Resveratrol Oligomers from *Vatica albiramis*

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Five new stilbenoids, vatalbinosides A−E (**1**−**5**), and 13 known compounds (**6**−**18**) were isolated from the stem of *Vatica albiramis*. The effects of these new compounds on interleukin-1β-induced production of matrix metalloproteinase-1 (MMP-1) in human dermal fibroblasts were examined. Three resveratrol tetramers, (−)-hopeaphenol (**6**), vaticanol C (**13**), and stenophyllol C (**14**), were identified as strong inhibitors of MMP-1 production.

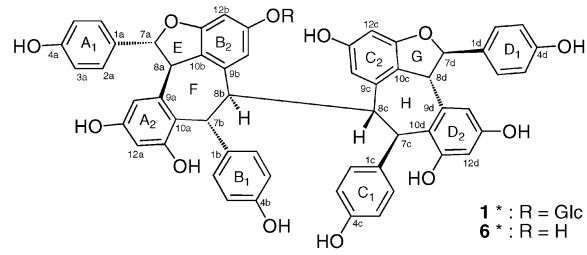
The genus *Vatica* belongs to the family Dipterocarpaceae with about 65 species distributed throughout Southeast Asia, especially in Indonesia and Malaysia,[1] south and east India, and Sri Lanka. This genus is well documented to be a good source of biologically active stilbenoids. These stilbenoids have antimicrobial,[2] antitumor,[3−5] and anti-HIV activities,[2] as well as regulate endoplasmic reticulum stress.[6] Various types of stilbene oligomers have been reported by us as constituents of the two species *V. rassak* and *V. pauciflora.*[7−11] Previous articles have reported that homogeneous oligomerization of resveratrols results in the production of stilbene oligomers, and these oligomers sometimes occur in the *O*-glucoside form. These oligmers are of special interest due to the numerous stereoisomers resulting from many asymmetric carbons and various frameworks (heterocyclic, bicyclic system). However, polar components of stilbene oligomers and their absolute configuration have not been discussed.

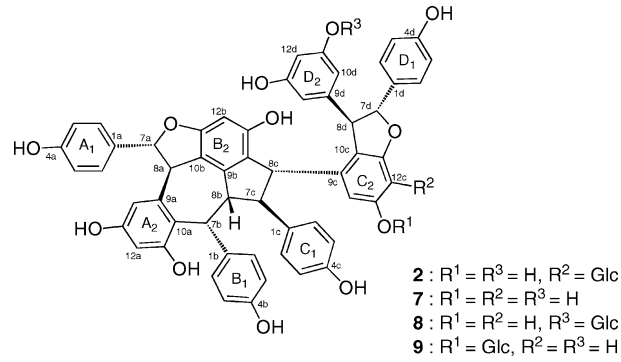
Our fundamental study of the phytochemical properties of the stem of *V. albiramis* (Dipterocarpaceae) has been undertaken to search for bioactive compounds. This paper reports the isolation of five new stilbene glucosides (**1**−**5**) along with 13 known compounds (**6**−**17** and bergenin). Their structures were elucidated by spectroscopic methods, including 1D (^{1}H and ^{13}C) and 2D NMR (DQF-COSY, HMQC, HMBC, NOESY, and ROESY) experiments and high-resolution (HR) FABMS analysis.

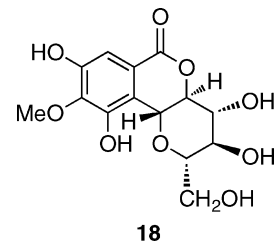
Matrix metalloproteinases (MMPs) are a superfamily of structurally related matrix-degrading enzymes that play important roles in tissue-destructive processes of various diseases such as cancer.[12] In skin dermal tissue, expression and activity of MMPs increase with aging and, thus, cause degradation and remodeling of the structural extracellular matrix.[13] MMP-1 (collagenase-1) and MMP-3 (stromelysin-1) play a major role in the multiple stages of cutaneous photoaging.[14] In the course of screening plant extracts that have an inhibitory effect on MMP-1 production in human dermal fibroblasts, we recently found that an acetone extract of the stem of *V. albiramis* exhibited a strong inhibitory effect on MMP-1 production. In the present study, we examined the inhibitory effect of stilbenoids isolated from *V. albiramis* on MMP-1 production in human dermal fibroblasts.

Results and Discussion

The dried and ground stem of *V. albiramis* was extracted with acetone. The resulting extract was separated by column chromatography using silica gel, Chromatorex DMS, Sephadex LH-20, and Chromatorex ODS to give 13 known compounds and five new stilbene glucosides, named vatalbinosides A−E (**1**−**5**). All five compounds showed a positive reaction with the Gibbs reagent. Structures of the known compounds were identified by comparing obtained spectroscopic data with those in the literature. The compounds were identified as (−)-hopeaphenol (**6**),[15] vaticanol B (**7**),[11] vaticasides B (**8**) and C (**9**),[10] (*E*)-(−)-ε-viniferin (**10**),[16] balanocarpol (**11**),[17] (−)-ampelopsin A (**12**),[18] vaticanol C (**13**),[11] stenophyllol C (**14**),[19] piceid (**15**), (*Z*)-(−)-ε-viniferin (**16**),[20] vateriaphenol A (**17**),[21] and bergenin (**18**).[3]







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Vatalbinoside A (**1**) was obtained as a yellow, amorphous solid. The molecular formula was deduced to be $C_{62}H_{52}O_{17}$ using the

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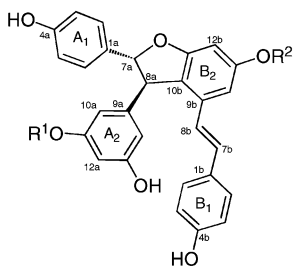
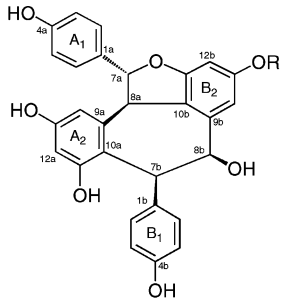
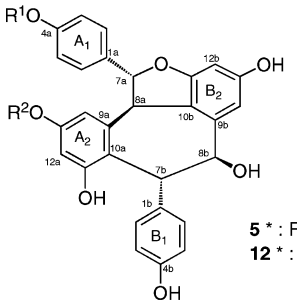


