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Tannins and Related Compounds. LXXI.[1] Isolation and Characterization of Mongolicins A and B, Novel Flavono-ellagitannins from *Quercus mongolica* var. *grosseserrata*

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Two novel flavono-ellagitannins, mongolicins A (**1**) and B (**4**), in which hydrolysable tannin and flavonoid moieties are connected through a carbon–carbon linkage, were isolated from the bark of *Quercus mongolica* var. *grosseserrata*, together with a large quantity of (+)-taxifolin 3-*O*-*β*-D-glucopyranoside (**3**).

Keywords——*Quercus mongolica* var. *grosseserrata*; Fagaceae; mongolicin A; mongolicin B; flavono-ellagitannin; (+)-taxifolin 3-*O*-*β*-D-glucopyranoside; vescalagin; tannin

In 1985, a series of unusual and unclassifiable tannins, stenophyllanins A, B and C,[2] which contain a hydrolyzable tannin moiety and a flavan 3-ol (catechin) unit (one of the component units of condensed tannins) in each molecule, were first isolated by us from the bark of *Quercus stenophylla* MAKINO (Japanese name: urajirogashi). Since then, several structurally related tannins, such as stenophynins A and B,[3] acutissimins A and B[4] and mongolicains A and B[5] (we now propose to classify this class tannins as "flavano-ellagitannins") have been isolated from plants of the genera *Quercus*, *Castanea* and *Castanopsis* (Fagaceae). In continuing our chemical examinations of the polyphenolic constituents in a variety of Fagaceous plants, we have now isolated two novel tannins, mongolicins A (**1**) and B (**4**), which contain in each molecule a *C*-glycosylated ellagitannin unit and a flavonoid moiety, from the bark of *Quercus mongolica* FISCHER var. *grosseserata* (BL.) REHD. *et* WILS. (Japanese name: mizunara). In addition, (+)-taxifolin 3-*O*-*β*-D-glucopyranoside (**3**), the component unit of **1** and **4**, was also isolated in good yield from this plant material. In this paper, we present details of the isolation and structure elucidation of these compounds and propose the name of "flavono-ellagitannins" for tannins such as **1** and **4**.

The aqueous acetone extract of the fresh bark of *Quercus mongolica* var. *grosseserrata* was initially subjected to Sephadex LH-20 column chromatography with water containing increasing amounts of methanol to afford five fractions (frs. I—V). By repeated chromatographies on MCI-gel CHP-20P, Bondapak C_{18}/Porasil B and Fuji-gel ODS-G3, mongolicins A (**1**) and B (**4**) were isolated from fraction III, which consists mainly of the flavano-ellagitannin, acutissimin A, while the earlier fractions (I and II) afforded compound **3** and vescalagin (**2**),[6] respectively, together with simple phenolic glycoside gallates and lower-molecular-weight tannins.

Compound **3** was positive to the ferric chloride reagent (a dark bluish-purple coloration).

