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Journal of Natural Products 2009, 72, 2, 298-300 (Note)

Publication Date (Web): January 27, 2009

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ABSTRACT

3-Alkylpyridinium Alkaloids from the Pacific Sponge *Haliclona* sp.

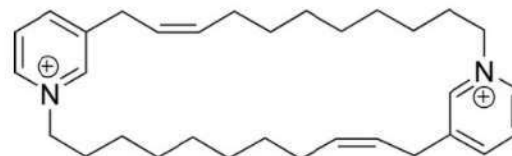
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ABSTRACT

Alstiphyllanines A-D, Indole Alkaloids from *Alstonia macrophylla*

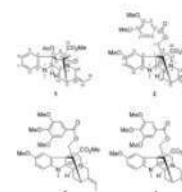
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Journal of Natural Products 2009, 72, 2, 304-307 (Note)

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ABSTRACT

Cytotoxic Triterpenoid Alkaloids from *Buxus microphylla*

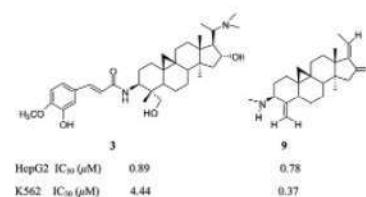
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Journal of Natural Products 2009, 72, 2, 312-311 (Note)

Publication Date (Web): January 9, 2009

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ABSTRACT

Piperidine and Tetrahydropyridine Alkaloids from *Lobelia siphilitica* and *Hippobroma longiflora*

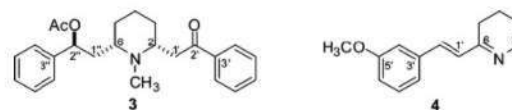
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ABSTRACT

Structural Revision of Stemoburkilline from an *E*-Alkene to a *Z*-Alkene

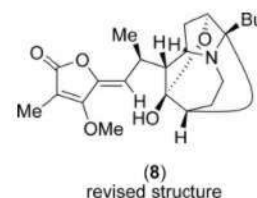
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Journal of Natural Products 2009, 72, 2, 316-318 (Note)

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ABSTRACT

Bioactive Sulfated Sesterterpene Alkaloids and Sesterterpene Sulfates from the Marine Sponge *Fasciospongia* sp.

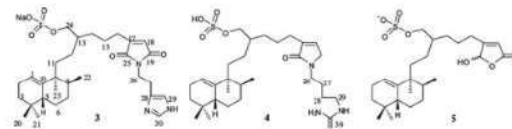
Guangmin Yao, Tamara P. Kondratyuk, Ghee T. Tan, John M. Pezzuto, and Leng Chee Chang*

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Publication Date (Web): January 29, 2009

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ABSTRACT



Alstiphyllanines A–D, Indole Alkaloids from *Alstonia macrophylla*

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Four new alkaloids, alstiphyllanines A–D (**1**–**4**), were isolated from *Alstonia macrophylla*, and their structures were determined by MS and 2D NMR analyses. Alkaloids **1**–**4** showed moderate antiplasmodial activity against *Plasmodium falciparum* and vasorelaxant activity against phenylephrine-induced contraction of isolated rat aorta.

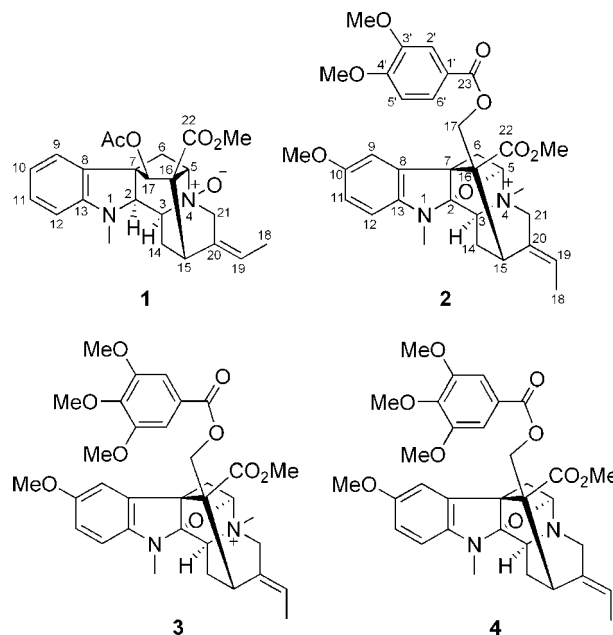
Alstonia species, which are widely distributed in tropical regions of Africa and Asia, are well-known rich sources of unique heterocyclic alkaloids having monoterpene indole skeletons and have attracted great interest from biogenetic¹ and biological points of view² due to their anticancer, antibacterial, anti-inflammatory, antitussive, and antimalarial properties.