3 * : $R^1 = R^2$ = Glc
10 * : $R^1 = R^2$ = H

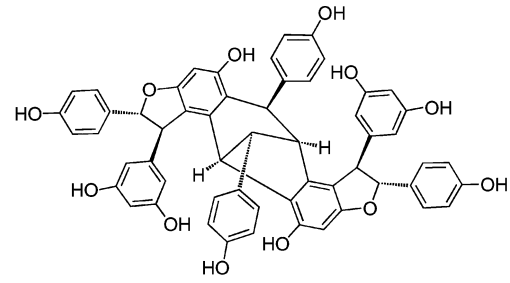


4 : R = Glc
11 : R = H



5 * : $R^1 = R^2$ = Glc
12 * : $R^1 = R^2$ = H

* : absolute configuration



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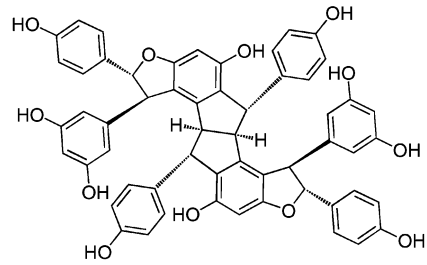

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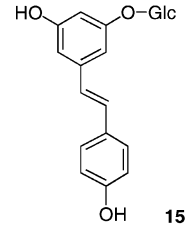

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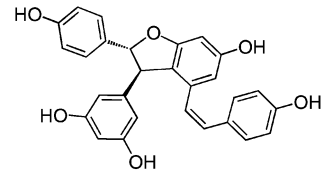

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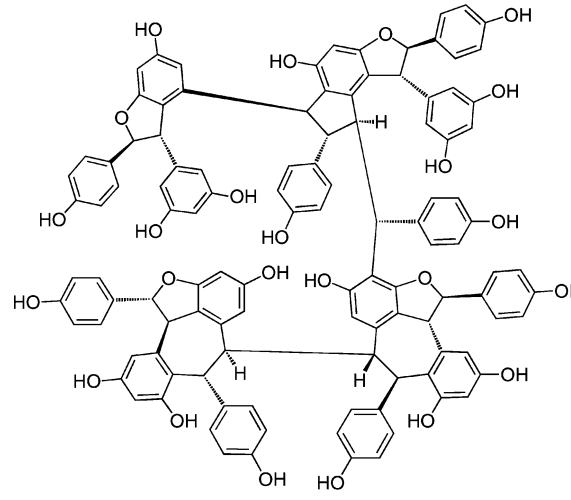

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pseudomolecular ion $[M - H]^-$ at *m/z* 1067.3134 from HRFABMS. NMR data of **1** [^{1}H and ^{13}C NMR spectra: Table 1 (in acetone-d_6) and Table S1 (in MeOH-d_4); HMBC and NOESY spectra: Table S2 (Supporting Information)] revealed the presence of four 4-hydroxyphenyl groups (designated as A_1−D_1), four 3,5-dioxygenated-1,2-disubstituted benzene rings (A_2−D_2), and one *O*-β-glucopyranose moiety. The presence of four sets of mutually coupled aliphatic protons (H-7a/H-8a, H-7b/H-8b, H-7c/H-8c, H-7d/H-8d) and a β-glucopyranose moiety [δ_C 105.1, 74.8, 77.7, 71.3, 76.7, and 62.4; anomeric proton at δ_H 4.15 ($J = 7.6$ Hz)] was supported by NMR data, and this led to the composition $C_{56}H_{42}O_{12}$ for the aglycone of **1**. The ^{1}H NMR spectrum (in DMSO-d_6) indicated phenolic OH groups (δ_H 8.40−9.57), which disappeared upon the addition of D_2O. In the HMBC spectrum, the significant ^3J correlations H-2a(6a)/C-7a, H-14a/C-8a, H-2b(6b)/C-7b, H-14b/C-8b, H-2c(6c)/C-7c, H-14c/C-8c, H-2d(6d)/C-7d, and H-14d/C-8d indicated that rings A_1, A_2, B_1, B_2, C_1, C_2, D_1, and D_2 are attached to C-7a, C-8a, C-7b, C-8b, C-7c, C-8c, C-7d, and C-8d, respectively. Thus, **1** was composed of four resveratrol units, A−D (unit A: ring A_1−C-7a−C-8a−ring A_2). Further correlations, H-8a/C-11b, H-7b/C-11a, H-7c/C-11d, and H-8d/C-11c, supported respective single bonds C-8a/C-10b, C-7b/C-10a, C-7c/C-10d, and C-8d/C-10c. The C−C bond (C-8b/C-8c) was not proved by a COSY correlation because the protons (H-8b and H-8c) were in close proximity. The assignment of H-signals (H-8b and H-8c) by ^1J HMQC cross-peaks (H-8b/C-8b and H-8c/C-8c) and ^3J HMBC cross-peaks (H-8b/C-14b and H-8c/C-14c) enabled the distinction of ^2J HMBC cross-peaks (H-8b/C-8c and H-8c/C-8b), which made it possible to clarify C-8b/C-8c connectivity (Figure 1). Although no long-range correlations between H-7a/C-11b and H-7d/C-11d were observed, the presence of two dihydrobenzofuran moieties (ring E: C-7a−C-8a−C-10b−C-11b−O, ring G: C-7d−C-8d−C-10c−C-11c−O) was deduced after considering the molecular formula of the aglycone ($C_{56}H_{42}O_{12}$). The long-range correlation between the anomeric proton (δ_H 4.06) and C-13b (δ_C 158.18) in the HMBC spectrum (in MeOH-d_4) confirmed that the glucosyloxy group was at C-13b.

The relative configuration of **1** was determined by NOESY experiments and analysis of coupling constants with the assistance of computer-aided molecular modeling (Figure 2). The significant NOEs observed among H-2a(6a)/H-8a, H-7a/H-14a, H-2d(6d)/H-8d, and H-7d/H-14d suggested that the two sets of methine protons on the two dihydrobenzofuran rings (ring E and ring G) are *trans*-oriented. The coupling constants, 11.8 Hz (H-7a/H-8a) and 12.4 Hz (H-7d/H-8d), are in agreement with diaxial orientations. In the NOESY spectrum, H-2b(6b) displayed significant cross-peaks with H-8a and H-8b, which indicated that ring B_1, H-8a, and H-8b are situated on the same side of the reference plane in ring F. These results suggested that **1A** has the same partial structure as hopeaphenol {(1*R**,6*S**,7*R**,11b*R**)-1,6,7,11b-tetrahydro-4,8,10-trihydroxy-1,7-bis(4-hydroxyphenyl)benzo[6,7]cyclohepta[1,2,3-*cd*]-benzofuran-6-yl group}. Furthermore, identical relative stereostructure in **1B** was shown by NOESY cross-peaks. These two units (**1A** and **1B**) may lead to two possible relative configurations of the aglycone, hopeaphenol and neohopeaphenol. The former [(−)-hopeaphenol (**6**) ($[\alpha]^{28}_D$ −402.9)][22] has no plane of symmetry, while the latter (*meso* form) has a plane of symmetry [neohopeaphenol ($[\alpha]_D$ 0)].[23] The negative specific rotation of the aglycone can be

