of **2** with those of **2a** indicated the presence of a glycosidation shift around the 14-position of **2**. Next, the relative stereostructure of **2** was determined by using NOESY experiment, in which NOE correlations were observed between the following proton pairs: H-2 and H-3β, H_3-13; H-3α and H-6α, H_2-14; H-3β and H_3-13; H-5 and H-6α, H_2-14, H_3-15; H-6α and H-7α; H-6β and H_3-13; H-7α and H-9; H-9 and H_3-15. On the basis of this evidence, foliachinenoside F (**2**) was determined as shown.

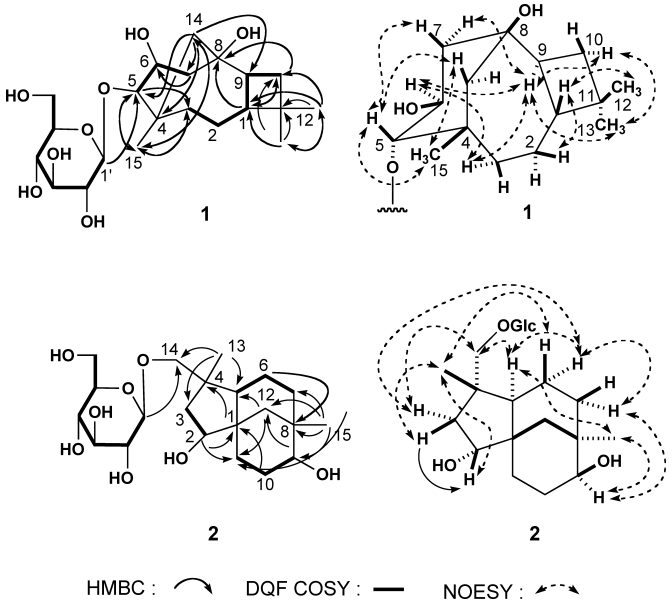

Fig. 1. Selected HMBC, DQF COSY, and NOE Correlations

Table 1. ^{13}C-NMR Data at (125 MHz) for **1**—**8**, **1a**, **2a**, **6a**, and **8a**

Position	**1**[a]	**1**[b]	**1a**[a]	**2**[b]	**3**[a]	**4**[a]	**5**[a]	**6**[a]	**6a**[c]	**7**[a]	**8**[a]	**8a**[c]
1	45.9	45.2	45.8	45.9	180.3	69.5	69.5	35.8	35.0	40.7	44.5	43.5
2	22.1	21.6	22.0	80.5	29.7	38.8	39.6	47.9	50.3	43.3	49.4	48.5
3	33.3	33.3	32.5	44.2	29.0	144.0	26.1	75.7	66.8	74.2	76.8	75.4
4	39.4	38.8	39.4	43.1	83.2	112.1	23.0[d]	43.9	44.7	44.1	48.6	47.7
5	96.3	97.1	84.5	46.0	36.6	23.0	23.1[d]	32.2	30.8	78.0	82.2	82.0
6	72.3	71.6	72.0	22.0	26.5			58.9	57.3	79.1	92.8	90.6
7	46.8	47.6	47.6	34.1	30.6			133.7	133.9	131.1	126.6	123.5
8	70.9	69.6	71.0	35.5	30.5			133.9	131.4	136.2	134.3	135.1
9	41.3	41.1	41.1	74.5	30.5			74.4	73.2	69.6	78.1	68.8
10	35.6	35.3	35.5	28.2	27.1			67.7	66.8	24.2	21.4	23.7
11	35.9	35.1	36.0	27.6	30.8			21.7	21.4	26.2	25.9	25.6
12	30.8	30.7	30.8	36.6	70.9			32.0	31.2	27.6	32.8	32.0
13	21.0	20.9	21.1	21.9				21.8	21.2	27.1	31.6	31.5
14	48.8	49.3	48.6	80.4								
15	30.2	30.0	30.1	29.5								
1′	107.1	107.6		105.6	104.4	104.4	104.4	102.8		103.2	102.8	
2′	76.2	76.4		75.3	75.2	75.1	75.1	75.2		75.2	75.4	
3′	78.5	78.8		78.8	78.2	78.0	78.0	78.1		78.1	78.1	
4′	71.5	71.6		71.8	71.7	71.6	71.6	71.8		71.9	71.5	
5′	78.1	78.5		78.6	78.0	76.9	76.9	77.9		78.0	78.0	
6′	62.7	62.8		63.0	62.8	69.5	69.5	62.9		63.1	62.7	
1″						105.2	105.1					
2″						72.4	72.4					
3″						74.2	74.2					
4″						69.5	69.4					
5″						66.7	66.8					

Measured in *a*) CD_3OD, *b*) pyridine-d_5, *c*) $CDCl_3$, *d*) interchangeable.

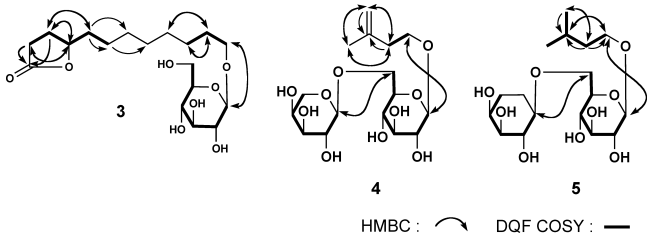

Fig. 2. Selected HMBC and DQF COSY Correlations

Foliachinenoside G (**3**), obtained as an amorphous colorless powder, showed absorption bands at 3420, 1761, and 1034 cm^{-1} assignable to hydroxyl, γ-lactone, and ether functions in the IR spectrum. The molecular formula $C_{18}H_{32}O_8$ of **3** was determined from the positive-ion FAB-MS at *m/z* 399 $(M+Na)^+$ and by HR-FAB-MS measurement. The acid hydrolysis of **3** liberated D-glucose, which was identified by HPLC analysis.[38] The ^{1}H-NMR (CD_3OD) and ^{13}C-NMR (Table 2) spectra[39] of **3** showed signals assignable to a methylene and a methine bearing an oxygen function {[δ 3.53, 3.90 (1H each, both td, J=6.7, 14.0 Hz, H_2-12), 4.54 (1H, m, H-4)]}, a γ-lactone carbon [δ_C 180.3 (C-1)] together with a β-D-glucopyranosyl part [δ 4.24 (d, J=7.7 Hz, H-1′)]. The relative structure of **3** was characterized by DQF COSY and HMBC experiments as shown in Fig. 2. Finally, the enzymatic hydrolysis **3** with β-glucosidase gave an aglycon, foliachinenol G (**3a**), whose molecular formula $C_{12}H_{22}O_3$ was determined from positive-ion chemical ionization (CI)-MS {*m/z* 215 $[M+1]^+$} and by HR-CI-MS measurement. The absolute stereostructure of the 3-position of **3** was characterized by comparison of the optical rotation of **3a** with those of known γ-butylolactones with an alkyl group at the 3-position. Namely, the optical rotations of known compounds, (*R*)-γ-dodecalactone and (*R*)-γ-undecalactone, with 4*R* orientation were reported to show positive {$[\alpha]_D^{20}$ +42.1° (MeOH), $[\alpha]_D^{20}$ +44.8° (MeOH), respectively}, while the optical rotations of known compounds, (*S*)-γ-dodecalactone and (*S*)-γ-undecalactone, with 4*S* orientation were reported to show negative {$[\alpha]_D^{20}$ −42.2° (MeOH), $[\alpha]_D^{20}$ −45.6° (MeOH), respectively}.[43] Since **3a** showed positive optical rotation {$[\alpha]_D^{27}$ +35.7° (MeOH)}, the absolute stereostructure of the 3-position of **3** was determined to be *R* orientation. On the basis of this evidence, foliachinenoside G (**3**) was determined as shown.

