Indonesian Medicinal Plants. III.[1] On the Constituents of the Bark of *Fagara rhetza* (Rutaceae). (1): Alkaloids, Phenylpropanoids, and Acid Amide

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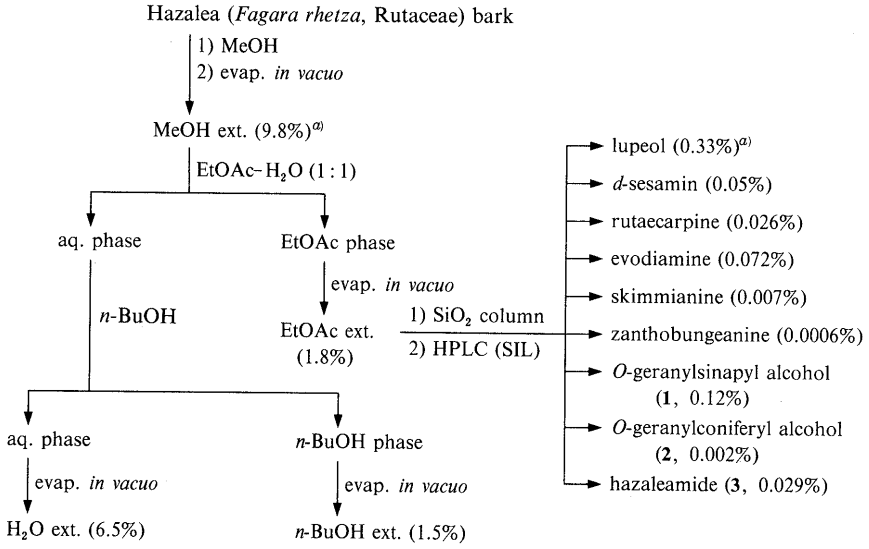
Two new phenylpropanoids, named *O*-geranylsinapyl alcohol (1) and *O*-geranylconiferyl alcohol (2), and a new acid amide, named hazaleamide (3), were isolated from the bark of *Fagara rhetza* (Rutaceae), an Indonesian medicinal plant from Flores Island, Indonesia. The chemical structures of 1, 2, and 3 have been elucidated on the basis of their chemical and physicochemical properties. Among the three new compounds, hazaleamide (3) was found to show a pungent taste and to exert a moderate antimalarial activity in an *in vitro* test system.

Keywords Indonesian medicinal plant; *Fagara rhetza*; Rutaceae; phenylpropanoid; *O*-geranylsinapyl alcohol; *O*-geranylconiferyl alcohol; acid amide; hazaleamide; pungent; antimalarial activity

As a continuation of our chemical characterization studies of Indonesian medicinal plants,[1,2] we have been investigating the chemical constituents of the bark of *Fagara rhetza* (ROXB.) DC. (Rutaceae), which was collected in August 1988 in the Bajawa area of Flores Island, Indonesia.[3] The bark of *Fagara rhetza*, which is called "Hazalea" in Flores Island, has been traditionally used as a remedy for malaria and for medical treatment of diarrhoea and vomiting.[3] We first engaged in the extensive chemical analysis of the whole constituents of the bark and afterwards the substances isolated were submitted to appropriate biological activity tests. In this paper, we report the chemical characterization of the alkaloidal, phenylpropanoidal, and acid amide constituents which were isolated from the ethyl acetate-soluble portion of the bark.

The methanol extract of the bark was partitioned into an ethyl acetate–water mixture. Separation and purification of the ethyl acetate-soluble portion, by silica gel column chromatography and subsequent high performance liquid chromatography (HPLC) with ordinary phase adsorbent, provided four known alkaloids (*i.e.*, rutaecarpine,[4,5] evodiamine,[5,6] skimmianine,[7,8] and zanthobungeanine[9]), two new phenylpropanoids named *O*-geranylsinapyl alcohol (**1**, 0.094% from the bark) and *O*-geranylconiferyl alcohol (**2**, 0.003%), and a new acid amide named hazaleamide (**3**, 0.025%), together with lupeol[4,10] and *d*-sesamin[4,8] (Chart 1).