Recently, several new indole alkaloids were isolated from extracts of *Alstonia* and *Kopsia* species collected in Indonesia and Malaysia.³ With an aim to isolate additional alkaloids with biological activities, purification of extracts of *Alstonia macrophylla* Wall. ex G. Don (Apocynaceae) collected in Indonesia led to four new alkaloids (**1**–**4**). This paper describes the isolation and structure elucidation of **1**–**4**, their antiplasmodial activity against *Plasmodium falciparum*, and their vasorelaxant activity against phenylephrine-induced contraction of isolated rat aorta.

Leaves of *A. macrophylla* were extracted with MeOH, and the extract was partitioned between EtOAc and 3% aqueous tartaric acid. Water-soluble materials, adjusted to pH 9 with saturated Na₂CO₃, were extracted with CHCl₃. The CHCl₃-soluble materials were subjected to an LH-20 column (CHCl₃/MeOH, 1:1) followed by a silica gel column (CHCl₃/MeOH, 1:0 → 0:1). The eluted fractions were further separated by C₁₈ HPLC (MeOH/H₂O/TFA) to afford **1** (5.5 mg, 0.0015%), **2** (1.4 mg, 0.0004%), **3** (3.9 mg, 0.0011%), and **4** (14.1 mg, 0.0039%), together with known alkaloids, vincamedine,⁴ burnamine-17-*O*-3',4',5'-trimethoxybenzoate,⁵ and 10-methoxy-*N*(1)-burnamine-17-*O*-veratrate.⁶

Compound **1**, [α]_D²⁴ –83 (c 1.0, MeOH), showed a pseudomolecular ion peak at *m/z* 425 (M + H)⁺ in the ESIMS, and the molecular formula C₂₄H₂₈N₂O₅ was established by HRESIMS [*m/z* 425.2063 (M + H)⁺]. IR absorptions implied the presence of carbonyl (1750 and 1680 cm⁻¹) functionalities. The ¹H NMR data (Table 1) showed the presence of four aromatic protons, an ethylidene side chain, a methyl ester, an acetyl, and an *N*-methyl group. The ¹³C NMR data (Table 2) revealed 24 carbon signals due to three sp² quaternary carbons, five sp² methines, two ester carbonyls, two sp³ quaternary carbons, five sp³ methines, three sp³ methylenes, and four methyl groups.

Partial structures C-9 to C-12, C-5 to C-6, C-2 to C-15, and C-18 to C-19 were deduced from detailed analysis of the ¹H–¹H COSY spectrum of **1**. The HMBC cross-peaks of H₃-18 to C-20 and H-19 to C-15 placed the ethylidene side chain at C-20. Connections to the indoline ring were elucidated by HMBC correlations for H-9 to C-7 and *N*-Me to C-2 and C-13. The HMBC correlations for H-17 to C-5 and C-6 and H-2 to C-17 indicated that **1** was an ajmaline-type alkaloid. Low-field chemical shifts at C-3, C-5, and



C-21 around *N*-4 (δ_C 70.2, 77.1, and 66.8, respectively) suggested that **1** was an *N*-oxide at *N*-4. Thus, **1** was an *N*-oxide of vincamedine.⁴ The relative stereochemistry of **1** was elucidated by NOESY correlations. The NOESY correlations of H-18 to H-21 and H-19 to H-15 indicated that the ethylidene side chain was *Z*. In addition, H-3 correlated with both H-2 and H-14a, and H-14b with H-17, indicating that H-2 was α -oriented and H-17 was β -oriented. Compound **1** was named alstiphyllanine A, and the absolute configuration was assigned by treatment of vincamedine⁴ with *m*-CPBA to afford the *N*-oxide whose spectroscopic data and specific rotation were identical with those of alstiphyllanine A (**1**).