Foliachinenosides H (**4**) and I (**5**), obtained as a colorless amorphous powder with negative optical rotation (**4**: $[\alpha]_D^{27}$ −18.0°; **5**: $[\alpha]_D^{28}$ −19.4° in MeOH), respectively. The IR spectra of **4** and **5** showed absorption bands due to hydroxyl and ether functions. The molecular formula ($C_{16}H_{28}O_{10}$ for **4**, $C_{16}H_{30}O_{10}$ for **5**) of **4** and **5** were determined from the positive- and negative-ion FAB-MS and by HR-FAB-MS measurements. The acid hydrolysis of **4** and **5** liberated D-glucose and L-arabinose, which were identified by HPLC analysis.[38] The ^{1}H-NMR (CD_3OD) and ^{13}C-NMR (Table 2) spectra[39] of **4** and **5** showed signals assignable to an aglycon part [**4** (3-methyl-3-butenol part) δ: 1.76 (3H, s, H_3-5), 2.35 (2H, dd, J=7.3, 7.3 Hz, H_2-2), 3.65, 3.99 (1H each, both td, J=7.3, 14.7 Hz, H_2-1), 4.74, 4.75 (1H each, both br s, H_2-4); **5** (3-methyl-3-butanol part) δ: 0.92 (6H, d, J=6.9 Hz, H_3-4, 5), 1.51 (2H, dd, J=6.9, 6.9 Hz, H_2-2), 1.74 (1H, m, H-3), 3.58, 3.92 (1H each, both td, J=6.9, 14.7 Hz, H_2-1)] together with a β-D-glucopyranosyl and an α-L-arabinopyranosyl parts [**4** δ: 4.27 (1H, d, J=7.7 Hz, H-1′), 4.31 (1H, d, J=6.7 Hz, H-1″), **5** δ: 4.24 (1H, d, J=7.6 Hz, H-1′), 4.31 (1H, d, J=6.8 Hz, H-1″)]. The positions of the glycoside moieties in **4** and **5** were clarified on the basis of a HMBC experiment, which showed long-range correlations between the following protons and carbons: H-1′ and C-1; H-1″ and C-6′. Furthermore, on the basis of the DQF-COSY and HMBC experiments on **4** and **5** (Fig. 2), foliachinenosides I (**4**) and J (**5**) were elucidated as shown.

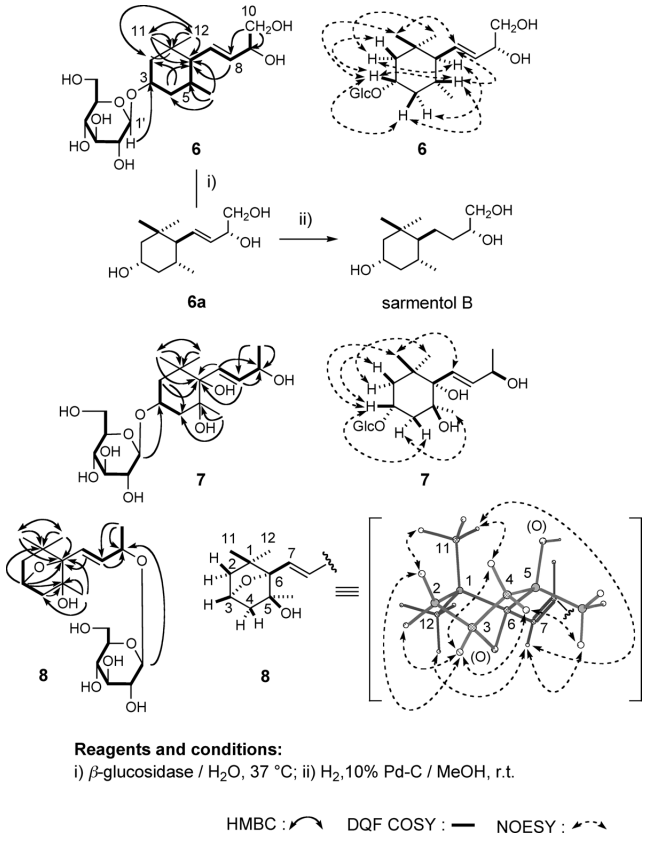

Fig. 3. Selected HMBC, DQF COSY, and NOESY Correlations

Foliasalacioside J (**6**) was obtained as a colorless amorphous powder with negative optical rotation ($[\alpha]_D^{26}$ −26.0° in MeOH). The IR spectrum showed absorption bands at 3400 and 1076 cm^{-1} assignable to hydroxyl and ether functions. The molecular formula $C_{19}H_{34}O_8$ of **6** was determined from the positive-ion FAB-MS at *m/z* 413 $(M+Na)^+$ and by HR-FAB-MS measurement. The acid hydrolysis of **6** liberated D-glucose.[38] The ^{1}H-NMR (CD_3OD) and ^{13}C-NMR (Table 1) spectra[39] of **6** showed signals assignable to three methyls [δ 0.86, 0.88 (3H each, both s, H_3-11, 12), 0.87 (3H, d, J=6.7 Hz, H_3-13)], a methylene and two methines bearing an oxygen function [δ 3.43 (1H, dd, J=7.3, 11.0 Hz, H-10a), 3.48 (1H, dd, J=4.6, 11.0 Hz, H-10b), 3.87 (1H, m, H-3), 4.10 (1H, m, H-9)] together with a β-D-glucopyranosyl part [δ 4.35 (1H, d, J=8.0 Hz, H-1′)]. As shown in Fig. 3, the DQF COSY experiment on **6** indicated the presence of partial structures written in bold lines, and in the HMBC experiment, long-range correlations were observed between the following protons and carbons: H-4 and C-2, 6; H-8 and C-6; H_2-10 and C-8, 9; H_3-11 and C-1, 2, 6, 12; H_3-12 and C-1, 2,

6, 11; H_3-13 and C-4, 5, 6; H-1′ and C-3. Thus, the planar structure of **6** was determined as shown. The relative stereostructure of **6** except for the 9-position was characterized by the NOESY experiment, which showed NOE correlations between the following proton pairs: H-2α and H-6, H_3-12; H-2β and H-3; H-3 and H-4β, H-5, H_3-11; H-4α and H-6; H-4β and H-5; H-5 and H-7; H-7 and H_3-11. Furthermore, the enzymatic hydrolysis of **6** with β-glucosidase gave an aglycon, foliasalaciol J (**6a**). Catalytic reduction of **6a** yielded a known megastigmane, sarmentol B.[44] Consequently, **6** was determined to be (3*S*,5*R*,6*R*,7*E*,9*R*)-megastigman-7-ene-3,9,10-triol 3-*O*-β-D-glucopyranoside.

Foliasalacioside K (**7**) was obtained as a colorless amorphous powder with negative optical rotation ($[\alpha]_D^{27}$ −5.6° in MeOH). The IR spectra of **7** showed absorption bands due to hydroxyl and ether functions. The molecular formula $C_{19}H_{34}O_9$ was determined from the positive-ion FAB-MS and by HR-FAB-MS measurements. The acid hydrolysis of **7** liberated D-glucose, which was identified by HPLC analysis.[38] The ^{1}H-NMR (CD_3OD) and ^{13}C-NMR (Table 1) spectra[39] of **7** showed signals assignable to four methyls [δ 0.85, 1.14, 1.19 (3H each, all s, H_3-12, 13, 11), 1.27 (3H, d, J=6.5 Hz, H_3-10)], two methines bearing an oxygen function [δ 4.17 (1H, m, H-3), 4.35 (1H, m, H-9)], two olefinic protons [δ 5.78 (1H, dd, J=6.3, 15.9 Hz, H-8), 6.05 (1H, dd, J=1.1, 15.9 Hz, H-7)] together with a β-D-glucopyranosyl part [δ 4.36 (1H, d, J=7.8 Hz, H-1′)]. The position of the glycoside moiety in **7** was clarified on the basis of the HMBC experiment, which showed long-range correlation between H-1′ and C-3. Furthermore, on the basis of the DQF-COSY and HMBC experiments, the planar structure of **7** was determined as shown in Fig. 3 and found to be same as (3*S*,5*R*,6*R*,7*E*,9*S*)-megastigman-7-ene-3,5,6,9-tetraol 3-*O*-β-D-glucopyranoside[45] and kiwiionoside [(3*S*,5*R*,6*R*,7*E*,9*R*)-megastigman-7-ene-3,5,6,9-tetraol].[46] Next, the relative stereostructure of **7** except for the 9-position was characterized by the NOESY experiment. Finally, enzymatic hydrolysis of **7** gave a known megastigmane, (3*R*,5*S*,6*S*,7*E*,9*R*)-megastigman-7-ene-3,5,6,9-tetraol (**7a**).[47] Consequently, the structure of **7** including the absolute configuration was elucidated and **7** was determined to be (3*R*,5*S*,6*S*,7*E*,9*R*)-megastigman-7-ene-3,5,6,9-tetraol 3-*O*-β-D-glucopyranoside.