O-Geranylsinapyl Alcohol and O-Geranylconiferyl Alcohol *O*-Geranylsinapyl alcohol (**1**) gave a molecular ion peak at *m/z* 346, which was assigned as $C_{21}H_{30}O_4$ from the high-resolution electron-impact mass spectrum (EI-MS).



a) The % yield from the bark

Chart 1

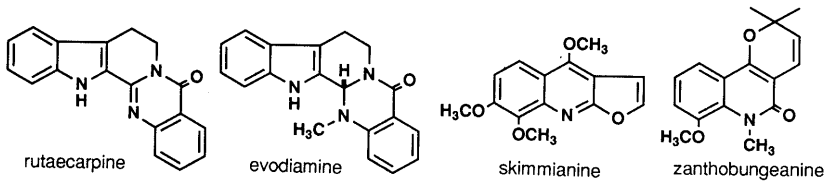


Fig. 1

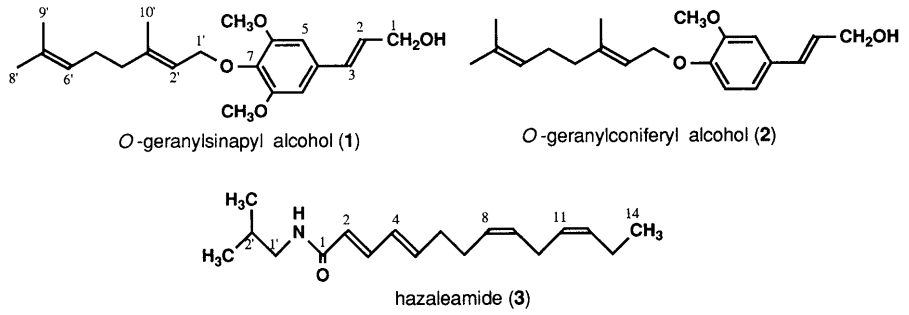


Fig. 2

TABLE I. ^{1}H- and ^{13}C-NMR Data for *O*-Geranylsinapyl Alcohol (**1**) in $CDCl_3$ (δ, δ_C in ppm)

C-No.	δ	δ_C	C-No.	δ	δ_C
C-1	4.53 (2H, d, J=5.6 Hz)	62.5 (t)	C-1′	4.71 (2H, d, J=7.3 Hz)	68.9 (t)
C-2	6.20 (1H, dt, J=15.6, 5.6 Hz)	127.9 (d)	C-2′	5.56 (1H, t, J=7.3 Hz)	119.9 (d)
C-3	6.57 (1H, d, J=15.6 Hz)	130.2 (d)	C-3′	—	140.7 (s)
C-4	—	130.8 (s)	C-4′	2.01 (2H, t, J=6.0 Hz)	39.1 (t)
C-5	6.60 (1H, s)	103.3 (d)	C-5′	2.06 (2H, br t, J=6.0 Hz)	26.0 (t)
C-6	—	153.7 (s)	C-6′	5.07 (1H, t-like)	123.6 (d)
C-7	—	136.1 (s)	C-7′	—	132.3 (s)
C-8	—	153.7 (s)	C-8′	1.64 (3H, s)	15.8 (q)
C-9	6.60 (1H, s)	103.3 (d)	C-9′	1.59 (3H, s)	17.1 (q)
$-OCH_3\times2$	3.85 (6H, s)	55.5 (q)	C-10′	1.67 (3H, s)	25.1 (q)

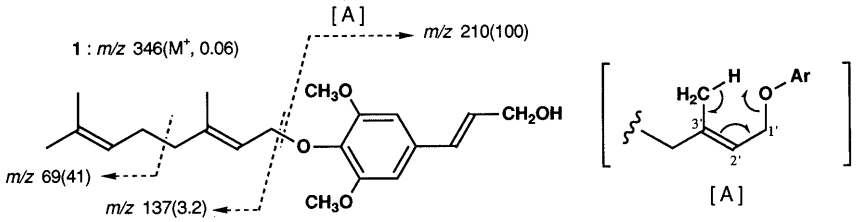


Fig. 3. Mass Fragmentation of *O*-Geranylsinapyl Alcohol (**1**)

The infrared (IR) spectrum of **1** showed absorption bands due to a hydroxyl group (3460 cm^{-1}) and carbon–carbon double bonds (1650 cm^{-1}), whereas the ultraviolet (UV) spectrum showed absorption maxima attributable to an aromatic ring.

The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **1** showed the signals assignable to three olefinic methyl groups (3H each at δ 1.59, 1.64, and 1.67), two methoxyl groups attached to an aromatic ring (δ 3.85, 6H), two aromatic protons (δ 6.60, 2H), four olefinic protons (δ 5.07, 1H, t-like; δ 5.56, 1H, t, J=7.3 Hz; δ 6.20, 1H, dt, J=15.6, 5.6 Hz; δ 6.57, 1H, d, J=15.6 Hz), and two allylic methylene groups both adjacent to an oxygen function (δ 4.53, 2H, d, J=5.6 Hz; δ 4.71, 2H, d, J=7.3 Hz). The coupling pattern of the aromatic protons indicated that the aromatic ring is symmetrically substituted. Distortionless enhancement by polarization transfer (DEPT) experiments *via* carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectroscopy showed the presence of five methyl-carbons, four methylene-carbons, six methine-carbons including two aromatic carbons, and six quaternary carbons including four aromatic carbons (Table I). Furthermore, the EI-MS of **1** provided a base ion peak at *m/z* 210, involving a sinapyl alcohol moiety, which was presumably generated *via* fragmentation [A]. It also gave a fragment ion peak at *m/z* 137 derived from the geranyl moiety, which was probably cleaved further to an ion of *m/z* 69, assigned as an isopropenyl ion, besides a molecular ion peak at *m/z* 346. These findings indicated that **1** contained one sinapyl alcohol and one geranyl moiety in its molecule.