Table 1. ^{1}H and ^{13}C NMR Data for Vatalbinosides A (**1**) and B (**2**)[a]

	vatalbinoside A (**1**)		vatalbinoside B (**2**)	
position	$\delta(^{1}H)$	$\delta(^{13}C)$	$\delta(^{1}H)$	$\delta(^{13}C)$
1a		130.5		130.7[h]
2a(6a)	7.16, d (8.4)	130.2	7.23, d (8.8)	130.2
3a(5a)	6.82, d (8.4)	116.0	6.79, d (8.8)	116.0[i]
4a		158.3		158.6
7a	5.83, d (12.0)	88.3	5.77, d (12.4)	90.4
8a	4.30, d (12.0)	49.5	4.45, d (12.4)	48.7
9a		141.8		141.7
10a		121.0		124.5
11a		158.6		155.7[j]
12a	6.55, d (2.0)	101.1	6.28, d (2.0)	101.6
13a		157.2[d]		156.4
14a	6.42 (br s)	106.9	6.11, d (2.0)	105.7
1b		134.9[e]		133.5
2b(6b)	6.91, d (8.8)	129.1	7.18, d (9.2)	130.7[h]
3b(5b)	6.59, d (8.8)[b]	115.2[i]	6.71, d (9.2)	115.5
4b		155.6		155.7[j]
7b	5.79 (br s)[c]	41.0	5.23, d (3.6)	37.0
8b	4.02 (dd, J = 10.2,4.2)	48.0	3.08 (br d, J = 11.6)	53.6
9b		140.5		143.2
10b		122.9		115.7
11b		158.4		158.8
12b	6.05, d (2.0)	100.8	6.07 (s)	96.5
13b		157.9[g]		154.9
14b	5.43, d (2.0)	116.2		122.4
1c		134.9[e]		131.7
2c(6c)	6.95, d (8.8)	129.2	6.41, d (8.8)	129.3
3c(5c)	6.59, d (8.8)[b]	115.2[f]	6.56, d (8.8)	115.9
4c		155.5		155.9
7c	5.79 (br s)[c]	41.2	4.11 (dd, J = 11.6, 10.8)	57.3
8c	4.02 (dd, J = 10.2,4.2)	48.1	4.61, d (10.8)	48.6
9c		140.4		141.2
10c		118.7		122.5
11c		159.2		155.9
12c	5.79, d (2.0)[c]	95.5		106.0
13c		157.2[a]		157.8
14c	5.07, d (2.0)	111.1	6.43 (s)	108.3
1d		130.9		134.5
2d(6d)	7.23, d (8.4)	130.4	7.21, d (8.8)	128.3
3d(5d)	6.79, d (8.4)	115.9	6.71, d (8.8)	116.0[f]
4d		157.9[g]		158.0
7d	6.18, d (12.4)	88.0	5.43, d (5.8)	94.6
8d	4.28, d (12.4)	49.4	4.75, d (5.8)	57.9
9d		141.9		147.8
10d		120.9	6.16 (br d)	107.9
11d		158.7		159.8
12d	6.58 (br s)	101.2	6.33 (t, J = 2.0)	102.2
13d		157.2[d]		159.8
14d	6.32 (br s)	106.4	6.16 (br d)	107.9
glucose-1	4.15, d (7.6)	105.1	4.75, d (9.6)	77.1
glucose-2	3.32−3.36 (m)	74.8	3.75 (dd, J = 9.6, 9.2)	73.6
glucose-3	3.67 (dd, J = 9.6, 9.2)	77.7	3.58 (dd, J = 9.2, 8.8)	79.5
glucose-4	3.49 (dd, J = 9.6)	71.3	3.55 (dd, J = 9.2, 8.4)	71.0
glucose-5	3.32−3.36 (m)	76.7	3.47 (m)	81.7
glucose-6	3.80 (br d),	62.4	3.88 (dd, J = 12.4, 2.8),	62.2
	3.72 (dd, J = 10.8, 4.0)		3.81 (dd, J = 12.4, 4.8)	

[a] In acetone-d_6; at 400 (^{1}H) and 100 (^{13}C) MHz, δ in ppm, J in Hz. [b−j] Overlapping.

explained by the specific rotation of **1** ($[\alpha]^{25}_{D}$ −320), even if the influence of the glucosyloxy group is considered. The absolute configuration of **6** was determined on the basis of an X-ray crystallographic analysis.[24] Enzymatic hydrolysis of **1** with β-glucosidase led to the generation of **6**. Therefore, vatalbinoside A (**1**) was elucidated as (−)-hopeaphenol 13b-*O*-β-glucopyranoside {(1*R*,6*S*,7*R*,11b*R*)-1,6,7,11b-tetrahydro-1,7-bis(4-hydroxyphenyl)-4-(β-D-glucopyranosyloxy)-6-[(1*R*,6*S*,7*R*,11b*R*)-1,6,7,11b-tetrahydro-4,8,10-trihydroxy-1,7-bis(4-hydroxyphenyl)benzo[6,7]cyclohepta-[1,2,3-*cd*]benzofuran-6-yl]benzo[6,7]cyclohepta[1,2,3-*cd*]benzofuran-8,10-diol}. A molecule with C_2 symmetry shows equivalence of the NMR resonances of the two units. This results in half the number of signals with double the intensity. It also complicates definition of the connectivity of the C_2 units and makes it impossible to detect NOESY cross-peaks between C_2 units.[15] A further problem is the difficulty in distinguishing cross-peaks such as H-2a(6a)/H-8a and H-2a(6a)/H-8d because H-8a and H-8d are equivalent. These problems not only prevent the determination of the stereostructure of the C_1 unit but also make it impossible to comprehend the relationship between the two C_1 units. In the case of **1**, the equivalent C_2 system of the aglycone is destroyed by the glycosyl group. The original number of signals observed, which enabled analysis of NOEs between units **1A** and **1B**, were as follows: H-14b/H-7c, H-14b/H-7d, H-14b/H-14d, H-14c/H-7a, H-14c/H-14a, and H-14c/H-7b (Table S2). To ascertain these results, a 3D structure of **1** (Figure 2) was generated by employing the PCMODEL 9.1 molecular modeling program software using the MMFF94 force field (MM2 type) for energy minimization.[25] The model reasonably