Foliasalacioside L (**8**) was obtained as an colorless amorphous powder with negative optical rotation ($[\alpha]_D^{27}$ −5.5° in MeOH). The molecular formula $C_{19}H_{32}O_8$ was determined from the positive-ion FAB-MS and by HR-FAB-MS measurements. The acid hydrolysis of **8** liberated D-glucose, which was identified by HPLC analysis.[38] The ^{1}H-NMR (CD_3OD) and ^{13}C-NMR (Table 1) spectra[39] of **8** showed signals assignable to four methyls [δ 0.85, 1.18, 1.40 (3H each, all s, H_3-12, 13, 11), 1.30 (3H, d, J=6.4 Hz, H_3-10)], two methines bearing an oxygen function [δ 4.34 (1H, m, H-3), 4.38 (1H, m, H-9)], two olefinic protons [δ 5.74 (1H, dd, J=5.8, 15.9 Hz, H-8), 5.80 (1H, d, J=15.9 Hz, H-7)] together with a β-D-glucopyranosyl part [δ 4.35 (1H, d, J=8.0 Hz, H-1′)]. The proton and carbon signals of **8** in the ^{1}H- and ^{13}C-NMR spectra were similar to those of 5,6-dihydro-5-hydroxy-3,6-epoxy-β-ionol,[48,49] except for the around of the 9-position. The position of the glycoside moiety in **8** was clarified on the basis of the HMBC experiment, which showed long-range correlation between the 1′-position and the 9-position. Furthermore, on the basis of the DQF-COSY and HMBC experiments on **8**, the planar structure of **8** was determined as shown (Fig. 3). Next, the relative stereostructure of **8** except for the 9-position was determined by a NOESY experiment, in which correlations were observed between the following proton pairs: H-2α and H-3; H-2β and H-3, H_3-11; H-3 and H-4α, H-4β; H-4α and H_3-13; H-4β and H_3-11; H-7 and H_3-11, H_3-12, H_3-13. The configuration at the 9-position of **8** was characterized by comparison of the carbon signal of the 9-position in the ^{13}C-NMR spectrum (CD_3OD) with those of known 9-hydroxymegastigman-7-ene 9-*O*-β-D-glucopyranosides. Namely, the ^{13}C-NMR signal of 9-hydroxymegastigman-7-ene 9-*O*-β-D-glucopyranosides, ampelopsisionoside (δ 77.6) and lauroside B (δ 77.0) with the 9*R* configuration were reported to be shifted downfield relative to those of lauroside A (δ 74.8) and lauroside C (δ 74.0) with the 9*S* configuration.[50,51] The carbon signal of the 9-position on **8** was observed at δ 78.1, so that the configuration of the 9-position was determined to be *R* form. Finally, enzymatic hydrolysis of **8** gave an aglycon, 5,6-dihydro-5-hydroxy-3,6-epoxy-β-ionol (**8a**),[48,49] whose relative stereostructure was determined by X-ray analysis at its nitrobenzoyl derivative. Consequently, foliasalacioside L (**8**) was determined to be (3*R**,5*S**,6*S**,7*E*,9*R*)-5,6-dihydro-5-hydroxy-3,6-epoxy-β-ionol 9-*O*-β-D-glucopyranoside.

Recently, we have reported the isolation and structure elucidation of several constituents with hepatoprotective effects from natural traditional medicine, *Hedychium coronarium*,[52] *Camellia sinensis*,[53] *Sedum sarmentosum*,[54,55] and *Rhodiola sachalinensis*,[56] and *Piper chaba*.[57] Since the MeOH extract from the leaves of *Salacia chinensis* showed the protective effects on D-GalN-induced cytotoxicity in primary cultured mouse hepatocytes [inhibition: 26% (100 μg/ml, $p<0.01$)], the activities of the principal constituents, **3**, **5**, **9**—**34**, were examined. As shown in Table 2, compounds, **12**, **23**, **29**, **31**, **32**, **33**, and **34**, were found to show the hepatoprotective effects. Particularly, lignans, eleutheroside E_2 (**31**) and 7*R*,8*S*-dihydrodehydrodiconiferyl alcohol 4-*O*-β-D-glucopyranoside (**32**), significantly showed the protective effects [inhibition (%) 41.4±3.6 ($p<0.01$), 45.5±2.7 ($p<0.01$) at 100 μM, respectively].

Experimental

General Experimental Procedures The following instruments were used to obtain physical data: specific rotations, Horiba SEPA-300 digital polarimeter (l=5 cm); IR spectra, Shimadzu FTIR-8100 spectrometer; EI-MS and high-resolution MS, JEOL JMS-GCMATE mass spectrometer; ^{1}H-NMR spectra, JEOL EX-270 (270 MHz) and JNM-LA500 (500 MHz) spectrometers; ^{13}C-NMR spectra, JEOL EX-270 (68 MHz) and JNM-LA500 (125 MHz) spectrometers with tetramethylsilane as an internal standard; and HPLC detector, Shimadzu RID-6A refractive index and SPD-10A*vp* UV–VIS detectors. HPLC column, Cosmosil 5C_{18}-MS-II (Nacalai Tesque Inc., 250×4.6 mm i.d.) and (250×20 mm i.d.) columns were used for analytical and preparative purposes, respectively. The following experimental conditions were used for chromatography: ordinary-phase silica gel column chromatography, Silica gel BW-200 (Fuji Silysia Chemical, Ltd., Aichi, Japan, 150—350 mesh); reversed-phase silica gel column chromatography, Chromatorex ODS DM1020T (Fuji Silysia Chemical, Ltd., Aichi, Japan, 100—200 mesh); TLC plates and precoated TLC plates with Silica gel 60F_{254} (Merck, 0.25 mm) (ordinary phase) and Silica gel RP-18 F_{254S} (Merck, 0.25 mm) (reversed phase); reversed-phase HPTLC, with Silica gel RP-18 WF_{254S} (Merck, 0.25 mm); and detection was achieved by spraying with 1% $Ce(SO_4)_2$–10% aqueous H_2SO_4 followed by heating.

Plant Material The dried leaves of *S. chinensis* were collected at Nakhon Si Thammarat province, Thailand in 2006 and identified by one of

Table 2. Effects of Constituents on D-GalN-Induced Cytotoxicity in Primary Cultured Mouse Hepatocytes[a)]

Treatment	Inhibition (%)				
Conc. (μM):	0	3	10	30	100
Foliachinenoside G (**3**)	0.0±3.2	1.1±3.0	−1.4±3.9	6.8±4.6	18.5±2.5**
12	0.0±2.4	−0.2±4.0	6.6±9.1	20.3±2.7*	33.7±2.8**
17	0.0±1.9	4.0±2.0	9.8±3.6	10.0±1.7	13.2±4.3*
18	0.0±4.8	−1.8±5.8	4.2±2.3	6.2±9.2	18.6±3.8
19	0.0±2.4	10.1±5.8	16.8±6.5	14.3±5.8	30.2±1.8**
Coniferin (**20**)	0.0±3.3	2.5±2.5	7.9±1.4	6.4±2.2	15.4±4.3**
cis-Syringin (**22**)	0.0±1.6	−1.1±2.7	6.0±3.7	7.2±4.1	14.6±2.5*
Dihydrosyringin (**23**)	0.0±2.5	9.1±5.4	22.5±6.0*	24.3±6.1**	30.8±1.1**
26	0.0±2.9	−4.9±1.7	1.2±1.8	6.6±2.6	11.8±2.5*
29	0.0±2.8	5.7±4.5	3.8±8.4	12.1±5.8	34.2±6.6**
30	0.0±3.6	−6.6±2.9	3.3±3.4	8.8±1.9	16.3±0.4*
Eleutheroside E_2 (**31**)	0.0±2.6	8.0±6.0	7.2±2.6	14.1±5.8	41.4±3.6**
32	0.0±1.2	17.5±6.6	20.3±10.8	23.4±6.4	45.5±2.7**
33	0.0±8.8	10.7±2.7	14.4±7.7	13.6±8.9	34.3±3.7*
34	0.0±2.5	16.8±3.5*	17.3±4.4**	25.0±2.3**	39.1±4.0**
Silybin[61,b)]	0.0±0.3	4.8±1.1	7.7±0.7	45.2±8.8**	—