Compound **2** showed a molecular ion peak at *m/z* 591 (M)⁺ in the ESIMS, and the molecular formula C₃₃H₃₉N₂O₈ was established by HRESIMS. The IR spectrum suggested the presence of carbonyl (1735 and 1715 cm⁻¹) groups. The ¹H NMR data (Table 1) indicated six aromatic protons, an ethylidene side chain, a methyl ester function, and three methoxy groups. The ¹³C NMR (Table 2) spectrum of **2** disclosed 33 carbon signals assigned to two ester carbonyls, seven sp² quaternary carbons, three sp³ quaternary carbons, seven sp² methines, three sp³ methines, four sp³ methylenes, and six methyls attached to nitrogen and/or oxygen atoms. HMBC cross-peaks of H₃-18 to C-20 and H-19 to C-15 indicated that the ethylidene side chain was at C-20. The position of each methyl group was confirmed by HMBC correlations of each *O*-Me to C-10, C-22, C-3', and C-4', *N*(1)-Me to C-2 and C-13, and *N*(4)-Me to C-3, C-5, and C-21. The HMBC correlations for H₂-6 and H₂-17 to C-7 indicated that **2** had a picraline-type skeleton.

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Table 1. ^1H NMR Data (J , Hz) of Alstiphyllanines A–D (**1–4**) in CD_3OD at 300 K^a

| | 1 | 2 | 3 | 4 |
|------------------|-----------------------|----------------|----------------|----------------------|
| 2 | 3.63 (brs) | | | |
| 3 | 4.63 (brs) | 4.23 (brs) | 4.23 (brs) | 4.26 (d, 3.8) |
| 5 | 4.69 (brs) | 5.42 (brs) | 5.43 (brs) | 5.57 (d, 3.2) |
| 6 | 2.74 (m) | 3.57 (d, 16.1) | 3.55 (d, 15.4) | 3.40 (d, 15.6) |
| | 2.70 (m) | 2.65 (d, 16.1) | 2.63 (d, 15.4) | 2.63 (dd, 15.6, 3.2) |
| 9 | 7.12 (d, 7.0) | 7.04 (s) | 7.0304 (s) | 7.04 (d, 2.1) |
| 10 | 6.82 (m) | | | |
| 11 | 7.21 (dd, 7.6, 7.5) | 6.42 (d, 7.6) | 6.38 (d, 8.0) | 6.39 (dd, 8.5, 2.1) |
| 12 | 6.79 (m) | 6.61 (d, 7.6) | 6.58 (d, 8.0) | 6.57 (d, 8.5) |
| 14 | 2.89 (m) | 2.50 (d, 16.0) | 2.28 (d, 15.3) | 2.35 (d, 15.6) |
| | 2.23 (dd, 12.0, 11.4) | 2.29 (d, 16.0) | 2.50 (d, 15.3) | 2.25 (d, 15.6) |
| 15 | 3.33 (m) | 3.65 (brs) | 3.67 (brs) | 3.71 (brs) |
| 17 | 5.61 (s) | 4.14 (d, 11.1) | 4.07 (d, 10.8) | 4.07 (d, 11.2) |
| | | 4.83 (m) | 4.9083 (m) | 4.89 (d, 11.2) |
| 18 | 1.62 (d, 6.4) | 1.75 (d, 7.0) | 1.74 (d, 6.1) | 1.75 (d, 6.9) |
| 19 | 5.58 (m) | 5.7658 (m) | 5.7658 (m) | 5.7858 (m) |
| 21 | 4.68 (m) | 4.30(m) | 4.32(m) | 4.01 (d, 17.2) |
| | 4.68 (m) | 4.30(m) | 4.36(m) | 4.20 (d, 17.2) |
| Ac | 1.89 (s) | | | |
| COOMe | 3.75 (s) | 3.77(s) | 3.79(s) | 3.79(s) |
| 10- <i>O</i> -Me | | 3.34 (s) | 3.28(s) | 3.27(s) |
| 3'- <i>O</i> -Me | | 3.88 (s) | 3.88(s) | 3.89(s) |
| 4'- <i>O</i> -Me | | 3.88 (s) | 3.81(s) | 3.81(s) |
| 5'- <i>O</i> -Me | | | 3.88 (s) | 3.89(s) |
| <i>N</i> (1)Me | 2.69 (s) | 3.00(s) | 2.99(s) | 2.99(s) |
| <i>N</i> (4)Me | | 3.28 (s) | 3.28(s) | |
| 2' | | 7.10 (s) | 6.87(s) | 6.88(s) |
| 5' | | 6.94 (d, 8.2) | | |
| 6' | | 7.24 (d, 8.2) | 6.87 (s) | 6.88(s) |