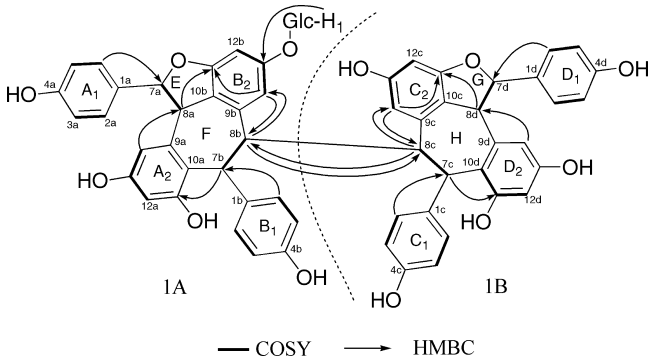


Figure 1. Selected correlations in the 2D NMR of **1**.

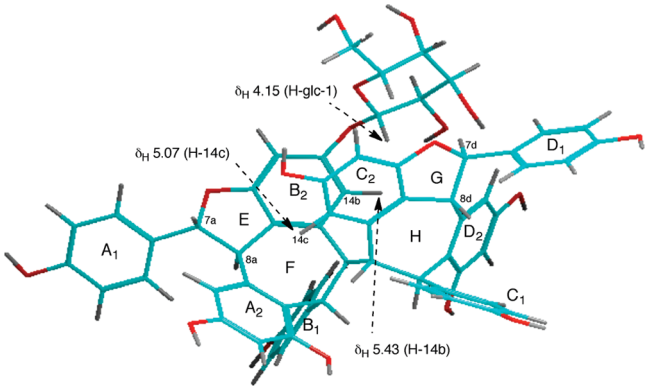


Figure 2. Stereostructure and shielding of protons (acetone-d_6) by anisotropy in **1**.

explains the anisotropic effects of rings A_2 and D_2, which cause shielding of aromatic protons H-14c (δ_H 5.07) and H-14b (δ_H 5.43), respectively. The anisotropy of ring C_2 also causes shielding of the anomeric proton (H-Glc-1, δ_H 4.06).

Vatalbinoside B (**2**) was obtained as a pale yellow, amorphous solid. The molecular formula was deduced to be $C_{62}H_{52}O_{17}$ from the $[M - H]^-$ ion at *m/z* 1067.3134 in the negative-ion HRFABMS, which corresponds to a monoglucoside of a resveratrol tetramer. The NMR data of **2** (Table 1) analyzed by 2D experiments exhibited signals of a *C*-β-glucopyranose [δ_C 77.1, 73.6, 79.5, 71.0, 81.7, and 62.2; anomeric proton at δ_H 4.75 (J = 9.6 Hz)] and four resveratrol units. Data analysis confirmed that the aglycone was vaticanol B (**7**). The position of the *C*-glucopyranosyl moiety was defined as C-12c from results of the HMBC spectrum, which displayed cross-peaks between the anomeric proton and three aromatic carbons (C-11c, C-12c, and C-13c: δ_C 155.9, 106.0, and 157.8) (Table S2). Therefore, vatalbinoside B (**2**) was elucidated as vaticanol B 12c-*C*-β-D-glucopyranoside {(3*S**,4*S**,4a*R**,5*R**,9b*R**,10*R**)-3-[(2*R**,3*R**)-3-(3,5-dihydroxyphenyl)-2,3-dihydro-6-hydroxy-7-(β-glucopyranosyl)-2-(4-hydroxyphenyl)benzofuran-4-yl]-3,4,4a,5,9b,10-hexahydro-4,5,10-tris(4-hydroxyphenyl)benz[5,6]azuleno-[7,8,1-*cde*]benzofuran-2,6,8-triol}. The absolute configuration of vaticanol B (**7**) has not been elucidated, and that of its glucosides [vatalbinoside B (**2**) and vaticasides B (**8**) and C (**9**)] is difficult to determine. Because they possessed the same 1,2-diaryldihydrobenzofuran chromophore as (2*R*,3*R*)-3-(3,5-dihydroxyphenyl)-6-hydroxy-2-(4-hydroxyphenyl)-2,3-dihydrobenzofuran-4-carbaldehyde (**19**), whose absolute configuration is known,[26] the CD spectra of **19** and **2** were compared (Figure 3). The CD spectrum of **2** and **19** showed a negative Cotton effect around 236 nm, which indicates a 7d*R*, 8d*R* configuration. Because there is no chiroptical data of 3,4,4a,5,9b,10-hexahydro-3,4,5,10-tetrakis(aryl)benz[5,6]azuleno[7,8,1-*cde*]benzofuran, the absolute configurations of the other asymmetric carbons could not be defined. The understanding of the chiroptical properties of **2** requires a spectroscopic database of diastereomeric and enantiomeric core skeletons of bicyclo[5.3.0]decadienes. Since it is difficult to obtain a single crystal of **2**, X-ray analysis was not performed. The absolute structures of the aglycones of **2**, **8**, and **9**—which are glucosides of vaticanol B (**7**)—are identical to the absolute structure of the agylcone of **7**, which was evidenced by the negative Cotton effect at 236 nm.

Vatalbinoside C (**3**) was obtained as a pale yellow, amorphous solid. The molecular formula was deduced to be $C_{40}H_{42}O_{16}$ from the $[M - H]^-$ ion at *m/z* 777.2400 from the negative-ion HRFABMS, which corresponded to a diglucoside of a resveratrol dimer.[27,28] The NMR data supported the presence of two β-glucopyranosyloxy groups (Table 2). The ^1H and ^{13}C NMR data of **3**, except for the β-glucopyranosyloxy group, showed close similarity to those of ε-viniferin (**10**). The HMBC, NOESY (Table S3), and