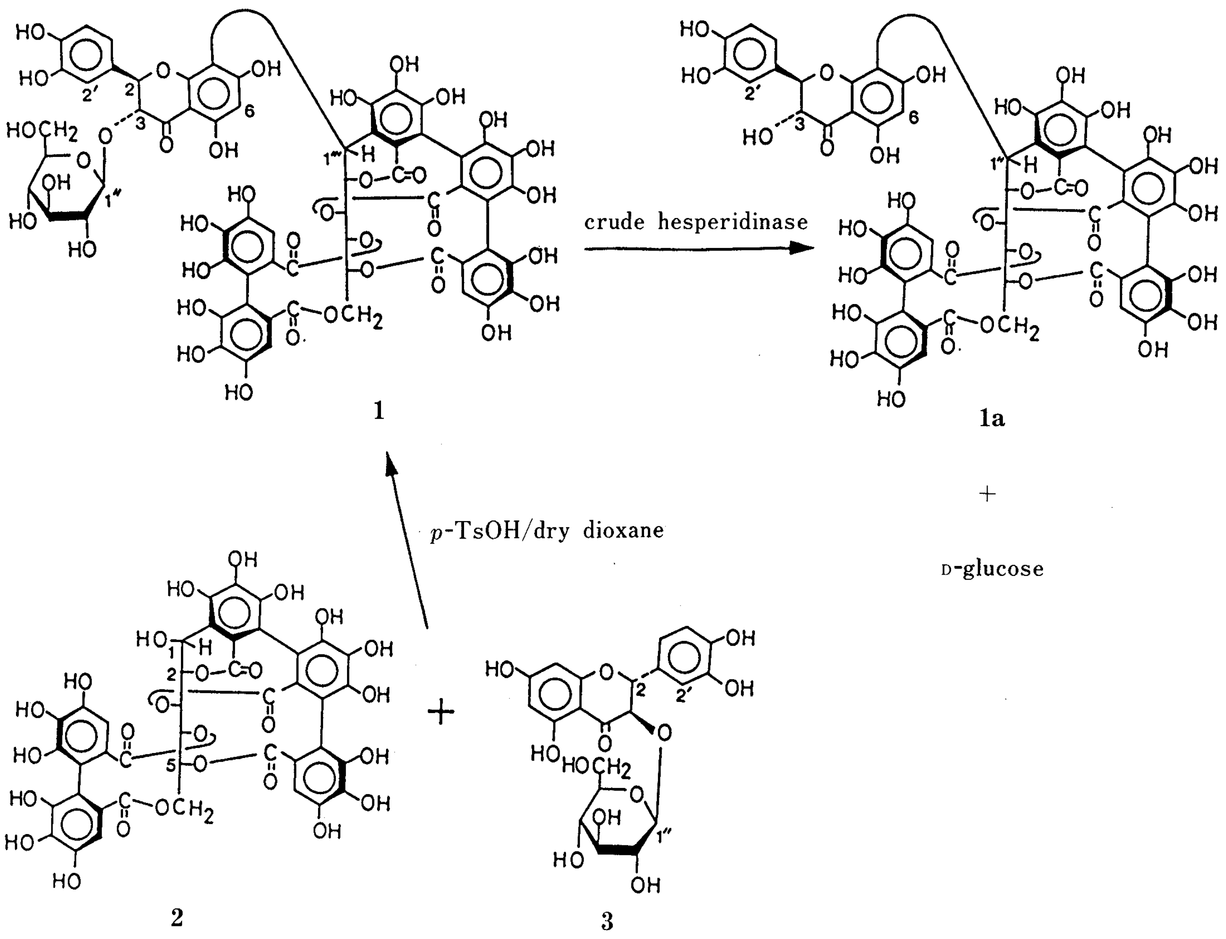


Chart 1

The proton-nuclear magnetic resonance (^{1}H-NMR) spectrum (Table I) of **3** was consistent with a 5,7,3′,4′-tetrahydroxyflavanonol structure, showing *trans*-coupled H-2 and H-3 signals at δ 5.36 and 4.95 (each 1H, d, $J=9$ Hz), respectively, and five aromatic signals at δ 5.98 (2H, s), 6.88 (2H, br s) and 7.07 (1H, br s) arising from the A- and B-rings. The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum (Table II) of **3** exhibited signals of a hexose moiety at δ 62.6, 71.1, 74.4, 77.4, 77.8 and 102.6, the chemical shifts being in good agreement with those reported for β-D-glucoside.

Acid hydrolysis of **3** with 5% sulfuric acid to give D-glucose and (+)-taxifolin confirmed its constitution, and the location of the D-glucose moiety was determined to be at the C-3 position, since the ^{13}C-NMR spectrum of **3** showed a lowfield shift of the C-3 signal (δ 76.9) as compared with that (δ 73.1) in the aglycone.[7)]

The configuration of the anomeric center was concluded to be β on the basis of the coupling constant ($J=7.5$ Hz) of the anomeric proton signal at δ 4.14. Therefore, compound **3** was characterized as (+)-taxifolin 3-*O*-β-D-glucopyranoside. Although the isolation of taxifolin 3-*O*-glucoside from *Chamaecyparis obtusa* ENDL. had previously been reported,[8)] neither the physicochemical data of the glucoside nor details of the structural elucidation were given.