^a δ in ppm.**Table 2.** ^{13}C NMR Data of Alstiphyllanines A–D (**1–4**) in CD_3OD at 300 K^a

| | 1 | 2 | 3 | 4 |
|------------------|-------|-------|-------|-------|
| 2 | 70.3 | 113.4 | 113.4 | 112.1 |
| 3 | 70.2 | 64.8 | 64.8 | 53.0 |
| 5 | 77.1 | 99.2 | 99.2 | 90.0 |
| 6 | 32.4 | 41.5 | 41.5 | 41.5 |
| 7 | 56.4 | 51.9 | 51.8 | 52.8 |
| 8 | 127.4 | 134.4 | 134.4 | 134.7 |
| 9 | 124.7 | 115.9 | 116.4 | 116.6 |
| 10 | 121.2 | 156.5 | 156.4 | 156.3 |
| 11 | 130.5 | 112.9 | 112.3 | 112.1 |
| 12 | 111.3 | 111.2 | 111.2 | 111.0 |
| 13 | 155.0 | 144.7 | 144.7 | 144.9 |
| 14 | 22.7 | 21.0 | 21.0 | 20.9 |
| 15 | 36.6 | 34.3 | 34.3 | 35.6 |
| 16 | 62.0 | 57.2 | 57.2 | 57.4 |
| 17 | 74.9 | 67.7 | 68.1 | 68.5 |
| 18 | 12.9 | 14.0 | 14.9 | 14.1 |
| 19 | 123.5 | 127.4 | 127.4 | 128.1 |
| 20 | 128.7 | 128.9 | 128.8 | 128.2 |
| 21 | 66.8 | 58.1 | 58.1 | 46.1 |
| 22 | 169.9 | 172.5 | 172.5 | 172.6 |
| 23 | 169.6 | 166.0 | 165.5 | 165.5 |
| 24 | 20.5 | | | |
| <i>N</i> (1)Me | 34.8 | 30.5 | 30.5 | 30.4 |
| <i>N</i> (4)Me | | 54.8 | 54.8 | |
| COOMe | 53.5 | 52.8 | 52.8 | 52.8 |
| 10- <i>O</i> -Me | | 55.5 | 55.5 | 55.5 |
| 3'- <i>O</i> -Me | | 56.3 | 56.6 | 56.5 |
| 4'- <i>O</i> -Me | | 56.5 | 61.1 | 61.1 |
| 5'- <i>O</i> -Me | | | 56.6 | 56.5 |
| 1' | | 122.4 | 125.1 | 125.2 |
| 2' | | 113.3 | 107.9 | 107.8 |
| 3' | | 149.9 | 154.1 | 154.1 |
| 4' | | 154.8 | 143.4 | 143.3 |
| 5' | | 111.7 | 154.1 | 154.1 |
| 6' | | 124.7 | 107.9 | 107.8 |

^a δ in ppm.