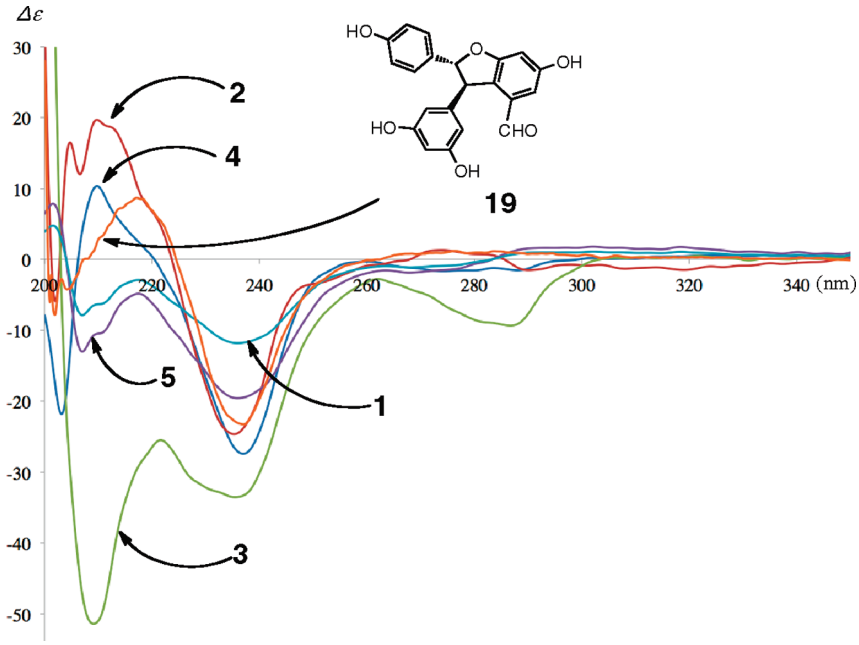


Figure 3. CD spectra of vatalbinosides A−E (**1**−**5**) and (2*R*,3*R*)-3-(3,5-dihydroxyphenyl)-6-hydroxy-2-(4-hydroxyphenyl)-2,3-dihydrobenzofuran-4-carbaldehyde (**19**) in MeOH.

Table 2. ^{1}H and ^{13}C NMR Data of Vatalbinosides C−E (**3**−**5**)[a]

	vatalbinoside C (**3**)		vatalbinoside D (**4**)		vatalbinoside E (**5**)	
position	δ(^{1}H)	δ(^{13}C)	δ(^{1}H)	δ(^{13}C)	δ(^{1}H)	δ(^{13}C)
1a		133.7		133.3[f]		134.1
2a(6a)	7.10 (d, J = 7.4)	128.1	7.52 (d, J = 8.6)	130.6	7.00 (d, J = 8.8)	130.0
3a(5a)	6.73 (d, J = 7.4)	116.2	6.96 (d, J = 8.6)	116.4	6.88 (d, J = 8.8)	117.7
4a		158.5		158.5[d]		159.2
7a	5.37 (d, J = 5.4)	94.7	5.73 (d, J = 9.6)	93.6	5.63 (d, J = 11.2)	88.7
8a	4.44 (d, J = 5.4)	57.8	5.24 (d, J = 9.6)	52.2	3.92 (d. J = 11.2)	50.3
9a		147.3		142.7		143.1
10a	6.38 (br s)	108.3		120.2		122.8
11a		159.9		157.3		160.1
12a	6.44 (d, J = 1.6)	103.6	6.20 (d, J = 2.2)	101.9	6.61 (d, J = 2.0)	104.1
13a		160.6[e]		156.8		157.9
14a	6.31 (br s)	109.9	6.28 (d, J = 2.2)	106.7	6.20 (br s)	108.4
1b		136.9		133.3[f]		132.6
2b(6b)	7.03 (d, J = 7.6)	128.9	6.75 (d, J = 8.8)	131.4	6.68 (d, J = 8.8)	129.1
3b(5b)	6.64 (d, J = 7.6)	116.4	6.45 (d, J = 8.8)	114.3	6.42 (d, J = 8.8)	115.7
4b		158.4[d]		155.6		156.3
7b	6.87 (d, J = 16.2)	131.1	4.95 (br s)	50.0	5.40 (d, J = 4.9)	44.3
8b	6.54 (d, J = 16.2)	123.2	5.45 (br s)	73.0	5.29 (d, J = 4.9)	71.6
9b		130.2		140.3		139.4
10b		122.7		116.9		119.4
11b		162.4		159.3		159.4
12b	6.56 (br s)	98.4	6.24 (d, J = 2.0)	97.3	6.01 (d, J = 2.2)	97.7
13b		160.6[e]		159.7		160.5
14b	6.95 (br s)	106.1	6.30 (d, J = 2.0)	106.7	6.40 (d, J = 2.2)	110.9
glucose1-1	4.80 (br d)[b]	102.0	4.67 (d, J = 7.6)	102.5	4.76 (d, J = 7.3)	104.8
glucose1-2	3.52 (m)[c]	74.9[c]	3.34 (m)	74.4	3.34 (m)	74.7
glucose1-3	3.52 (m)[c]	78.2[c]	3.44 (dd, J = 8.4, 8.0)	77.6	3.29 (m)	78.1
glucose1-4	3.43 (m)[c]	71.4[c]	3.42 (dd, J = 8.8, 8.0)	71.1	3.28 (m)	71.2
glucose1-5	3.44 (m)[c]	77.9[c]	3.38 (m)	77.2	3.29 (m)	77.9
glucose1-6	3.75, 3.94 (m)[c]	62.5[c]	3.67 (dd, J = 12.0 5.0)	62.5	3.75, 3.56 (m)	62.5[g]
			3.81 (dd, J = 12.0 2.8)			
glucose2-1	4.98 (d, J = 7.6)	102.6			4.76 (d, J = 7.3)	102.0
glucose2-2	3.44 (m)[c]	74.7[c]			3.30 (m)	74.9
glucose2-3	3.44 (m)[c]	77.8[c]			3.29 (m)	78.0
glucose2-4	3.46 (m)[c]	70.9[c]			3.28 (m)	71.3
glucose2-5	3.31 (m)[c]	77.7[c]			3.29 (m)	78.3
glucose2-6	3.69, 3.78 (m)[c]	62.1[c]			3.75, 3.56 (m)	62.5[g]

[a] In methanol-d_4; at 400 (^{1}H) and 100 (^{13}C) MHz, δ in ppm, J in Hz. [b] Masked by large H_2O signal. Assigned by HMQC spectrum. [c] Assigned glucose units (H atoms and C atoms) are interchangeable between Glc1 and Glc2. Protons were assigned by HMQC spectrum. [d] Interchangeable. [e−g] Overlapping.