In the correlation spectroscopy *via* long-range coupling (COLOC) NMR experiments, **1** was shown to have ^{1}H–^{13}C correlations between the signals of aromatic protons at C-5 and C-9 (δ 6.60, 2H) and the carbon signals of C-3 (δ_C 130.2) and C-7 (δ_C 136.1), and also between the signals of methylene protons at C-1′ (δ 4.71) and the aromatic carbon signal of C-7 (δ_C 136.1). The ^{1}H–^{13}C correlations between the proton at C-3 (δ 6.57) and the carbons at C-4 (δ_C 130.8) and C-9 (δ_C 103.3) were also observed (Fig. 4). Furthermore, the ^{1}H-NMR nuclear Overhauser and exchange spectroscopy (NOESY) experiments indicated that the methoxyl protons on the aromatic ring of **1** (at C-6 and C-8) were spatially close to the methylene protons at C-1′ and also to the aromatic protons at C-5 and C-9 (Fig. 5). The NMR spectral evidence suggests that the sinapyl alcohol is combined through an ether linkage at C-7 with the geranyl moiety, and consequently the structure of **1** has been determined to be 7-*O*-geranylsinapyl alcohol.

O-Geranylconiferyl alcohol (**2**) showed a molecular ion peak at *m/z* 316, corresponding to $C_{20}H_{28}O_3$, in the high-resolution EI-MS. The EI-MS also showed a fragment ion peak at *m/z* 180 as the base peak (formed *via* [A]), which was 30 mass units (CH_2O) smaller than the base peak of *m/z* 210 for *O*-geranylsinapyl alcohol (**1**), and two prominent ion peaks: one at *m/z* 137 which was derived from the geranyl moiety and another at *m/z* 69 formed by splitting of the terminal isopropenyl moiety. The IR and UV spectra of **2** showed similar absorption patterns to those of **1**. The ^{1}H-NMR spectrum of **2** exhibited the presence of a 1,2,4-trisubstituted aromatic ring (δ 6.82, 1H, d, J=8.3 Hz; δ 6.89, 1H, dd, J=1.8, 8.3 Hz; δ 6.94, 1H, d, J=1.8 Hz) and one methoxyl group on the aromatic ring (δ 3.88, 3H), besides a geranyloxy moiety (Table II). These findings led to the presumption that **2** is a demethoxyl derivative of *O*-geranylsinapyl alcohol (**1**).

Finally, the COLOC experiments (Fig. 7) and the NOESY experiments (Fig. 8) on **2** clarified that the geranyl moiety is attached through an ether linkage to the hydroxyl group at C-7 of coniferyl alcohol. So, the chemical structure of **2** has been determined to be 7-*O*-geranylconiferyl alcohol.

Hazaleamide In the high-resolution EI-MS, hazaleamide (**3**) gave a molecular ion peak at *m/z* 275, which corresponds to $C_{18}H_{29}NO$. The IR spectrum of **3** showed absorption bands due to an acid amide group (3300, 1656, 1540 cm^{-1}) and carbon–carbon double bonds (1629 cm^{-1}). The UV spectrum of **3** suggested presence of a conjugated unsaturated carbonyl function (260 nm, ε=32000).

The ^{1}H-NMR spectrum of **3** showed signals ascribable to one primary methyl, two secondary methyls, one methylene group (δ 3.14) attached directly to a nitrogen atom, four allylic methylene protons [δ 2.05 (2H), 2.18 (4H), 2.75 (2H)], one amide proton, and eight olefinic protons (δ 5.20, dt, J=10.6, 6.6 Hz for 11-H; δ 5.25—5.35, m for 8-H, 9-H, 12-H; δ 5.81, d, J=15.2 Hz for 2-H; δ 6.02, dt, J=15.3, 6.6 Hz for 5-H; δ 6.13, dd, J=10.2, 15.3 Hz for 4-H; δ 7.16, dd, J=10.2, 15.2 Hz for 3-H). In the ^{13}C-NMR spectrum, signals due to three methyls, five methylenes, one methine, eight olefinic carbons, and one carbonyl carbon were observed (Table III). From these