Compound **1** (mongolicin A) gave a dark bluish-purple coloration similar to that of **3** with the ferric chloride reagent. The 100 MHz ^{1}H-NMR spectrum, measured at room temperature, showed exceedingly complex and broad signals, probably caused by dynamic rotational isomerism, which has sometimes been encountered in flavano-ellagitannins[2,3)] and proanthocyanidins,[9)] and the spectrum revealed little about the structure of this compound.

TABLE I. ^{1}H-NMR (400 MHz) Spectral Data for Compounds **1**—**4** (δ-Values, Measured in Acetone-d_6)

	3	**1**	**4**	**2**
Flavanonol				
H-2	5.36 (d, J=9)	4.99 (d, J=8)	5.39 (d, J=9)	
H-3	4.95 (d, J=9)	4.82 (m)	5.08 (d, J=9)	
H-6	5.98 (s)	6.10—6.20$^{a)}$	—	
H-8	5.98 (s)	—	6.20 (m)	
H-2′	7.07 (br s)	6.88—6.99$^{a)}$	7.14 (br s)	
H-5′	6.88 (br s)	6.63—6.80$^{a)}$	6.92 (d, J=8)	
H-6′	6.88 (br s)	6.63—6.80$^{a)}$	6.97 (br d, J=8)	
Glucopyranose				
H-1	4.14 (d, J=7.5)	4.05$^{a)}$	4.13 (d, J=8)	
H-2	3.32 (m)	3.23 (m)	3.37 (m)	
H-3	3.32 (m)	3.28 (m)	3.37 (m)	
H-4	3.37 (t, J=9)	3.37 (t, J=9)	3.46 (t, J=8)	
H-5	3.17 (ddd, J=2.5, 5.5, 9)	3.17 (m)	3.21 (m)	
H-6	3.66 (dd, J=12.5, 5.5) 3.79 (dd, J=12.5, 2.5)	3.66 (dd, J=11, 5) 3.80 (d, J=11)	3.75 (m) 3.84 (d, J=11)	
Polyalcohol				
H-1		4.50 (s)	4.63 (s)	4.92 (d, J=2)
H-2		5.23$^{a)}$	5.12 (s)	5.30 (t, J=2)
H-3		4.85 (d, J=7)	4.86 (d, J=8)	4.59 (dd, J=8, 2)
H-4		5.23$^{a)}$	5.27 (t, J=8)	5.23 (t, J=8)
H-5		5.63 (d, J=8)	5.65 (d, J=8)	5.66 (dd, J=3, 8)
H-6		4.08 (d, J=12) 4.80 (d, J=12)	4.08 (d, J=12) 4.90 (d, J=12)	4.08 (br d, J=13) 5.08 (dd, J=13, 3)
Arom.-H		6.43—6.78 (3H, m)	6.67 (s) 6.82 (s) 6.90 (s)	6.67 (s) 6.82 (2H, s)

a) The coupling patterns are not clear due to broaden and/or overlapping of signals.

On the other hand, the 400 MHz ^{1}H-NMR spectrum (Table I), although similarly duplicated, exhibited two aliphatic methine signals at δ 4.82 (1H, m)$^{10)}$ and 4.99 (1H, d, J=8 Hz), and four aromatic signals at δ 6.10—6.20 (1H in toral) and δ 6.63—6.99 (3H in total), the chemical shifts being consistent with the presence of a flavanonol framework. In addition, three aromatic resonances at δ 6.43—6.78 and the lowfield signals due to a polyalcohol methylene (δ 4.08, 4.80) and methines (δ 4.85, 5.23, 5.63) bearing acyl groups were analogous to those found in the *C*-glycosylated ellagitannin, vescalagin (**2**).$^{6a)}$