Compounds, **5**, **9**—**11**, **13**—**16**, **21**, **24**, **25**, **27**, and **28**, did not show the effects (inhibition: <12% at 100 μM). *a*) Each value represents the mean±S.E.M. (n=4). Significantly different from the control, * p<0.05, ** p<0.01. (—): Cytotoxicity. *b*) Commercial silybin (Funakoshi Co., Ltd., Tokyo, Japan) was used as a reference compound.

authors (Rajamangala University of Technology Srivijaya, Pongpiriyadacha Y.). A voucher of the plant is on file in our laboratory (2006. Thai-06).

Extraction and Isolation The dried leaves of *S. chinensis* LINN. (5.8 kg) were finely cut and extracted 3 times with MeOH under reflux for 3 h. Evaporation of the solvent under reduced pressure provided a MeOH extract (756 g, 13.0%). The MeOH extract (712 g) was partitioned into an EtOAc–H_2O (1 : 1, v/v) mixture to furnish an EtOAc-soluble fraction (222 g, 4.1%) and an aqueous phase. The aqueous phase was further extracted with *n*-BuOH to give an *n*-BuOH-soluble fraction (130 g, 2.4%) and a H_2O-soluble fraction (361 g, 6.6%). The EtOAc fraction (200 g) was subjected to ordinary-phase silica gel column chromatography [3.8 kg, hexane–EtOAc (40 : 1→10 : 1→5 : 1→1 : 1, v/v)→$CHCl_3$–MeOH–H_2O (10 : 3 : 1, v/v/v, lower layer)→MeOH] to give 16 fractions [Fr. 1 (0.7 g), Fr. 2 (1.3 g), Fr. 3 (28.3 g), Fr. 4 (0.9 g), Fr. 5 (9.0 g), Fr. 6 (14.9 g), Fr. 7 (3.2 g), Fr. 8 (10.7 g), Fr. 9 (9.1 g), Fr. 10 (6.2 g), Fr. 11 (4.2 g), Fr. 12 (13.8 g), Fr. 13 (4.1 g), Fr. 14 (43.2 g), Fr. 15 (16.9 g), Fr. 16 (26.3 g)]. Fraction 10 (6.2 g) was subjected to Sephadex LH-20 column chromatography [200 g, MeOH–$CHCl_3$ (1 : 1, v/v)] to give two fractions [Fr. 10-1, Fr. 10-2 (3.6 g)]. Fraction 10-2 (3.6 g) was subjected to reversed-phase silica gel column chromatography [120 g, CH_3CN–H_2O (75 : 25→85 : 15→90 : 10→100 : 5, v/v)→CH_3CN→$CHCl_3$] to give nine fractions [Fr. 10-2-1, Fr. 10-2-2, Fr. 10-2-3, Fr. 10-2-4, Fr. 10-2-5, Fr. 10-2-6, Fr. 10-2-7 (49 mg), Fr. 10-2-8, Fr. 10-2-9]. Fraction 10-2-7 (49 mg) was isolated with HPLC [MeOH–H_2O (96 : 4, v/v)] to give 1,2-di-9,12,15-octadecatrienoyl-*sn*-glycerol (**34**, 10 mg, 0.00023%). Fraction 14 (43.2 g) was subjected to reversed-phase silica gel column chromatography [1.2 kg, MeOH–H_2O (60 : 40→70 : 30, v/v)→CH_3CN–H_2O (65 : 35→75 : 25→85 : 15, v/v)→CH_3CN→$CHCl_3$] to give six fractions [Fr. 14-1, Fr. 14-2, Fr. 14-3, Fr. 14-4, Fr. 14-5 (11.6 g), Fr. 14-6]. Fraction 14-5 (11.6 g) was separated with silica gel NH column chromatography [400 g, hexane–EtOAc (1 : 10, v/v)→$CHCl_3$–MeOH (50 : 1→50 : 3→50 : 10, v/v)→MeOH] to give four fractions [Fr. 14-5-1, Fr. 14-5-2 (5.5 g), Fr. 14-5-3, Fr. 14-5-4]. Fraction 14-5-2 (5.5 g) was further isolated with reversed-phase silica gel column chromatography [160 g, MeOH–H_2O (70 : 30→80 : 20→90 : 10, v/v)→MeOH→CH_3CN] to give five fractions [Fr. 14-5-2-1, Fr. 14-5-2-2, Fr. 14-5-2-3, Fr. 14-5-2-4, Fr. 14-5-2-5 (3.9 g)]. A part of fraction 14-5-2-5 (1.9 g) was subjected to HPLC (MeOH) to furnish (2*S*)-2,3-*O*-di-(9,12,15-octadecatrienoyl)glyceryl]-β-D-galactopyranoside (**33**, 149 mg, 0.0066%). Fraction 16 (26.3 g) was subjected to Diaion HP-20 column chromatography (1.5 kg, H_2O→MeOH) to give a H_2O-eluted fraction (15.2 g) and a MeOH-eluted fraction (10.8 g), respectively. The MeOH-eluted fraction (10.8 g) was subjected to reversed-phase silica gel column chromatography [480 g, MeOH–H_2O (20 : 80→30 : 70→40 : 60→50 : 50→70 : 30, v/v)→MeOH] to give 11 fractions [Fr. 16-1, Fr. 16-2 (766 mg), Fr. 16-3 (403 mg), Fr. 16-4 (1.3 g), Fr. 16-5, Fr. 16-6, Fr. 16-7, Fr. 16-8, Fr. 16-9, Fr. 16-10, Fr. 16-11]. Fraction 16-2 (766 mg) was purified by HPLC {[1] MeOH–H_2O (30 : 70, v/v), [2] MeOH–H_2O (26 : 74, v/v)} to furnish foliachinenoside I (**5**, 15 mg, 0.00033%), (3*Z*)-3-hexen-1-ol 6-*O*-α-L-arabinopyranosyl-β-D-glucopyranoside (**10**, 11 mg, 0.00025%), and (*E*)-coumaroyl-1-*O*-β-D-glucopyranoside (**25**, 9.1 mg, 0.00020%). Fraction 16-3 (403 mg) was subjected to HPLC {[1] MeOH–H_2O (30 : 70, v/v)}, [2] CH_3CN–MeOH–H_2O (10 : 9 : 81, v/v)] to furnish (3*Z*)-3-hexen-1-ol 6-*O*-α-L-arabinopyranosyl-β-D-glucopyranoside (**10**, 11 mg, 0.00025%). Fraction 16-4 (1.3 g) was separated by HPLC {[1] MeOH–H_2O (30 : 70, v/v), [2] [CH_3CN–MeOH–H_2O (10 : 9 : 81, v/v/v)] to furnish 7*R*,8*S*-dihydrodehydrodiconiferyl alcohol 4-*O*-β-D-glucopyranoside (**32**, 12 mg, 0.00028%).