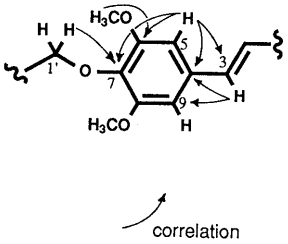


Fig. 4. COLOC Experiment on **1**

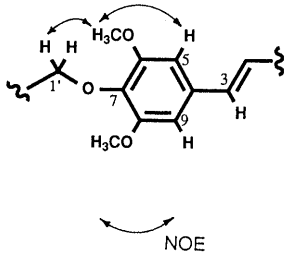


Fig. 5. NOESY Experiment on **1**

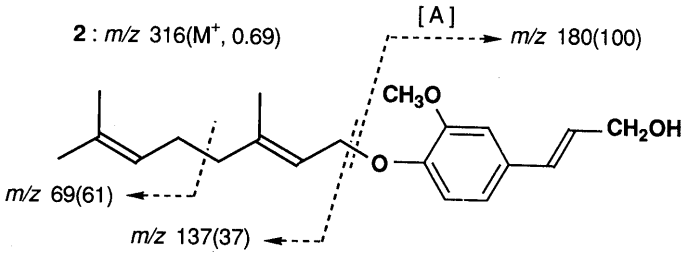


Fig. 6. Mass Fragmentation of *O*-Geranylconiferyl Alcohol (**2**)

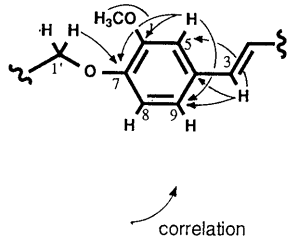


Fig. 7. COLOC Experiment on **2**

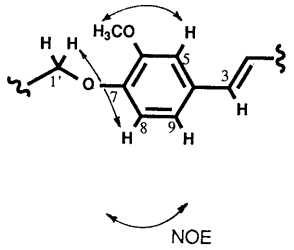


Fig. 8. NOESY Experiment on **2**

TABLE II. ^{1}H- and ^{13}C-NMR Data for *O*-Geranylconiferyl Alcohol (**2**) in $CDCl_3$ (δ, δ_C in ppm)

C-No.	δ	δ_C	C-No.	δ	δ_C
C-1	4.30 (2H, d, J=5.8 Hz)	63.0 (t)	C-1′	4.61 (2H, d, J=6.7 Hz)	65.4 (t)
C-2	6.24 (1H, dt, J=16.0, 5.8 Hz)	126.5 (d)	C-2′	5.52 (1H, t, J=6.7 Hz)	119.4 (d)
C-3	6.54 (1H, d, J=16.0 Hz)	130.2 (d)	C-3′	—	140.1 (s)
C-4	—	129.6 (s)	C-4′	2.05 (2H, t, J=7.0 Hz)	39.1 (t)
C-5	6.94 (1H, d, J=1.8 Hz)	108.8 (d)	C-5′	2.10 (2H, br t, J=7.0 Hz)	25.9 (t)
C-6	—	149.0 (s)	C-6′	5.08 (1H, t-like)	123.5 (d)
C-7	—	147.6 (s)	C-7′	—	131.5 (s)
C-8	6.82 (1H, d, J=8.3 Hz)	112.7 (d)	C-8′	1.64 (3H, s)	16.2 (q)
C-9	6.89 (1H, dd, J=1.8, 8.3 Hz)	119.1 (d)	C-9′	1.59 (3H, s)	17.3 (q)
–OCH_3	3.88 (3H, s)	55.3 (q)	C-10′	1.72 (3H, s)	25.3 (q)

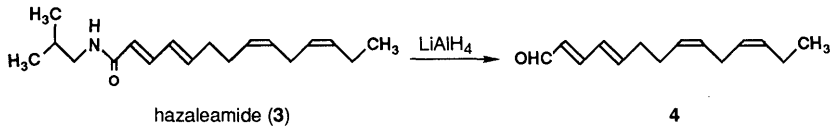


Chart 2

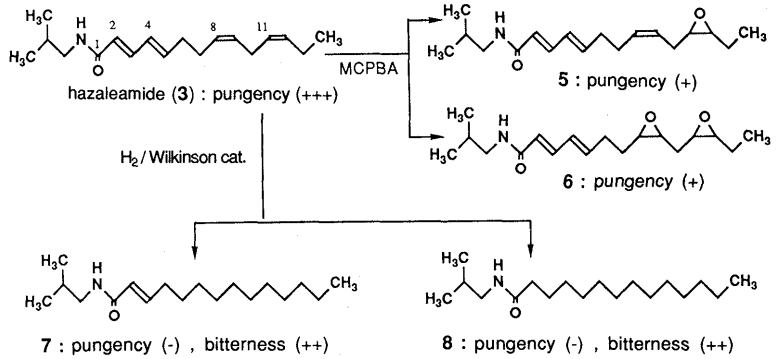


Fig. 9

TABLE III. ^{13}C-NMR Data for Hazaleamide (**3**), **5**, and **6** (Major and Minor) (in $CDCl_3$, δ_C in ppm)