The ^{13}C-NMR spectrum (Table II) was more informative than the ^{1}H-NMR spectrum. The chemical shifts of two aliphatic signals at δ 83.5 and 76.7, and one carbonyl signal at δ 196.6, assignable to flavanonol C-2, C-3 and C-4 carbons, respectively, as well as those of the signals due to a hexose moiety (δ 62.4, 70.9, 74.3, 77.2, 77.7, 102.1), were similar to those of **3**. Furthermore, in the aromatic region, the signal patterns of the A- and B-ring carbons in the flavanonol moiety were almost the same as those of **3**, except for the lowfield shift (δ 106.9) of the C-6 or C-8 signal. In the aliphatic region, **1** showed signals due to the C_6-polyalcohol moiety, which were analogous to those found in the case of vescalagin (**2**), but the C-1 signal appeared at extremely high field (δ 38.5), suggesting that the C-1 position has a *C*-substituent. From these spectral observations, **1** was presumed to be a condensation product of vescalagin (**2**) and (+)-taxifolin 3-*O*-β-D-glucopyranoside (**3**), which are mutually connected through a carbon-to-carbon linkage. This presumption was also supported by analyses of the mass spectra; the negative fast atom bombardment mass spectrum (FAB-MS) of **1** exhibited the $(M-H)^-$ peak at m/z 1381, in agreement with its molecular mass, while the appearance of the

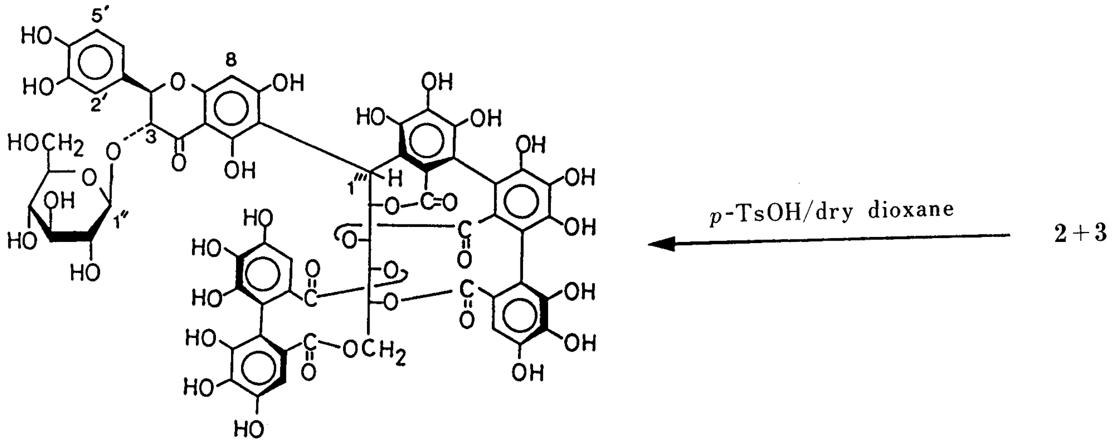
Table II. ^{13}C-NMR (100 MHz) Spectral Data for Compounds **1**—**4** (δ-Values, Measured in Acetone-d_6)