The relative stereochemistry of **2** was elucidated by NOESY correlations. NOESY correlations of H-19 to H-21 and H₃-18 to

H-15 indicated that the geometry of the C19–C20 double bond was *E*. NOESY correlations of *N*(4)-Me to H-5, H-14 to H-17, and H-18 to methoxy protons at C-22 indicated that C-22 and *N*(4)-Me were α -oriented. Thus, the structure of **2** was assigned as shown, and it was named alstiphyllanine B. Treatment of 10-methoxy-*N*(1)-burnamine-17-*O*-veratrate⁶ with methyl iodide afforded an *N*-methyl derivative, whose spectroscopic data and specific rotation were identical with **2** and confirmed the absolute configuration.

Compound **3**, $[\alpha]_{\text{D}}^{24} -32$ (*c* 1.0, MeOH), had the molecular formula $\text{C}_{34}\text{H}_{41}\text{N}_2\text{O}_9$ as established by HRFABMS, larger than **2** by a CH_2O unit. ^1H and ^{13}C NMR data of **3** (Tables 1 and 2) were analogous to those of **2** with a *N*(4)-Me-picraline-type skeleton, although one aromatic proton of the veratrate of **2** was not observed for **3**. The gross structure of **3** was elucidated by 2D NMR (^1H – ^1H COSY, HOHAHA, HMQC, and HMBC) data, and the relative stereochemistry of **3** (alstiphyllanine C) was assigned as **2** with a 3,4,5-trimethoxybenzoate instead of a veratrate at C-17.

The molecular formula, $\text{C}_{33}\text{H}_{38}\text{N}_2\text{O}_9$, of compound **4**, $[\alpha]_{\text{D}}^{24} -54$ (*c* 1.0, MeOH), was established by HRFABMS, smaller than that of **3** by a CH_3 unit. Analyses of ^1H – ^1H COSY, HOHAHA, HMQC, and HMBC spectra of **4** indicated a picraline-type backbone without the *N*(4)-Me. *N*-Methylation of **4** with methyl iodide afforded **3**, and **4** was named alstiphyllanine D.

Malaria caused by parasites of the genus *Plasmodium* is one of the leading infectious diseases in many tropical and some temperate regions.⁷ The emergence of widespread chloroquine-resistant and multiple-drug-resistant strains of malaria parasites has prompted the need for development of new therapeutic agents against malaria.⁸ Alstiphyllanines A–D (**1–4**) showed moderate in vitro antiparasitic activity against *Plasmodium falciparum* 3D7 (IC₅₀ **1**, 6.85 $\mu\text{g}/\text{mL}$; **2**, 0.34 $\mu\text{g}/\text{mL}$; **3**, 6.20 $\mu\text{g}/\text{mL}$; **4**, 2.75 $\mu\text{g}/\text{mL}$) and no cytotoxicity against HeLa cells (IC₅₀ >25 $\mu\text{g}/\text{mL}$ for **1–4**). Alstiphyllanines B–D (**2–4**), possessing picraline-type skeletons, which arise through a corynanthe-type skeleton,⁹ were more active than alstiphyllanine A (**1**), with an ajmaline-type skeleton.⁹

Alstiphyllanines **1–4** also showed a slow relaxation activity against phenylephrine (PE, 3×10^{-7} M)-induced contractions of

thoracic rat aortic rings with endothelium (**1**, 70%; **2**, 35%; **3**, 40%; **4**, 42% at 3×10^{-5} M, respectively).

Experimental Section

General Experimental Procedures. ^1H and 2D NMR spectra were recorded on a Bruker AV 400 spectrometer, and chemical shifts were referenced to the residual solvent peaks (δ_{H} 3.31 and δ_{C} 49.0 for methanol- d_4). Standard pulse sequences were employed for the 2D NMR experiments. ^1H - ^1H COSY, HOHAHA, and NOESY spectra were measured with spectral widths of both dimensions of 4800 Hz, and 32 scans with two dummy scans were accumulated into 1K data points for each of 256 t_1 increments. NOESY spectra in the phase-sensitive mode were measured with a mixing time of 800 ms. For HMQC spectra in the phase-sensitive mode and HMBC spectra, a total of 256 increments of 1K data points were collected. For HMBC spectra with Z-axis PFG, a 50 ms delay time was used for long-range C-H coupling. Zero-filling to 1K for F_1 and multiplication with squared cosine-bell windows shifted in both dimensions were performed prior to 2D Fourier transformation.