	3	**5**	**6** (major)	**6** (minor)
C-1	166.4	166.2	166.1	166.1
C-2	122.6	122.3	122.6	122.7
C-3	139.8	140.9	140.4	140.5
C-4	128.4	128.9	129.1	129.2
C-5	140.7	141.6	140.5	140.6
C-6	32.4	32.7	29.7	29.8
C-7	26.1	26.1	27.2	27.2
C-8	128.0	131.0	56.2	55.9
C-9	128.5	124.9	54.3[a]	54.2[a]
C-10	25.0	26.7	27.0	26.8
C-11	126.5	56.5[a]	54.4[a]	54.3[a]
C-12	131.3	58.3[a]	58.1	57.7
C-13	20.0	21.0	21.2	21.0
C-14	13.7	10.6	10.4	10.5
C-1′	46.6	46.9	46.9	46.9
C-2′	28.1	28.6	28.5	28.5
C-3′	19.7	20.1	20.0	20.0

a) The assignments in each column may be interchangeable.

physical data, **3** was presumed to be an acid amide compound having four double bonds.

Since reduction of **3** with lithium aluminum hydride in tetrahydrofuran (THF) provided a C_{14}-aldehyde (**4**), the carbon chain length of the acid part was shown to be C_{14} whereas that of the amine part was C_4. By taking into consideration the accumulated evidence mentioned above and two-dimensional (2D) NMR data for **3**, the structure of hazaleamide (**3**) has been revealed to be *N*-isobutyl-2,4,8,11-tetradecatetraenamide. It was concluded that both Δ^2 and Δ^4 have *E* configurations from the proton–proton coupling constants ($J_{2,3}=15.2$ Hz and $J_{4,5}=15.3$ Hz) observed in the ^{1}H-NMR spectrum. On the other hand, the geometries of Δ^8 and Δ^{11} were ascertained to be *Z* from the chemical shifts of C-7 (δ_C 26.1), C-10 (δ_C 25.0), and C-13 (δ_C 20.0) in the ^{13}C-NMR spectrum.[11] Consequently, the structure of hazaleamide has been elucidated to be **3** as shown.

It is known that naturally occurring acid amide compounds [*e.g.* sanshools[12] isolated from *Zanthoxylum piperitum* (Rutaceae) and capsaicin[13] isolated from *Capsicum annuum* (Solanaceae)] exhibit a pungent taste. Hazaleamide (**3**) isolated here was therefore tested, and found, as expected, to have a durable paralytic pungent taste, at the concentration of 1×10^{-6} mol/l.

In regard to the quality of pungent taste, it has been suggested that the structure of the amine moiety is mostly responsible. We were interested in the effect of the double bonds in the acid part of **3** on the pungent taste, so we prepared four derivatives of hazaleamide (**3**) and examined their tastes. Oxidation of **3** with *m*-chloroperbenzoic acid in chloroform afforded a monoepoxide (**5**) and a mixture of two isomeric diepoxides (**6**) in 45% and 25% yields, respectively. The diepoxide (**6**) was shown to be a mixture of *syn* and *anti* isomers (in *ca.* 3:7 ratio) by HPLC analysis. Furthermore, hydrogenation of **3** over a Wilkinson catalyst[14] afforded a hexahydroderivative (**7**) and an octahydroderivative (**8**) in 26% and 50% yields, respectively. The structures of these derivatives (**5**, **6**, **7**, **8**) were ascertained on the basis of their physical data (see Experimental).

Among these compounds, the monoepoxide (**5**) and the diepoxide mixture (**6**) were found to show similarly weak pungent taste, while the hexahydroderivative (**7**) and the octahydroderivative (**8**) were found to show a bitter taste instead of a pungent taste. These findings show that the double bonds in the acid part of **3** have an effect on the strength and quality of the pungent taste.

In conclusion, it is interesting to note that, among the constituents characterized above from the ethyl acetate-soluble portion of the bark of *Fagara rhetza*, hazaleamide (**3**) was found to exhibit an inhibitory activity (IC_{50} 43 μM) towards the proliferation of malarial *Plasmodium falciparum* (a chloroquine-resistant strain) in human erythrocytes.[15]

In parallel studies, we have chemically investigated the constituents of the *n*-butanol- and water-soluble portions of the bark (Chart 1). The results will be reported in a forthcoming paper.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are recorded as read. UV spectra were obtained with a Hitachi 330 spectrophotometer. IR spectra were taken with a Hitachi 260-30 spectrometer. EI-MS were taken on a JEOL JMS-D300 spectrometer. ^{1}H- and ^{13}C-NMR spectra were measured with a JEOL GX-500 spectrometer (500 MHz) or a JEOL EX-270 spectrometer (270 MHz). For HPLC, a Shimadzu LC-6A was used. Column chromatography was carried out using Kieselgel 60 (70—230 mesh, Merck). Thin-layer chromatography (TLC) was conducted on precoated Kieselgel $60F_{254}$ plates (0.2 mm, Merck). Detection of the spots was carried out by spraying 1% $Ce(SO_4)_2$/10% H_2SO_4 on the TLC plates, followed by heating at 110 °C.