The *n*-BuOH-soluble fraction (100.0 g) was subjected to Diaion HP-20 column chromatography (1.5 kg, H_2O→MeOH→acetone) to give a H_2O-eluted fraction (49.8 g, 1.19%), a MeOH-eluted fraction (39.2 g, 0.93%) and an acetone-eluted fraction (11.0 g, 0.26%), respectively. The MeOH-eluted fraction (39.2 g) was subjected to ordinary-phase silica gel column chromatography {480 g, $CHCl_3$–MeOH (10 : 1, v/v)→$CHCl_3$–MeOH–H_2O [(10 : 3 : 1, v/v/v, lower layer)→(7 : 3 : 1, v/v/v, lower layer)→(6 : 4 : 1, v/v/v, lower layer)]→MeOH} to give ten fractions [Fr. 1 (0.5 g), Fr. 2 (0.6 g), Fr. 3 (1.3 g), Fr. 4 (7.3 g), Fr. 5 (3.0 g), Fr. 6 (6.7 g), Fr. 7 (1.6 g), Fr. 8 (2.4 g), Fr. 9 (9.3 g), Fr. 10 (3.5 g)] as reported previously.[7)] Fraction 3 (1.3 g) was subjected to reversed-phase silica gel column chromatography [480 g, MeOH–H_2O (10 : 90→20 : 80→30 : 70→40 : 60→50 : 50→60 : 40, v/v)→MeOH] to give five fractions [Fr. 3-1, Fr. 3-2, Fr. 3-3 (389 mg), Fr. 3-4 (131 mg), Fr. 3-5]. Fraction 3-3 (389 mg) was separated by HPLC {[1] MeOH–H_2O (40 : 60, v/v), [2] CH_3CN–MeOH–H_2O (15 : 8 : 77, v/v/v)} to furnish eleutheroside E_2 (**31**, 7.0 mg, 0.00017%). Fraction 3-4 (131 mg) was separated by HPLC {[1] MeOH–H_2O (40 : 60, v/v), [2] CH_3CN–MeOH–H_2O (15 : 8 : 77, v/v/v)} to furnish foliachinenoside G (**3**, 7.0 mg, 0.00017%). Fraction 4 (7.3 g) was subjected to reversed-phase silica gel column chromatography [220 g, H_2O→MeOH–H_2O (10 : 90→20 : 80→30 : 70→40 : 60→60 : 40, v/v)→MeOH→$CHCl_3$] to give 10 fractions [Fr. 4-1, Fr. 4-2, Fr. 4-3 (1.1 g), Fr. 4-4, Fr. 4-5, Fr. 4-6 (652 mg), Fr. 4-7 (1.3 g), Fr. 4-8 (413 mg), Fr. 4-9, Fr. 4-10]. Fraction 4-3 (1.1 g) was separated by HPLC {[1] MeOH–H_2O (15 : 85 and 20 : 80, v/v), [2] CH_3CN–MeOH–H_2O (8 : 8 : 84 and 10 : 8 : 82, v/v/v)} to furnish foliasalacioside J (**6**, 7.0 mg, 0.00017%), 2,4,6-trimethoxyphenol 1-*O*-β-D-glucopyranoside (**11**, 6.9 mg, 0.00016%), benzyl alcohol β-D-glucopyranoside (**12**, 1.3 mg, 0.00003%), violutoside (**15**, 16 mg, 0.00039%), 2,6-dimethoxy-4-(2-hydroxyethyl)phenol 1-*O*-β-D-glucopyranoside (**17**, 3.3 mg, 0.00008%), coniferin (**20**, 10 mg, 0.00024%), syringin (**21**, 124 mg, 0.0029%), *cis*-syringin (**22**, 10.0 mg, 0.00024%), dihydrosyringin (**23**, 10.1 mg, 0.00024%), (*E*)-coumaroyl-1-*O*-β-D-glucopyranoside (**25**, 2.5 mg, 0.00006%), 1-[(2*Z*)-3-(4-hydroxyphenyl)-2-propenoate]-β-D-glucopyranoside (**26**, 2.1 mg, 0.00005%), myzodendrone (**27**, 10 mg, 0.00024%), and hovetrichoside A (**28**, 4.4 mg, 0.00010%). Fraction 4-6 (652 mg) was subjected to HPLC {[1] MeOH–H_2O (30 : 70 and 26 : 74, v/v), [2] CH_3CN–MeOH–H_2O (12 : 8 : 80, v/v/v)} to furnish (3*Z*)-3-hexen-1-ol 6-*O*-α-L-arabinopyranosyl-β-D-glucopyranoside (**10**, 6.8 mg, 0.00016%), syringin (**21**, 8.7 mg, 0.00021%) and 4,7,9-trihydroxy-3,3′-dimethoxy-8-*O*-4′-neolignan-9′-*O*-β-D-glucopyranoside[7*S*,8*R*-*erythro*

form] (**29**, 8.1 mg, 0.00019%). Fraction 4-7 (1.3 g) was separated by HPLC {[1] MeOH–H_2O (40 : 60, v/v), [2] CH_3CN–MeOH–H_2O (15 : 8 : 77, v/v/v)} to furnish foliasalaciosides L (**8**, 3.1 mg, 0.00007%), (3*Z*)-3-hexen-1-ol 6-*O*-α-L-arabinopyranosyl-β-D-glucopyranoside (**10**, 5.1 mg, 0.00012%), eugenyl vicianoside (**18**, 30 mg, 0.00070%), and syringaresinol mono-β-D-glucopyranoside (**30**, 17 mg, 0.00040%). Fraction 4-8 (413 mg) was subjected to HPLC {[1] MeOH–H_2O (40 : 60, v/v), [2] CH_3CN–MeOH–H_2O (15 : 8 : 77, v/v/v)} to furnish foliachinenoside E (**1**, 3.9 mg, 0.00009%), eugenyl vicianoside (**18**, 4.2 mg, 0.00010%) and syringaresinol mono-β-D-glucopyranoside (**30**, 3.5 mg, 0.00008%). Fraction 5 (3.0 g) was subjected to reversed-phase silica gel column chromatography [90 g, MeOH–H_2O (10 : 90→20 : 80→30 : 70→40 : 60→50 : 50, v/v)→MeOH] to give seven fractions [Fr. 5-1, Fr. 5-2 (196 mg), Fr. 5-3 (212 mg), Fr. 5-4 (224 mg), Fr. 5-5, Fr. 5-6 (400 mg), Fr. 5-7]. Fraction 5-2 (196 mg) was purified by HPLC {[1] MeOH–H_2O (24 : 76, v/v), [2] CH_3CN–MeOH–H_2O (10 : 8 : 82, v/v/v)} to furnish foliachinenoside H (**4**, 11.6 mg, 0.00028%), 3-methylbut-2-en-1-ol 6-*O*-α-L-arabinopyranosyl-β-D-glucopyranoside (**9**, 32 mg, 0.00077%), benzyl alcohol 6-*O*-α-L-arabinopyranosyl-β-D-glucopyranoside (**13**, 34 mg, 0.00080%). Fraction 5-3 (212 mg) was separated by HPLC {[1] MeOH–H_2O (26 : 74, v/v), [2] CH_3CN–MeOH–H_2O (10 : 8 : 82, v/v/v)} to furnish foliachinenoside I (**5**, 35 mg, 0.00083%), benzyl alcohol 6-*O*-α-L-arabinopyranosyl-β-D-glucopyranoside (**13**, 19 mg, 0.00045%), benzyl β-primeveroside (**14**, 6.0 mg, 0.00041%), and *trans*-*p*-sinapoyl-β-D-glucopyranoside (**24**, 29 mg, 0.00068%). Fraction 5-4 (224 mg) was purified by HPLC {[1] MeOH–H_2O (26 : 74, v/v), [2] CH_3CN–MeOH–H_2O (10 : 8 : 82, v/v/v)} to furnish (3*Z*)-3-hexen-1-ol 6-*O*-α-L-arabinopyranosyl-β-D-glucopyranoside (**10**, 34 mg, 0.00080%) and 2-phenethyl alcohol 6-*O*-α-L-arabinopyranosyl-β-glucopyranoside (**16**, 14 mg, 0.00033%). Fraction 5-6 (400 mg) was subjected to HPLC {[1] MeOH–H_2O (40 : 60, v/v)}, [2] CH_3CN–MeOH–H_2O (15 : 8 : 75, v/v/v)} to furnish foliachinenoside F (**2**, 5.4 mg, 0.00013%), eugenyl vicianoside (**18**, 6.2 mg, 0.00015%), 2,6-dimethoxy-4-(2-propenyl)phenol 6-*O*-β-D-glucopyranosyl β-D-glucopyranoside (**19**, 4.6 mg, 0.00011%). Fraction 6 (6.7 g) was subjected to reversed-phase silica gel column chromatography [220 g, MeOH–H_2O (10 : 90→20 : 80→30 : 70→40 : 60→50 : 50→60 : 40→100 : 0, v/v)→$CHCl_3$] to give 11 fractions [Fr. 6-1, Fr. 6-2 (859 mg), Fr. 6-3, Fr. 6-4, Fr. 6-5, Fr. 6-6, Fr. 6-7, Fr. 6-8, Fr. 6-9, Fr. 6-10, Fr. 6-11]. Fraction 6-2 (859 mg) was separated by HPLC {[1] MeOH–H_2O (25 : 75, v/v), [2] CH_3CN–MeOH–H_2O (7 : 7 : 86, v/v/v)} to furnish to foliachinenoside H (**4**, 9.0 mg, 0.00021%), foliachinenoside I (**5**, 19 mg, 0.00045%), foliasalacioside K (**7**, 6.6 mg, 0.00016%), 3-methylbut-2-en-1-ol 6-*O*-α-L-arabinopyranosyl-β-D-glucopyranoside (**9**, 38 mg, 0.00089%), and benzyl alcohol 6-*O*-α-L-arabinopyranosyl-β-D-glucopyranoside (**13**, 58 mg, 0.0012%). The known compounds were identified by comparison of their physical data ($[\alpha]_D$, ^{1}H-NMR, ^{13}C-NMR, and MS) with reported values.