	3	**1**	**4**	**2**
Flavanonol				
C-2	83.1	83.5	83.1	
C-3	76.9	76.7	76.5	
C-4	195.6	196.6	196.0	
C-4a	102.6	103.5	102.3	
C-5	165.1	164.0	166.2	
C-6	97.4	97.6	107.5	
C-7	168.7	166.6	167.4$^{a)}$	
C-8	96.4	106.9	96.2	
C-8a	163.8	163.0	162.3	
C-1′	128.7	127.9	128.7	
C-2′	116.1	116.1	116.4	
C-3′	147.0	146.7	146.9	
C-4′	146.1	146.7	146.9	
C-5′	116.4	116.4	116.4	
C-6′	120.9	120.5	121.2	
Glucopyranose				
C-1	102.6	102.1	102.5	
C-2	74.4	74.3	74.0	
C-3	77.4	77.2	77.1	
C-4	71.1	70.9	70.7	
C-5	77.8	77.7	77.4	
C-6	62.6	62.4	62.2	
Polyalcohol				
C-1		38.5	37.2	66.1
C-2		77.3	77.9	78.3
C-3		72.3	72.0	71.7
C-4		70.9	70.5	69.1
C-5		71.5	71.4	70.0
C-6		66.2	66.1	66.0
Arom.-C		107.5	107.6	107.9
		109.1	109.2	108.7
		109.8	109.6	109.2
-COO-		166.1 (×2)	166.2	165.5
		167.4	167.3$^{a)}$	165.9
		167.6	167.6 (×2)	166.9
		169.7	169.7	167.6
				169.6

a) Assignments may be interchanged.

$(M-H)^-$ peak at m/z 1219 in the negative FAB-MS of **1a**, which was obtained, together with D-glucose, by enzymatic hydrolysis of **1**, was consistent with the desglucosyl structure. Moreover, the fact that refluxing of a mixture of **2** and **3** in dry dioxane containing *p*-toluenesulfonic acid successfully yielded **1**, together with **4** and **1a**, strongly indicated that **1** consists of vescalagin and (+)-taxifolin 3-*O*-β-D-glucopyranoside moieties, which are linked at the C-1 position and the A-ring, respectively, through a carbon–carbon bond. From the derivation of **1** from **2**, which has known chiralities,[6b)] it is obvious that the atropisomerism of the biphenoyl and the triphenoyl groups in **1** is in the *S*- and *S*,*S*-series, respectively.

In the ^{1}H-NMR spectrum of **1**, the polyalcohol C-1 proton signal appeared as a singlet at δ 4.50, and this small coupling constant, similar to that ($J=2$ Hz) of **2**, indicated that the C-1 atom has the same configuration as that of **2**.[6a)]



4

Chart 2

The location of the substituent in the A-ring of the taxifolin moiety was concluded as follows. In the ^{1}H-NMR spectrum of **1**, a methine signal assignable to the flavanonol C-2 proton was observed relatively upfield (δ 4.99) as compared with that (δ 5.36) in **3**, indicating that there is an anisotropic interaction between the C-2 proton and the substituent (vescalagin unit),[11] and that the substituent is therefore located at the C-8 position of the taxifolin moiety. In addition, the above-mentioned broadening and duplication of signals in the ^{1}H-NMR spectrum also supported this conclusion, because in the case of a C-8 substitution system, the rotation about the bond between the flavanonol and vescalagin moieties seems to be restricted by a through-space interaction of the flavanonol B-ring and the vescalagin moiety.[2,3] On the basis of these chemical and spectroscopic findings, the structure of mongolicin A was determined to be as represented by the formula **1**.

Compound **4** (mongolicin B) showed the same coloration (dark bluish-purple) as that of **1** with the ferric chloride reagent. The negative FAB-MS with the $(M-H)^{-}$ peak at m/z 1381 indicated the same molecular mass as that of **1**. The ^{1}H-NMR spectrum (Table I) was amenable to first-order analysis, differing from the case in **1**. However, the presence of similar functional groups in **4** was found in the ^{1}H- and ^{13}C-NMR spectra (Table II). Furthermore, the appearance of a singlet signal at δ 4.63 due to the polyalcohol C-1 proton indicated the same configuration of the C-1 atom as that of **1**. The similar chemical shift (δ 5.39) of the flavanonol C-2 proton signal to that (δ 5.36) of **3** suggested that there is no anisotropic interaction between the C-2 proton and the aromatic ring in the substituent (vescalagin moiety), and that the vescalagin moiety is therefore attached to the C-6 position of the flavanonol moiety.

Since **4** was synthesized by condensation of **2** and **3** as mentioned above, the atropisomerism of the hexahydroxydiphenoyl ester group and the triphenoyl ester moiety was considered to be in the *S*- and *S*,*S*-series, respectively.