Isolation of *O*-Geranylsinapyl Alcohol (1), *O*-Geranylconiferyl Alcohol (2), and Hazaleamide (3) The air-dried bark (10 kg) of *Fagara rhetza* (Rutaceae), which was collected in the Bajawa area of Flores Island, Indonesia in 1988, was extracted with MeOH under reflux and the solvent was evaporated off under reduced pressure from the extract to give the MeOH extract (980 g, 9.8% from the bark). The MeOH extract was partitioned into EtOAc–H_2O (1 : 1). The EtOAc phase was taken and concentrated under reduced pressure to give the EtOAc extract (180 g, 1.8%), while the water phase was treated with *n*-BuOH with shaking. The *n*-BuOH-soluble portion and the water-soluble portion were separated and concentrated under reduced pressure to give the *n*-BuOH extract (150 g, 1.5%) and the H_2O extract (650 g, 6.5%), respectively. The EtOAc extract (50 g) was subjected to column chromatography (SiO_2 1.5 kg, *n*-hexane, *n*-hexane : EtOAc = 10 : 1 → 1 : 2, EtOAc, and MeOH) to give fr. 1 (0.5 g), fr. 2 (12.0 g), fr. 3 (11.1 g), fr. 4 (4.2 g), fr. 5 (6.2 g), fr. 6 (5.0 g), and fr. 7 (7.3 g). Fraction 2 was crystallized from $CHCl_3$ to afford lupeol[4,10] (9.2 g, 0.26% from the bark). Fraction 3 was further purified by column chromatography (SiO_2 500 g, *n*-hexane : EtOAc = 3 : 2) to give fr. 3-1 (130 mg), fr. 3-2 (5.1 g), fr. 3-3 (2.5 g), fr. 3-4 (900 mg), fr. 3-5 (350 mg), and fr. 3-6 (85 mg). Fraction 3-2 was crystallized from $CHCl_3$ to afford *d*-sesamin[4,8] (1.4 g, 0.04%), while the mother liquor was concentrated under reduced pressure and the residue was subjected to HPLC (Zorbax SIL, *n*-hexane : EtOAc = 4 : 1) to afford hazaleamide (**3**, 820 mg, 0.025%). Fraction 3-3 was crystallized from MeOH to afford rutaecarpine[4,5] (720 mg, 0.02%). Crystallization of fr. 4 from MeOH afforded evodiamine[5,6] (2.0 g, 0.06%). Fraction 5 was purified by column chromatography (SiO_2 400 g, *n*-hexane : EtOAc = 3 : 1 and EtOAc) to give fr. 5-1 (210 mg), fr. 5-2 (990 mg), fr. 5-3 (440 mg), fr. 5-4 (1.95 g), fr. 5-5 (123 mg), and fr. 5-6 (211 mg). Fraction 5-3 was then purified by HPLC (Zorbax SIL, *n*-hexane : EtOAc = 2 : 1) to afford *O*-geranylconiferyl alcohol (**2**, 90 mg, 0.003%) and zanthobungeanine[9] (30 mg, 0.001%). Fraction 6 was also purified by HPLC (Zorbax SIL, *n*-hexane : EtOAc = 3 : 1) to afford *O*-geranylsinapyl alcohol (**1**, 3.4 g, 0.094%) and skimmianine[7,8] (190 mg, 0.006%).

O-Geranylsinapyl Alcohol (**1**): A colorless oil. IR (film) cm^{-1}: 3460, 1650. UV λ_{max}^{MeOH} nm (ε): 219 (37000), 266 (17300). ^{1}H-NMR: as given in Table I. ^{13}C-NMR: as given in Table I. EI-MS *m/z* (%): 346 (M^+, 0.06), 210 (100). High-resolution EI-MS *m/z*: Calcd for $C_{21}H_{30}O_4$: 346.2142. Found: 346.2139 (M^+).

O-Geranylconiferyl Alcohol (**2**): A colorless oil. IR (film) cm^{-1}: 3400, 1640. UV λ_{max}^{MeOH} nm (ε): 210 (26000), 261 (16400). ^{1}H-NMR: as given in Table II. ^{13}C-NMR: as given in Table II. EI-MS *m/z* (%): 316 (M^+, 0.7), 180 (100). High-resolution EI-MS *m/z*: Calcd for $C_{20}H_{28}O_3$: 316.2036. Found: 316.2036 (M^+).