Foliachinenoside E (**1**): An amorphous colorless powder; $[\alpha]_D^{27}$ +9.8° (c=0.20, MeOH); IR (KBr) ν_{max}: 3400, 2932, 1076, 758 cm^{-1}; ^{1}H-NMR (500 MHz, pyridine-d_5) δ: 0.99, 1.02, 1.36 (3H each, all s, H_3-13, 12, 15), 1.38 (1H each, m, H-2α, 3β), 1.51 (1H, m, H-2β), 1.61 (1H, d, J=13.4 Hz, H-14β), 1.68 (1H, dd, J=8.3, 9.3 Hz, H-10α), 2.01 (1H, dd, J=9.3, 9.3 Hz, H-10β), 2.04 (1H, m, H-3α), 2.11 (1H, m, H-1), 2.14 (1H, br d, J=13.4 Hz, H-14α), 2.15 (1H, m, H-7β), 2.46 (1H, m, H-9), 2.62 (1H, m, H-7α), 3.61 (1H, d, J=8.9 Hz, H-5), 4.44 (1H, m, H-6′a), 4.52 (1H, dd, J=2.4, 11.6 Hz, H-6′b), 4.60 (1H, m, H-6), 5.17 (1H, d, J=7.9 Hz, H-1′); ^{1}H-NMR (500 MHz, CD_3OD) δ: 1.00, 1.00, 1.09 (3H each, all s, H_3-13, 12, 15), 1.17 (1H, m, H-3β), 1.17 (1H, d, J=13.7 Hz, H-14β), 1.71 (1H, m, H-3α), 1.79 (1H, br d, J=13.7 Hz, H-14α), 1.35 (1H, m, H-2α), 1.43 (1H, m, H-7β), 1.49 (1H, m, H-2β), 1.54 (2H, m, H_2-10), 1.88 (1H, m, H-1), 2.01 (1H, m, H-7α), 2.19 (1H, m, H-9), 3.15 (1H, d, J=9.7 Hz, H-5), 3.69 (1H, dd, J=5.5, 11.7 Hz, H-6′a), 3.82 (1H, dd, J=2.0, 11.7 Hz, H-6′b), 4.05 (1H, m, H-6), 4.47 (1H, d, J=7.6 Hz, H-1′); ^{13}C-NMR data (125 MHz, CD_3OD and pyridine-d_5) δ_C: given in Table 1; Positive-ion FAB-MS m/z 439 $[M+Na]^+$; HR-FAB-MS m/z 439.2314 (Calcd for $C_{21}H_{36}O_8Na$ $[M+Na]^+$, 439.2308).

Foliachinenoside F (**2**): An amorphous colorless powder; $[\alpha]_D^{27}$ −22.0° (c=0.27, MeOH); IR (KBr) ν_{max}: 3400, 2928, 1075, 1036 cm^{-1}; ^{1}H-NMR (pyridine-d_5, 500 MHz) δ: 1.07 (1H, br d, J=12.5 Hz, H-12a), 1.16, 1.21 (3H each, both s, H_3-13, 15), 1.26 (1H, m, H-7α), 1.40 (1H, m, H-7β), 1.50 (1H, m, H-6β), 1.59 (1H, m, H-11α), 1.63 (1H, m, H-6α), 1.92 (1H, m, H-10β), 1.95 (1H, dd, J=4.0, 10.4 Hz, H-5), 2.00 (1H, dd, J=5.5, 12.5 Hz, H-3β), 2.14 (1H, d, J=12.5 Hz, H-12b), 2.17 (1H, m, H-10α), 2.23 (1H, dd, J=7.9, 12.5 Hz, H-3α), 2.40 (1H, m, H-11β), 3.56, 4.10 (1H each, both d, J=9.2 Hz, H_2-14), 3.58 (1H, m, H-9), 4.12 (1H, dd like, J=5.5, 7.9 Hz, H-2), 4.41 (1H, dd, J=5.5, 11.0 Hz, H-6′a), 4.60 (1H, dd, J=2.4, 11.0 Hz, H-6′b), 4.90 (1H, d, J=7.9 Hz, H-1′); ^{13}C-NMR data (125 MHz, pyridine-d_5) δ_C: given in Table 1; Positive-ion FAB-MS m/z 439 $[M+Na]^+$; HR-FAB-MS m/z 439.2303 (Calcd for $C_{21}H_{36}O_8Na$ $[M+Na]^+$, 439.2308).

Foliachinenoside G (**3**): An amorphous colorless powder; $[\alpha]_D^{29}$ −3.0° (c=0.38, MeOH); IR (KBr) ν_{max}: 3420, 2934, 1761, 1034 cm^{-1}; ^{1}H-NMR (CD_3OD, 500 MHz) δ: 1.86, 2.33 (1H each, both m, H_2-3), 1.35 (6H, m, H_2-7, 8, 9), 1.39 (2H, m, H_2-10), 1.39, 1.44 (1H each, both m, H_2-6), 1.59, 1.72 (1H each, both m, H_2-5), 1.62 (2H, m, H_2-11), 2.55 (2H, m, H_2-2), 3.53, 3.90 (1H each, both td, J=6.7, 14.0 Hz, H_2-12), 3.66 (dd, J=5.2, 11.6 Hz, H-6′a), 3.85 (dd, J=1.5, 11.6 Hz, H-6′b), 4.24 (d, J=7.7 Hz, H-1′), 4.54 (1H, m, H-4); ^{13}C-NMR data (CD_3OD, 125 MHz) given in Table 1; Positive-ion FAB-MS m/z 399 $[M+Na]^+$; HR-FAB-MS m/z 399.2001 (Calcd for $C_{18}H_{32}O_8Na$ $[M+Na]^+$, 399.1995).

Foliachinenoside H (**4**): An amorphous colorless powder; $[\alpha]_D^{27}$ −18.0° (c=0.63, MeOH); IR (KBr) ν_{max}: 3440, 2940, 1090 cm^{-1}; ^{1}H-NMR (CD_3OD, 500 MHz) δ: 1.76 (3H, s, H_3-5), 2.35 (2H, dd, J=7.3, 7.3 Hz, H_2-2), 3.65, 3.99 (1H each, both td, J=7.3, 14.7 Hz, H_2-1), 4.74, 4.75 (1H each, both br s, H_2-4), 4.27 (1H, d, J=7.7 Hz, H-1′), 4.31 (1H, d, J=6.7 Hz, H-1″); ^{13}C-NMR data (125 MHz, CD_3OD) given in Table 1; Positive-ion FAB-MS m/z 403 $[M+Na]^+$; Negative-ion FAB-MS m/z 379 $[M-H]^-$; HR-FAB-MS m/z 403.1586 (Calcd for $C_{16}H_{28}O_{10}Na$ $[M+Na]^+$, 403.1580).