Based upon this physicochemical evidence, mongolicin B was concluded to be represented by the formula **4**.

Quercus mongolica var *grosseserrata*, one of the richest sources of tannins in Fagaceous plants, produces a variety of unique and unclassifiable tannins such as "flavano-ellagitannins" and "flavono-ellagitannins" togehter with many hydrolyzable[12] and condensed tannins. We have concomitantly isolated another novel class of tannins named "procyanidino-ellagitannins" from this plant material and wish to present details of its structure elucidation in the succeeding paper.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-4 digital polarimeter. Ultraviolet (UV) and circular dichroism (CD) spectra were obtained with Hitachi 100-50 and JASCO J-20 spectrometers, respectively. Field desorption (FD)- and FAB-MS were obtained with a JEOL JMS DX-300 instrument. ^{1}H- and ^{13}C-NMR spectra were taken with JEOL PS-100, FX-100, GX-270 and GX-400 spectrometers, using tetramethylsilane as an internal standard, and chemical shifts are given in δ (ppm). Column chromatography was performed with Kieselgel 60 (70—230 mesh, Merck), Sephadex LH-20 (25—100 μm, Pharmacia Fine Chemicals Co., Ltd.), MCI-gel CHP-20P (75—150 μm, Mitsubishi Chemical Industries, Ltd.), Fuji-gel ODS-G3 (43—65 μm, Fuji Gel Hanbai Co., Ltd.) and Bondapak C_{18}/Porasil B (37—75 μm, Waters Associates, Inc.). Thin-layer chromatography (TLC) was carried out on precoated Kieselgel 60 F_{254} plates (Merck) and precoated cellulose plates (Funakoshi), using solvent systems of benzene–ethyl formate–formic acid (5:4:1, 1:7:1 and 1:5:2) and 2% acetic acid, respectively, and spots were detected by UV illumination and by spraying 2% ethanolic $FeCl_3$, 10% sulfuric acid and anisaldehyde–sulfuric acid reagents.

Isolation of 1, 3 and 4——The fresh bark (18 kg) of *Quercus mongolica* var. *grosseserrata* (collected in Oita Prefecture, Japan) was chopped into small pieces, and extracted at room temperature with 80% aqueous acetone three times. After removal of the acetone by evaporation under reduced pressure (*ca.* 40 °C), the aqueous solution (*ca.* 3 l) was subjected to Sephadex LH-20 column chromatography using H_2O with increasing amounts of MeOH and then with H_2O–acetone (1:1) to give five fractions; frs. I (130 g), II (320 g), III (132 g), IV (29 g) and V (2.3 g). Fraction I was applied to a column of MCI-gel CHP-20P using H_2O with increasing amounts of MeOH to give further four fractions; frs. I-1—I-4. Rechromatography of fr. I-2 on Fuji-gel ODS-G3 (H_2O–MeOH) and Bondapak C_{18}/Porasil B (H_2O–MeOH) afforded compound **3** (*ca.* 10 g). Fraction III was subjected to Sephadex LH-20 column chromatography using 80% aqueous MeOH to give further six fractions; frs. III-1—III-6. Fraction III-5 was rechromatographed over Sephadex LH-20 (EtOH, 50% MeOH), MCI-gel CHP-20P (H_2O–MeOH) and Bondapak C_{18}/Porasil B (H_2O–MeOH) to yield compounds **1** (550 mg) and **4** (230 mg).

Mongolicin A (1)——An off-white amorphous powder, $[\alpha]_D^{23}$ $-74.0°$ ($c=0.67$, MeOH). *Anal.* Calcd for $C_{62}H_{46}O_{37} \cdot 3H_2O$: C, 51.81; H, 3.65. Found: C, 51.37; H, 3.78. Negative FAB-MS *m/z*: 1381 $(M-H)^-$. CD ($c=6.03 \times 10^{-5}$, MeOH) $[\theta]$ (nm): -66336 (300), -39802 (280), -53069 (268), $+112771$ (235). UV λ_{max}^{MeOH} nm (log ε): 280 (5.03), 230 sh (4.69).