Hazaleamide (**3**): A colorless oil. IR (film) cm^{-1}: 3300, 1656, 1629, 1540. UV λ_{max}^{MeOH} nm (ε): 260 (32000). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.90 (6H, d, J = 6.6 Hz, 2′-CH_3 × 2), 0.92 (3H, t, J = 7.5 Hz, 14-H_3), 1.79 (1H, m, 2′-H), 2.05 (2H, dq, J = 7.5, 7.5 Hz, 13-H_2), 2.18 (4H, br s, 6-H_2, 7-H_2), 2.75 (2H, t-like, 10-H_2), 3.14 (2H, dd, J = 6.6, 6.6 Hz, 1′-H_2), 5.20 (1H, dt, J = 10.6, 6.6 Hz, 11-H), 5.25—5.35 (3H, m, 8-H, 9-H, 12-H), 5.81 (1H, d, J = 15.2 Hz, 2-H), 6.02 (1H, dt, J = 15.3, 6.6 Hz, 5-H), 6.13 (1H, dd, J = 10.2, 15.3 Hz, 4-H), 6.84 (1H, br s, amide proton), 7.16 (1H, dd, J = 10.2, 15.2 Hz, 3-H). ^{13}C-NMR: as given in Table III. EI-MS *m/z* (%): 275 (M^+, 7.5), 67 (100). High-resolution EI-MS *m/z*: Calcd for $C_{18}H_{29}NO$: 275.2249. Found: 275.2250 (M^+).

Reduction of Hazaleamide (3) with $LiAlH_4$ Giving 4 A solution of hazaleamide (**3**, 30 mg, 0.11 mmol) in tetrahydrofuran (THF, 2 ml) was added to a suspension of $LiAlH_4$ (5 mg, 0.13 mmol) in THF (1 ml) in an ice-bath. The reaction mixture was then stirred at room temperature for 3 d. The reaction mixture was treated with Et_2O saturated with water and the resulting precipitate was removed by filtration. The filtrate was concentrated under reduced pressure to give a product, which was purified by column chromatography (SiO_2 3 g, benzene : EtOAc = 10 : 1) to afford an aldehyde (**4**, 5 mg, 0.025 mmol, 22%) and to recover **3** (18 mg, 0.065 mmol recovery).

4: A colorless oil. IR ($CHCl_3$) cm^{-1}: 1681, 1638. UV λ_{max}^{MeOH} nm (ε): 262 (29800). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.90 (3H, t, J = 7.5 Hz, 14-H_3), 2.00 (2H, dq, J = 7.2, 7.5 Hz, 13-H_2), 2.20 (4H, m, 6-H_2, 7-H_2), 2.71 (2H, t-like, 10-H_2), 5.24—5.38 (4H, m, 8-H, 9-H, 11-H, 12-H), 6.01 (1H, dd, J = 7.9, 15.1 Hz, 2-H), 6.22 (1H, dt, J = 16.6, 5.2 Hz, 5-H), 6.27 (1H, dd, J = 9.9, 15.2 Hz, 4-H), 7.00 (1H, dd, J = 9.9, 15.1 Hz, 3-H), 9.46 (1H, d, J = 7.9 Hz, 1-H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ_C: 14.3 (14-C), 20.6 (13-C), 25.6 (10-C), 26.2 (7-C), 33.1 (6-C), 126.9 (11-C), 128.2 (8-C), 129.0 (9-C), 129.4 (4-C), 130.3 (12-C), 132.1 (2-C), 146.2 (5-C), 152.6 (3-C), 193.9 (1-C). *Anal.* Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.17; H, 9.81.

Epoxidation of Hazaleamide (3) Giving 5 and 6 A solution of hazaleamide (**3**, 100 mg, 0.36 mmol) in $CHCl_3$ (2.0 ml) was treated with *m*-chloroperbenzoic acid (135 mg, 1.5 eq), and the mixture was stirred at room temperature for 2 h. After addition of aqueous saturated Na_2CO_3 to the reaction mixture, the whole was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product, which was purified by column chromatography (SiO_2 5 g, *n*-hexane : EtOAc = 20 : 1) to afford a monoepoxide (**5**, 48 mg, 45%) and a diepoxide mixture (**6**, 28 mg, 25%). The diepoxide mixture (**6**) was analyzed by HPLC (Zorbax ODS, CH_3CN : H_2O = 3 : 10) to determine the ratio of diastereomers as *ca.* 3 : 2.