Foliachinenoside I (**5**): An amorphous colorless powder; $[\alpha]_D^{28}$ −19.4° (c=1.11, MeOH); IR (KBr) ν_{max}: 3450, 2943, 1076 cm^{-1}; ^{1}H-NMR (CD_3OD, 500 MHz) δ: 0.92 (6H, d, J=6.9 Hz, H_3-4, 5), 1.51 (2H, dd, J=6.9, 6.9 Hz, H_2-2), 1.74 (1H, m, H-3), 3.58, 3.92 (1H each, both td, J=6.9, 14.7 Hz, H_2-1), 4.24 (1H, d, J=7.6 Hz, H-1′), 4.31 (1H, d, J=6.8 Hz, H-1″); ^{13}C-NMR data (125 MHz, CD_3OD) given in Table 1; Positive-ion FAB-MS m/z 405 $[M+Na]^+$; Negative-ion FAB-MS m/z 381 $[M-H]^-$; HR-FAB-MS m/z 405.1740 (Calcd for $C_{16}H_{30}O_{10}Na$ $[M+Na]^+$, 405.1737).

Foliasalacioside J (**6**): An amorphous colorless powder; $[\alpha]_D^{26}$ −26.0° (c=0.29, MeOH); IR (KBr) ν_{max}: 3400, 2926, 1634, 1076 cm^{-1}; ^{1}H-NMR (CD_3OD, 500 MHz) δ: 0.86, 0.88 (3H each, both s, H_3-11, 12), 0.87 (3H, d, J=6.7 Hz, H_3-13), 1.02 (1H, m, H-4α), 1.16 (1H, m, H-2α), 1.35 (1H, m, H-6), 1.57 (1H, m, H-5), 1.85 (1H, m, H-2β), 2.12 (1H, m, H-4β), 3.43 (1H, dd, J=7.3, 11.0 Hz, H-10a), 3.48 (1H, dd, J=4.6, 11.0 Hz, H-10b), 3.87 (1H, m, H-3), 4.10 (1H, m, H-9), 4.35 (1H, d, J=8.0 Hz, H-1′), 5.41 (1H, dd, J=5.0, 15.8 Hz, H-8), 5.42 (1H, dd like, J=10.3, 15.8 Hz, H-7); ^{13}C-NMR data (CD_3OD, 125 MHz) δ_C: given in Table 1; Positive-ion FAB-MS m/z 413 $[M+Na]^+$; HR-FAB-MS m/z 413.2160 (Calcd for $C_{19}H_{34}O_8Na$ $[M+Na]^+$, 413.2151).

Foliasalacioside K (**7**): An amorphous colorless powder, $[\alpha]_D^{26}$ −5.6° (c=0.33, MeOH). IR (KBr): 3430, 2934, 1076 cm^{-1}; ^{1}H-NMR (CD_3OD, 500 MHz) δ: 0.85, 1.14, 1.19 (3H each, all s, H_3-12, 13, 11), 1.27 (3H, d, J=6.5 Hz, H_3-10), 1.59 (1H, ddd like, J=1.9, 4.4, 12.1 Hz, H-2β), 1.68 (1H, dd, J=12.1, 12.1 Hz, H-2α), 1.85 (1H, dd, J=12.8, 12.8 Hz, H-4α), 1.94 (1H, ddd like, J=1.9, 4.3, 12.8 Hz, H-4β), 4.17 (1H, m, H-3), 4.35 (1H, m, H-9), 4.36 (1H, d, J=7.8 Hz, H-1′), 5.78 (1H, dd, J=6.3, 15.9 Hz, H-8), 6.05 (1H, dd, J=1.1, 15.9 Hz, H-7); ^{13}C-NMR data (CD_3OD, 125 MHz) δ_C: given in Table 1; Positive-ion FAB-MS m/z 429 $[M+Na]^+$; HR-FAB-MS m/z 429.2094 (Calcd for $C_{19}H_{34}O_9Na$ $[M+Na]^+$, 429.2101).

Foliasalacioside L (**8**): An amorphous colorless powder; $[\alpha]_D^{26}$ −5.5° (c=0.11, MeOH); IR (KBr): 3420, 2934, 1078 cm^{-1}; ^{1}H-NMR (CD_3OD, 500 MHz) δ: 0.85, 1.18, 1.40 (3H each, all s, H_3-12, 13, 11), 1.30 (3H, d, J=6.4 Hz, H_3-10), 1.58 (1H, d like, J=11.6 Hz, H-2β), 1.64 (1H, d like, J=12.2 Hz, H-4β), 1.76 (1H, ddd like, J=2.2, 6.4, 11.6 Hz, H-2α), 1.95 (1H, ddd like, J=2.2, 5.8, 12.2 Hz, H-4α), 4.34 (1H, m, H-3), 4.35 (1H, d, J=8.0 Hz, H-1′), 4.38 (1H, m, H-9), 5.74 (1H, dd, J=5.8, 15.9 Hz, H-8), 5.80 (1H, d, J=15.9 Hz, H-7); ^{13}C-NMR data (CD_3OD, 125 MHz) δ_C: given in Table 1; Positive-ion FAB-MS m/z 411 $[M+Na]^+$; HR-FAB-MS m/z 411.2000 (Calcd for $C_{19}H_{32}O_8Na$ $[M+Na]^+$, 411.1995).

Acid Hydrolyses of 1—8 A solution of **1**—**8** (1.0 mg each) in 1 M HCl (1.0 ml) was heated under reflux for 3 h. After cooling, the reaction mixture was extracted with EtOAc. The aqueous layer was subjected to HPLC analysis under the following conditions, respectively: HPLC column, Kaseisorb LC NH_2-60-5, 4.6 mm i.d.×250 mm (Tokyo Kasei Co., Ltd., Tokyo, Japan); detection, optical rotation [Shodex OR-2 (Showa Denko Co., Ltd., Tokyo, Japan); mobile phase, CH_3CN–H_2O (85 : 15, v/v); flow rate 0.8 ml/min]. Identification of (i) L-arabinose from **4** and **5** and (ii) D-glucose from **1**—**8** present in the aqueous layer was carried out by comparison of its retention time and optical rotation with those of authentic sample, t_R: (i) 10.2 min (L-arabinose, positive optical rotation) and (ii) 12.8 min (D-glucose, positive optical rotation).

Enzymatic Hydrolysis of 1 with β-Glucosidase A solution of **1**, **3**, **6**, **7**, and **8** (3.0, 5.1, 5.0, 2.0, 2.0 mg, respectively) in H_2O (1.0 ml) was treated with β-glucosidase (20.6, 10.3, 10.2, 6.5, 6.5 mg, respectively) and the solution was stirred at 37 °C for 24 h (for **3**, **7**) or 48 h (for **1**, **6**, **8**). After EtOH

was added to the reaction mixture, the solution was centrifuged at 4000 rpm for 10 min. The supernatant solution was concentrated under vacuum to give a residue, which was purified by HPLC [MeOH–H_2O (**1**, **6**, **7**: 40 : 60, **3**: 50 : 50, **8**: 55 : 45, v/v)] to furnish **1a** (0.5 mg), **3a** (1.8 mg), **6a** (1.8 mg), **7a** (0.8 mg), and **8a** (1.0 mg), respectively.