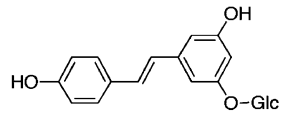
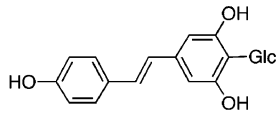
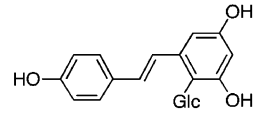
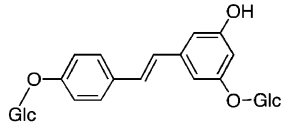
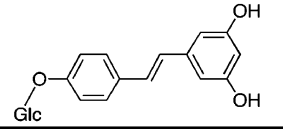
CD spectra (Figure 3) confirmed that the aglycone of **3** was (−)-ε-viniferin (**10**), which was further supported by the generation of **10** by enzymatic hydrolysis of **3** with β-glucosidase. The positions of the glucosyloxy groups were determined to be C-11a and C-13b by HMBC and NOESY correlations of aromatic atoms in rings A_2 and B_2 with anomeric protons (H-Glc1-1 and H-Glc2-1). Vatalbinoside C (**3**) was elucidated as 1-(β-D-glucopyranosyloxy)-5-{(2*R*,3*R*)-6-(β-glucopyranosyloxy)-2-(4-hydroxyphenyl)-4-[(*E*)-4-hydroxystyryl]-2,3-dihydrobenzofuran-3-yl}benzene-3-ol. The aglycone of **3** is an enantiomer of tingitanol isolated from *Iris tingitana* (Iridaceae).[28]

Vatalbinosides D (**4**) and E (**5**) were obtained as pale yellow, amorphous solids. Their molecular formulas were deduced to be $C_{34}H_{32}O_{12}$ ([M − H]$^-$, *m*/*z* 631.1809) and $C_{40}H_{42}O_{17}$ ([M − H]$^-$, *m*/*z* 793.2336), respectively, from negative-ion HRFABMS. The presence of one and two β-glucopyranosyloxy group(s) in the respective compounds was supported by their NMR spectra. The ^{1}H and ^{13}C NMR data of **4** and **5** (Table 2), except for the β-glucopyranosyloxy group(s), showed close similarity to those of balanocarpol (**11**)[17] and ampelopsin A (**12**),[18] respectively. The HMBC and NOESY spectra (Table S3) and the respective generation of aglycones (**11** and **12**) by enzymatic hydrolysis of **4** and **5** with β-glucosidase confirmed the aglycones (balanocarpol for **4**; ampelopsin A for **5**). The positions of the *O*-β-D-glucopyranosyl moieties were defined by NOEs (C-13b for **4**; C-4a and C-11a for **5**). Using CD spectroscopy, and for the same reasons as described for **2**, the configuration of two methine stereogenic centers in the 1,2-diaryl-dihydrobenzofuran skeleton of **4** and balanocarpol could not be elucidated. Takaya et al. determined the stereostructure of (+)-ampelopsin A, which has the absolute configurations 7a*S* and 8a*S* in a 1,2-diaryl-dihydrobenzofuran skeleton.[29] The CD curve of **5** was similar to that of (−)-ampelopsin A. Thus, vatalbinoside E (**5**) was elucidated as (−)-ampelopsin A 4a,11a-*O*-β-D-diglucopyranoside ((1*R*,6*S*,7*R*,11b*R*)-1,6,7,11b-tetrahydro-8-(β-D-glucopyranosyloxy)-4,6,10-trihydroxy-7-(4-(β-D-glucopyranosyloxy)-phenyl)-1-(4-hydroxyphenyl)benzo[6,7]cyclohepta[1,2,3-*cd*]benzofuran).

The absolute structures of most stilbenoids from Dipterocarpaceae plants have not been determined, except for (−)-hopeaphenol (**6**),[24] (−)-ε-viniferin (**10**),[30] shorealactone,[31] and uliginosides A−C.[26] In the present study, we have determined the absolute configuration of three new glucosides of resveratrol oligomers **1**, **3**, and **5**.

Glucosides of stilbenoids and their oligomers as well as their aglycones have been isolated from Dipterocarpaceae,[2,3,5−11,16,17,21−24,26,27,31−35] Vitaceae,[18,36] Gnetaceae,[37,38] Welwitschiaceae,[39] Iridaceae,[28] and Umbelliferae.[40] Each family has a regiospecific biosynthetic pathway for glycosylation to the stilbene unit(s), represented by blocking units, as listed in Table 3. Among these units, piceid (1-(β-D-glucopyranosyloxy)-5-[(1*E*)-2-(4-hydroxyphenyl)ethenyl]benzene-3-ol; **15**), 2-(β-D-glucopyransoyl)-5-[(1*E*)-2-(4-hydroxyphenyl)ethenyl]benzene-1,3-diol, and 4-(β-D-glucopyransoyl)-5-[(1*E*)-2-(4-hydroxyphenyl)ethenyl]benzene-1,3-diol are found in Dipterocarpaceae. In dipterocarpaceaeous plants, *C*-glucosides have been found only in the genera *Shorea*[26,27] and *Hopea,*[33] and *O*-glucosides have been found to have only one glucopyranosyl moiety.[8−10,21,34,35]

Table 3. Blocking Units as Glucosylated Resveratrol in Oligostilbenoid and Distribution

Blocking unit	Distribution in Plants	Distribution in Dipterocarpaceae
	Dipterocarpaceae Vitaceae Gnetaceae Welwitschiaceae Umbelliferae	*Vatica* *Vateria* *Upuna* *Cotylelobium* *Shorea*
	Dipterocarpaceae	*Shorea*
	Dipterocarpaceae	*Hopea*
	Gnetaceae Welwitschiaceae	
	Gnetaceae Welwitschiaceae	

The novel aspects found in these new compounds (**1**−**5**) are as follows: (1) vatalbinoside B (**2**) is the first example of a *C*-glucopyranoside from the genus *Vatica* and the second occurrence of a *C*-glucopyranoside of a resveratrol tetramer;[41] (2) vatalbinosides C (**3**) and E (**5**) have two *O*-D-glucopyranosyl moieties, which is the first case in the Dipterocarpaceae; and (3) the blocking unit (1-(*β*-D-glucopyranosyloxy)-5-[(1*E*)-2-(4-(*β*-D-glucopyranosyloxy)-phenyl)ethenyl]benzene-3-ol) found in **5** is the first instance in this family. Our present structural characterization of **1**−**5** not only adds new features to the biogenesis of stilbene oligomers but also demonstrates the additional diversity of resveratrol oligomers in dipterocarpaceaeous plants.