5: A colorless oil. IR ($CHCl_3$) cm^{-1}: 3330, 1657, 1624, 1503. UV λ_{max}^{MeOH} nm (ε): 258 (29600). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.91 (6H, d, J = 6.9 Hz, 2′-CH_3 × 2), 1.03 (3H, t, J = 7.5 Hz, 14-H_3), 1.48—1.67 (2H, m, 13-H_2), 1.79 (1H, m, 2′-H), 2.20 (5H, br s, 6-H_2, 7-H_2, 10-Ha), 2.28—2.39 (1H, m, 1-Hb), 2.85—2.96 (2H, m, 11-H, 12-H), 3.15 (2H, dd, J = 6.9, 6.9 Hz, 1′-H_2), 5.45—5.50 (2H, m, 8-H, 9-H), 5.60 (1H, br s, amide proton), 5.76 (1H, d, J = 15.2 Hz, 2-H), 6.06 (1H, dt, J = 15.2, 6.3 Hz, 5-H), 6.18 (1H, dd, J = 10.3, 15.2 Hz, 4-H), 7.17 (1H, dd, J = 10.3, 15.2 Hz, 3-H). ^{13}C-NMR: as given in Table III. EI-MS *m/z* (%): 156 ($M^+ - C_8H_{13}O$, 78), 57 (isobutyl, 100). *Anal.* Calcd for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 74.09; H, 9.98; N, 4.79.

6: A white amorphous solid. IR ($CHCl_3$) cm^{-1}: 3345, 1669, 1639, 1514. UV λ_{max}^{MeOH} nm (ε): 258 (32300). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.91 (6H, d, J = 6.6 Hz, 2′-CH_3 × 2), 1.05 (3H, t, J = 7.6 Hz, 14-H_3), 1.52—1.81 (7H, m, 7-H_2, 10-H_2, 13-H_2, 2′-H), 2.31—2.39 (2H, m, 6-H_2), 2.91—2.99 (2H, m, 11-H, 12-H), 3.10—3.17 (4H, 8-H, 9-H, 1′-H_2), 5.56 (1H, br s, amide proton), 5.77 (1H, d, J = 15.2 Hz, 2-H), 6.02 (1H, dt, J = 6.3, 15.2 Hz, 5-H), 6.19 (1H, dd, J = 10.3, 15.2 Hz, 4-H), 7.17 (1H, dd, J = 10.3, 15.2 Hz, 3-H). ^{13}C-NMR: as given in Table III. EI-MS *m/z* (%): 307 (M^+, 4), 57 (100). *Anal.* Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.19; H, 9.47; N, 4.52.

Hydrogenation of Hazaleamide (3) Giving 7 and 8 A solution of hazaleamide (**3**, 200 mg, 0.72 mmol) in benzene (3.0 ml) was treated with tris(triphenylphosphine)rhodium chloride (150 mg) and the mixture was stirred under an H_2 atmosphere at room temperature for 5 h. After addition of EtOH (2 ml) to the reaction mixture, the whole was filtered to remove the catalyst. The filtrate was concentrated under reduced pressure to give a product. Purification of the product by column chromatography (SiO_2, 5 g, benzene : EtOAc = 10 : 1) afforded **7** (63 mg, 26%) and **8** (103 mg, 50%).

7: A colorless oil. IR ($CHCl_3$) cm^{-1}: 3350, 1672, 1633, 1511. UV λ_{max}^{MeOH} nm (ε): 210 (10300). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.90 (3H, t, J = 7.5 Hz, 14-H_3), 0.91 (6H, d, J = 6.6 Hz, 2′-CH_3 × 2), 1.24 (18H, br s, 5-H_2—13-H_2), 1.81 (1H, m, 2′-H), 2.15 (2H, m, 4-H_2), 3.13 (2H, dd, J = 6.6, 6.6 Hz, 1′-H_2), 5.59 (1H, br s, amide proton), 5.75 (1H, d, J = 15.2 Hz, 2-H), 6.80 (1H, dt, J = 15.2, 7.5 Hz, 3-H). EI-MS *m/z* (%): 281 (M^+, 28), 209 (100). High-resolution EI-MS *m/z*: Calcd for $C_{18}H_{35}NO$: 281.2716. Found: 281.2718 (M^+).

8: A white amorphous solid. IR ($CHCl_3$) cm^{-1}: 3400, 1655, 1500. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.76 (3H, t, J = 6.9 Hz, 14-H_3), 0.81 (6H, d, J = 6.6 Hz, 2′-CH_3 × 2), 1.15 (22H, br s, 3-H_2—13-H_2), 1.66 (1H, m, 2′-H), 2.07 (2H, t, J = 7.6 Hz, 2-H_2), 2.98 (2H, dd, J = 6.6, 6.6 Hz, 1′-H_2), 5.45 (1H, br s, amide proton). EI-MS *m/z* (%): 283 (M^+, 4), 115 (100). High-resolution EI-MS *m/z*: Calcd for $C_{18}H_{37}NO$: 283.2873. Found: 283.2872 (M^+).

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