Compound **1a**: Colorless oil; $[\alpha]_D^{23}$ +5.0° (c=0.02, MeOH); IR (film) ν_{max}: 3390, 2932, 1040, 754 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD) δ: 1.00, 1.00, 0.99 (3H each, all s, H_3-12, 13, 15), 1.14 (1H, m, H-3β), 1.14 (1H, d, J=13.4 Hz, H-14β), 1.65 (1H, m, H-3α), 1.76 (1H, br d, J=13.4 Hz, Hα-14), 1.37 (1H, m, H-2α), 1.41 (1H, m, H-7β), 1.50 (1H, m, H-2β), 1.54 (2H, m, H_2-10), 1.90 (1H, m, H-1), 2.01 (1H, m, H-7α), 2.18 (1H, m, H-9), 3.01 (1H, d, J=8.6 Hz, H-5), 3.80 (1H, m, H-6); ^{13}C-NMR data (125 MHz, CD_3OD) δ_C: given in Table 1; EI-MS m/z 254 $[M]^+$ (4), 236 (84), 218 (34), 203 (19), 162 (53), 161 (84), 143 (100); HR-FAB-MS m/z 254.1886 (Calcd for $C_{15}H_{26}O_3$ $[M]^+$, 254.1882).

Compound **3a**: A white powder; $[\alpha]_D^{27}$ +35.7° (c=0.07, MeOH); IR (KBr) ν_{max}: 3400, 2936, 1755, 1470 cm^{-1}; ^{1}H-NMR (CD_3OD, 500 MHz) δ: 1.86, 2.33 (1H each, both m, H_2-3), 1.35 (10H, m, H_2-6, 7, 8, 9, 10), 1.52 (2H, m, H_2-11), 1.62, 1.72 (1H each, both m, H_2-5), 2.55 (2H, m, H_2-2), 3.54 (t, J=6.7 Hz, H_2-12), 4.54 (1H, m, H-4); ^{13}C-NMR (CD_3OD, 125 MHz) δ_C: 180.3 (C-1), 29.7 (C-2), 29.0 (C-3), 83.2 (C-4), 36.5 (C-5), 26.5 (C-6), 30.6 (C-7), 30.5 (C-7), 30.5 (C-8), 30.5 (C-9), 27.1 (C-10), 33.7 (C-11), 63.0 (C-12); Positive-ion CIMS m/z 215 $[M+1]^+$ (100), 197 (18); HR-CI-MS m/z 215.1639 (Calcd for $C_{12}H_{23}O_3$ $[M+1]^+$, 215.1647).

Compound **6a**: An amorphous colorless powder; $[\alpha]_D^{28}$ −9.9° (c=0.09, MeOH); IR (film) ν_{max}: 3370, 2923, 1640, 754 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.84, 0.85 (3H each, both s, H_3-11, 12), 0.85 (3H, d, J=6.4 Hz, H_3-13), 0.92 (1H, m, H-4α), 1.12 (1H, dd, J=11.9, 11.9 Hz, H-2α), 1.34 (1H, m, H-6), 1.56 (1H, m, H-5), 1.74 (1H, ddd like, J=2.4, 4.3, 11.9 Hz, H-2β), 2.02 (1H, m, H-4β), 3.50 (1H, m, H-10a), 3.65 (1H, m, H-10b), 3.80 (1H, m, H-3), 4.25 (1H, m, H-9), 5.43 (1H, dd, J=10.3, 15.8 Hz, H-7), 5.44 (1H, dd, J=5.2, 15.8 Hz, H-8); ^{1}H-NMR (pyridine-d_5, 500 MHz) δ: 0.88, 0.96 (3H each, both s, H_3-11, 12), 0.89 (3H, d, J=6.6 Hz, H_3-13), 1.23 (1H, m, H-4α), 1.42 (1H, dd, J=9.2, 10.3 Hz, H-6), 1.46 (1H, dd like, J=11.7, 11.7 Hz, H-2α), 1.54 (1H, m, H-5), 2.01 (1H, ddd like, J=2.2, 4.1, 11.7 Hz, H-2β), 2.24 (1H, m, H-4β), 4.05 (1H, m, H-3), 4.06 (2H, m, H_2-10), 4.74 (1H, m, H-9), 5.69 (1H, dd, J=10.3, 15.8 Hz, H-7), 5.84 (1H, dd, J=5.2, 15.8 Hz, H-8); ^{13}C NMR data ($CDCl_3$, 125 MHz) δ_C: given in Table 1; Positive-ion FAB-MS m/z 251 $[M+Na]^+$; HR-FAB-MS m/z 251.1631 (Calcd for $C_{13}H_{24}O_3Na$ $[M+Na]^+$, 251.1623).

Compound **8a**[58]: An amorphous colorless powder; $[\alpha]_D^{27}$ −11.4° (c=0.05, MeOH); IR (film): 3390, 2926, 1638, 1129, 1032, 970 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.88, 1.23, 1.41 (3H each, all s, H_3-12, 13, 11), 1.30 (3H, d, J=6.4 Hz, H_3-10), 1.59 (1H, d like, J=11.6 Hz, H-2β), 1.66 (1H, br d like, J=12.2 Hz, H-4β), 1.82 (1H, ddd, J=2.4, 6.1, 11.6 Hz, H-2α), 2.03 (1H, ddd like, J=2.4, 6.5, 12.2 Hz, H-4α), 4.37 (1H, m, H-3), 4.38 (1H, m, H-9), 5.71 (1H, br d, J=15.9 Hz, H-7), 5.80 (1H, dd, J=5.8, 15.9 Hz, H-8); ^{13}C-NMR data (CD_3OD, 125 MHz) δ_C: given in Table 1; Positive-ion FAB-MS m/z 249 $[M+Na]^+$; HR-FAB-MS m/z 249.1471 (Calcd for $C_{13}H_{22}O_3Na$ $[M+Na]^+$, 249.1467).

Enzymatic Hydrolysis of 2 with β-Glucosidase and Cellulase (1 : 1) To a solution of **2** (3.4 mg) in 0.2 M acetate buffer (pH 3.8, 1.0 ml), was added 8.1 mg of β-glucosidase and 8.1 mg cellulase and stirred at 37 °C for 48 h. After EtOH was added to the reaction mixture, the solution was centrifuged at 4000 rpm for 10 min. The supernatant solution was concentrated under vacuum to give a residue, which was purified by HPLC [MeOH–H_2O (55 : 45, v/v)] to furnish **2a** (1.8 mg).

Hydrogenation of 6 A solution of **6** (1.4 mg) in MeOH (1.0 ml) was treated with 10% Pd–C (5 mg) and the whole mixture was stirred at room temperature under an H_2 atmosphere for 36 h. The catalyst was filtered off and the solvent was evaporated under reduced pressure to yield a residue, which was purified by HPLC [MeOH–H_2O (40 : 60, v/v)] to give sarmentol B (0.5 mg).

Protective Effect on Cytotoxicity Induced by D-GalN in Primary Cultured Mouse Hepatocytes The hepatoprotective effects of the constituents were determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay using primary cultured mouse hepatocytes. Hepatocytes were isolated from male ddY mice (30—35 g) by collagenase perfusion method.[59,60] The cell suspension at 4×10^4 cells in 100 μl William's E medium containing fetal calf serum (10%), penicillin G (100 units/ml), and streptomycin (100 μg/ml) was inoculated in a 96-well microplate, and precultured for 4 h at 37 °C under a 5% CO_2 atmosphere. The fresh medium (100 μl) containing D-GalN (2 mM) and a test sample were added and the hepatocytes were cultured for 44 h. The medium was exchanged with 100 μl of the fresh medium, and 10 μl of MTT (5 mg/ml in phosphate buffered saline) solution was added to the medium. After 4 h culture, the medium was removed, 100 μl of isopropanol containing 0.04 M HCl was then added to dissolve the formazan produced in the cells. The optical density (OD) of the formazan solution was measured by microplate reader at 562 nm (reference: 660 nm). Inhibition (%) was obtained by following formula.

$$\text{inhibition (\%)} = [(\text{OD(sample)} - \text{OD (control)})/(\text{OD (normal)} - \text{OD (control)})] \times 100$$

Statistics Values were expressed as means±S.E.M. For statistical analysis, one-way analysis of variance followed by Dunnett's test was used. Probability (p) values less than 0.05 were considered significant.

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