In the present study, each constituent isolated from the stem of *V. albiramis* was examined for its ability to inhibit MMP-1 production. MMP expression levels are relatively low in unstimulated cells, but some are induced by various extracellular stimuli including inflammatory cytokines, such as interleukin (IL)-1*β*. Thus, MMP-1 release from human dermal fibroblasts was initiated by the addition of IL-1*β* and was examined by western blot analysis of the conditioned medium. As shown in Figure 4, treatment with several resveratrol oligomers (**1**, **2**, **6**, **7**, **13**, **14**, and **17**) at 1 *μ*M blocked IL-1*β*-induced MMP-1 production, but did not induce inhibitory activities of cell growth (data not shown). Three resveratrol oligomers (**6**, **13**, and **14**) displayed significant inhibitory effects on MMP-1 production. These results suggest the following important points of SAR: (1) the active compounds have four or more resveratrol units; (2) the structure of each active resveratrol tetramer (**1**, **2**, **6**, **7**, **13**, and **14**) has two *trans*-oriented dihydrobenzofuran rings and a sequence of four −CH− groups; (3) resveratrol dimers (**3**−**5**, **10**−**12**, and **16**) have no or less effect than active tetramers on MMP-1 production; and (4) compounds **2** and **17** have a partial structure of **6**, which has a strong potency. This indicates

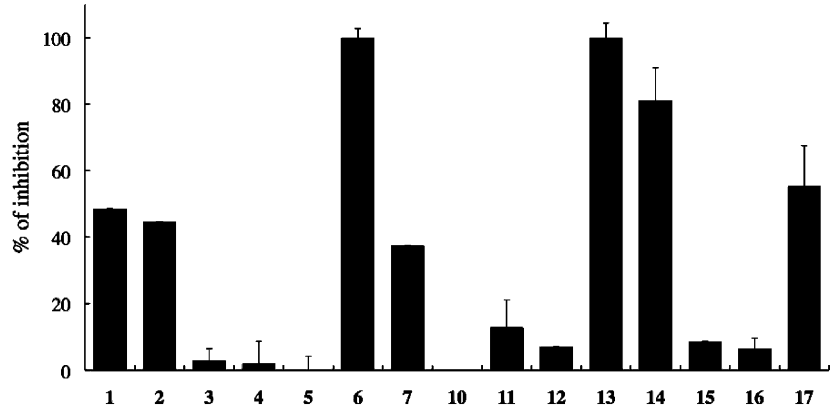


Figure 4. Inhibition of IL-1*β*-induced MMP-1 production in human dermal fibroblasts.

that a substitution on **6** would weaken its effects, such as *O*-glucosylation and further oligomerized resveratrols. The stem of *V. albiramis* contains resveratrol tetramers **6**, **7**, and **13** in large quantities, which explains the effect of the acetone extract. In previous decades, resveratrol tetramers, including **6**, **7**, and **13**, have mostly been isolated from several dipterocarpaceaeous plants. These stilbenoids and extracts containing resveratrol tetramers are considered to be useful resources for cosmetic agents. A limited number of inhibitors of MMP-1 production have been identified from nature, and the current discovery is the first report of oligostilbenoids as candidates for preventing cutaneous photoaging. Further studies at the molecular level are required to explain the detailed mechanisms underlying the effect of stilbenoids on MMP-1 production and are currently underway in our laboratory.

Experimental Section

General Experimental Procedures. The following instruments were used: optical rotations: JASCO P-1020 polarimeter; UV spectra: Shimadzu UV-3100 spectrophotometer (in MeOH solution); CD spectra: JASCO J-820 spectrometer (in MeOH solution); ^{1}H and ^{13}C NMR spectra: JEOL JNM AL-400 (chemical shift values in ^{1}H NMR spectra are presented as δ values with TMS as the internal standard); FABMS: JEOL JMS-DX-300 instrument.

The following adsorbents were used for purification: analytical TLC: Merck Kieselgel 60 F_{254} (0.25 mm); preparative TLC: Merck Kieselgel 60 F_{254} (0.5 mm); column chromatography: Merck Kieselgel 60, Pharmacia Fine Chemicals AB Sephadex LH-20, and Fuji Silysia Chemical Chromatorex, Waters Sep-Pak C_{18} cartridges; vacuum liquid chromatography (VLC): Merck Kieselgel 60; medium-pressure column chromatography (MPLC): Fuji Silysia Chemical Chromatorex ODS (100−200 mesh).

Plant Material. *V. albiramis* was collected from Borneo Island, Malaysia, in April 2002 and identified by J. Josue, head of the forest product branch at the Forest Research Center, Sandakan Sabah, Malaysia. A voucher specimen, number DP-026, has been deposited at the herbarium of Gifu Pharmaceutical University.

Extraction and Isolation. The dried and ground stem of *V. albiramis* (30 kg) was extracted with acetone (120 L, 24 h × 2, at room temperature). Evaporation produced a dry solid (2.3 kg). A part (2.0 kg) of the acetone extract was divided into five fractions (400 g each), and each one was subjected to column chromatography (120 × 12 cm) on silica gel (5 kg), eluted with a mixture of $CHCl_3$/MeOH, increasing in polarity. Nine fractions (Frs.1−9) were obtained from the initial five fractions, and these five fractions were combinations of appropriate fractions according to TLC (Gibbs test) (fraction: solvent system (total solvent eluted), amount; Fr.1: $CHCl_3$ (30 L), 222 g, Fr.2: $CHCl_3$/MeOH, 10:1 (30 L), 30 g, Fr.3: $CHCl_3$/MeOH, 10:1 (30 L), 155 g, Fr.4: $CHCl_3$/MeOH, 8:1 (20 L), 82 g, Fr.5: $CHCl_3$/MeOH, 7:1 (50 L), 412 g, Fr.6: $CHCl_3$/MeOH, 6:1 (50 L), 450 g, Fr.7: $CHCl_3$/MeOH, 5:1 (25 L), 84 g, Fr.8: $CHCl_3$/MeOH, 5:1 (40 L), 234 g, Fr.9: MeOH (30 L), 430 g). Compounds **10** (10 g), **11** (2 g), **12** (2 g), and **16** (20 mg) were obtained from Fr.3 by further purification by column chromatography over Sephadex LH-20 (MeOH) and Sep-Pak C_{18} (MeOH/H_2O system). After purification using column chromatography over Sephadex LH-20 (MeOH) and ODS (MeOH/H_2O system), compounds **7** (250 g), **13** (21 g), **15** (1.2 g), and bergenin (25 g) were obtained from Fr.5 and compounds **6** (120 g) and **14** (4 g) were obtained from Fr.6. Purification of the ninth fraction by silica gel column chromatography ($CHCl_3$/MeOH gradient system), Sephadex LH-20 (MeOH), Sep-Pak C_{18} (MeOH/H_2O system), VLC (EtOAc/$CHCl_3$/MeOH/H_2O system), reversed-phase MPLC (MeOH/H_2O system), and PTLC (EtOAc/$CHCl_3$/MeOH/H_2O system) achieved the isolation of compounds **1** (78.8 mg), **2** (24.4 mg), **3** (59.6 mg), **4** (19.1 mg), **5** (21.8 mg), **8** (2 g), **9** (2 g), and **17** (3 g).