Enzymatic Hydrolysis of 1 with Crude Hesperidinase——**1** (40 mg) was shaken for 22 h with crude hesperidinase in water (3 ml) at room temperature. The reaction mixture was applied to a column of Sephadex LH-20 with H_2O containing increasing amounts of MeOH to afford compound **1a** (20 mg), an off-white amorphous powder, $[\alpha]_D^{23}$ $-80.8°$ ($c=0.48$, MeOH). *Anal.* Calcd for $C_{56}H_{36}O_{32} \cdot 11/2H_2O$: C, 50.95; H, 3.58. Found: C, 50.84; H, 3.25. Negative FAB-MS *m/z*: 1219 $(M-H)^-$. ^{1}H-NMR (100 MHz, acetone-d_6 + D_2O) ppm: 4.40—4.90 (5H, m, 1″,3″,6″,2,3-H), 5.04—5.32 (2H, m, 2″,4″-H), 5.56 (1H, d, $J=6$ Hz, 5″-H), 6.04 (1H, s, 6-H), 6.40—6.84 (5H, m, arom.-H), 7.02 (1H, s, arom.-H). ^{13}C-NMR (25.05 MHz, acetone-d_6 + D_2O) ppm: 38.5 (C-1″), 65.8 (C-6″), 71.1 (C-4″), 72.0 (C-5″), 72.8 (C-3″), 77.0 (C-2″), 85.3 (C-2), 97.6 (C-6), 106.6, 107.1, 108.6 (unsubstituted arom.-C), 163.1, 163.5, 165.5, 165.8, 167.2, 169.4 (COO), 199.6 (C=O).

Mongolicin B (4)——An off-white amorphous powder, $[\alpha]_D^{23}$ $-28.0°$ ($c=0.70$, MeOH). *Anal.* Calcd for $C_{62}H_{46}O_{37} \cdot 5H_2O$: C, 50.54; H, 3.83. Found: C, 50.11; H, 4.04. Negative FAB-MS *m/z*: 1381 $(M-H)^-$.

Preparation of 1, 4 and 1a——A mixture of (+)-taxifolin 3-*O*-β-D-glucopyranoside (**3**) (1.9 g) and vescalagin (**2**) (1.8 g) in dry dioxane (60 ml) containing *p*-toluenesulfonic acid (55 mg) was heated under reflux for 2.5 h with stirring. The reaction mixture, after concentration (*ca.* 20 ml) under reduced pressure, was applied to a Sephadex LH-20 column. Elution with EtOH containing increasing amounts of MeOH and then with H_2O–acetone (1:1) gave a mixture of condensation products, which was repeatedly chromatographed over Bondapak C_{18}/Porasil B (H_2O–40% MeOH) to yield compounds **1** (140 mg), **4** (150 mg) and **1a** (23 mg).

(+)-Taxifolin 3-*O*-β-D-glucopyranoside (3)——An off-white amorphous powder, $[\alpha]_D^{29}$ $+38.0°$ ($c=1.05$, EtOH), CD ($c=4.32 \times 10^{-5}$, MeOH) $[\theta]_{20}$ (nm): $+16198$ (325), 0 (308), -32395 (293). UV λ_{max}^{MeOH} nm (log ε): 290 (4.16), 250 (4.60), 225 sh (4.01).

Acid Hydrolysis of 3——**3** (100 mg) was dissolved in 50% aqueous EtOH (10 ml) containing sulfuric acid (0.5 ml) and the mixture was refluxed for 2 h. After removal of EtOH by evaporation under reduced pressure, the aqueous solution was applied to a column of Sephadex LH-20. Stepwise elution with H_2O containing increasing amounts of MeOH gave (+)-taxifolin (48 mg), colorless needles, mp 139—140 °C, $[\alpha]_D^{20}$ $+22.5°$ ($c=0.49$, EtOH).

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