Vatalbinoside A (1): pale yellow solid; UV (MeOH) 226 (4.97), 282 (4.28); CD (*c* 18.7 μM, MeOH) nm ($\Delta\varepsilon$) 236 (−11.8); $[\alpha]^{25}_D$ −320 (*c* 0.1, MeOH); ^{1}H and ^{13}C NMR spectroscopic data, Table 1; HMBC and NOESY correlations, Table S2; FABMS, *m/z* 1067 $[M - H]^-$; HRFABMS, *m/z* 1067.3134 (calcd for $C_{62}H_{51}O_{17}$, 1067.3126) $[M - H]^-$.

Vatalbinoside B (2): pale yellow solid; UV (MeOH) 284 (4.50); CD (*c* 18.7 μM, MeOH) nm ($\Delta\varepsilon$) 236 (−24.5); $[\alpha]^{25}_D$ −16 (*c* 0.1, MeOH); ^{1}H and ^{13}C NMR spectroscopic data, Table 1; HMBC and NOESY correlations, Table S2; FABMS, *m/z* 1067 $[M - H]^-$; HRFABMS, *m/z* 1067.3132 (calcd for $C_{62}H_{51}O_{17}$, 1067.3126) $[M - H]^-$.

Vatalbinoside C (3): pale yellow solid; UV (MeOH) 227 (4.65), 284 (4.14), 325 (4.29); CD (*c* 25.7 μM, MeOH) nm ($\Delta\varepsilon$) 236 (−33.5), 288 (−9.2); $[\alpha]^{25}_D$ −72 (*c* 0.1, MeOH); ^{1}H and ^{13}C NMR spectroscopic data, Table 2; HMBC and NOESY correlations, Table S3; FABMS, *m/z* 777 $[M - H]^-$; HRFABMS, *m/z* 777.2400 (calcd for $C_{40}H_{41}O_{16}$, 777.2394) $[M - H]^-$.

Vatalbinoside D (4): pale yellow solid; UV (MeOH) 227 (4.71), 283 (4.13); CD (*c* 31.6 μM, MeOH) nm ($\Delta\varepsilon$) 237 (−27.4); $[\alpha]^{25}_D$ −44 (*c* 0.1, MeOH); ^{1}H and ^{13}C NMR spectroscopic data, Table 2; HMBC and NOESY correlations, Table S3; FABMS, *m/z* 631 $[M - H]^-$; HRFABMS, *m/z* 631.1809 (calcd for $C_{34}H_{31}O_{12}$, 631.1816) $[M - H]^-$.

Vatalbinoside E (5): pale yellow solid; UV (MeOH) 226 (4.57), 285 (3.77); CD (*c* 25.2 μM, MeOH) nm ($\Delta\varepsilon$) 236 (−19.6); $[\alpha]^{25}_D$ −142 (*c* 0.1, MeOH); ^{1}H and ^{13}C NMR spectroscopic data, Table 2; HMBC and NOESY correlations, Table S3; FABMS, *m/z* 793 $[M - H]^-$; HRFABMS, *m/z* 793.2360 (calcd for $C_{40}H_{41}O_{17}$, 793.2343) $[M - H]^-$.

Enzymatic Hydrolysis of 1 and 3−5. Separate solutions of **1** (1 mg), **3** (1 mg), **4** (1 mg), and **5** (1 mg) in phosphate buffer (pH 6, 1.0 mL) were treated with β-glucosidase (1 mg/mL) for 24 h at 37 °C. Each reaction solution was evaporated to dryness, and the resultant residue was purified by PTLC (EtOAc/$CHCl_3$/MeOH/H_2O, 80:40:11:2) to obtain the respective aglycones [**6** (0.3 mg), **10** (0.3 mg), **11** (0.2 mg), and **12** (0.3 mg)]. The structures were confirmed by ^{1}H NMR spectra.

Materials for MMP-1 Assay. The antibody against MMP-1 was obtained from Daiichi Fine Chemical (Toyama, Japan). Anti-mouse antibody conjugated with horseradish peroxidase and the ECL western blotting detection system were obtained from GE Healthcare (Piscataway, NJ). IL-1β was obtained from Chemicon (Temecula, CA). Other reagents used were of the highest quality available.

Cell Culture. Human dermal foreskin fibroblasts were purchased from Kurabo (Osaka, Japan). Cells were cultured in Dulbecco's modified Eagle's medium supplemented with 10% (v/v) fetal bovine serum at 37 °C in a humidified, CO_2-controlled (5%) incubator.

Measurement of MMP-1 Secretion. MMP-1 secretion was analyzed by western blot analysis. In brief, cells (2×10^5 cells/mL) were seeded and cultured until confluent, treated for 24 h with stilbenoids isolated from *V. albiramis*, and stimulated with IL-1β (10 ng/mL) for 24 h. Supernatants were collected and concentrated by acetone precipitation. Aliquots of concentrated supernatants were subjected to sodium dodecyl sulfate−polyacrylamide gel electrophoresis. Proteins were then transferred electrophoretically to a polyvinylidene fluoride membrane (Hybond-P; GE healthcare). After blocking in Tris-buffered saline containing 5% skim milk and 0.05% Tween-20 for 1 h at room temperature, the blots were incubated with the appropriate primary antibody overnight at 4 °C and further incubated with horseradish peroxidase-conjugated secondary antibody for 1 h at room temperature. The proteins were visualized using an ECL western blot detection system according to the manufacture's instructions, and gel images were obtained with a LAS 4000 imaging system (Fuji Film, Tokyo, Japan). Band intensity was quantified by a densitometer (ATTO densitograph).

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Note Added after ASAP Publication: This paper was published on the Web on August 24, 2010, with Table S1 missing from the Supporting Information file. The revised SI was reposted on September 3, 2010.

Supporting Information Available: 1D NMR spectra (^{1}H and ^{13}C NMR spectra); tables of HMBC and NOESY data for compounds **1**−**5**. This information is available free of charge via the Internet at http://pubs.acs.org.

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