Material. Leaves of *Alstonia macrophylla* were collected at Purwodadi Botanical Garden in 2006. The botanical identification was made by Ms. Sri Wuryanti, Purwodadi Botanical Garden, Indonesia. A voucher specimen has been deposited at Purwodadi Botanical Garden, Pasuruan, Indonesia.

Extraction and Isolation. The air-dried pulverized leaves of *A. macrophylla* (363.5 g) were extracted with MeOH. The MeOH extract (43.8 g) was treated with 3% tartaric acid (pH 2) and then partitioned with EtOAc. The aqueous layer was treated with saturated Na_2CO_3 (aq) to pH 9 and extracted with CHCl_3 to give an alkaloidal fraction (2.06 g). The alkaloidal fraction was purified by LH-20 column chromatography (CC) ($\text{CHCl}_3/\text{MeOH}$, 1:0) and SiO_2 CC ($\text{CHCl}_3/\text{MeOH}$, 1:0 \rightarrow 0:1), and the fraction eluted by MeOH was purified by ODS HPLC ($\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{CF}_3\text{CO}_2\text{H}$, 39:61:0.1; flow rate, 2 mL/min; UV detection at 254 nm) to afford **1** (5.5 mg, 0.0015%), **2** (1.4 mg, 0.0004%), **3** (3.9 mg, 0.0011%), and **4** (14.1 mg, 0.0039%), together with known alkaloids, vincamedine,⁴ burnamine-17-*O*-3',4',5'-trimethoxybenzoate,⁵ and 10-methoxy-*N*(1)-burnamine-17-*O*-veratrate.⁶

Alstiphyllanine A (1): brown, amorphous solid; $[\alpha]_{\text{D}}^{24}$ -83 (c 1.0, MeOH); IR (film) ν_{max} 1750 and 1680 cm^{-1} ; UV (MeOH) λ_{max} 290 (ϵ 1400), 245 (ϵ 3200), and 202 nm (ϵ 13 000); ^1H and ^{13}C NMR data (Tables 1 and 2); ESIMS m/z 425 ($\text{M} + \text{H}^+$); HRESIMS m/z 425.2063 [$\text{M} + \text{H}^+$], (calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_5$, 425.2076).

Alstiphyllanine B (2): brown, amorphous solid; $[\alpha]_{\text{D}}^{24}$ -88 (c 1.0, MeOH); IR (film) ν_{max} 1735 and 1715 cm^{-1} ; UV (MeOH) λ_{max} 295 (ϵ 4300), 265 (ϵ 5500), 243 (ϵ 6700), 220 (ϵ 1400), and 202 nm (ϵ 2400); ^1H and ^{13}C NMR, see Tables 1 and 2; ESIMS m/z 591 (M^+); HRESIMS m/z 591.2725 [M^+], (calcd for $\text{C}_{33}\text{H}_{39}\text{N}_2\text{O}_8$, 591.2706).

Alstiphyllanine C (3): brown, amorphous solid; $[\alpha]_{\text{D}}^{24}$ -32 (c 1.0, MeOH); IR (film) ν_{max} 1735 and 1715 cm^{-1} ; UV (MeOH) λ_{max} 300 (ϵ 3000), 270 (ϵ 4800), 240 (ϵ 6000), and 202 nm (ϵ 26 000); ^1H and ^{13}C NMR, see Tables 1 and 2; ESIMS m/z 621 (M^+); HRESIMS m/z 621.2806 [M^+] (calcd for $\text{C}_{34}\text{H}_{41}\text{N}_2\text{O}_9$, 621.2812).

Alstiphyllanine D (4): brown, amorphous solid; $[\alpha]_{\text{D}}^{24}$ -54 (c 1.0, MeOH); IR (film) ν_{max} 1735 and 1715 cm^{-1} ; UV (MeOH) λ_{max} 300 (ϵ 2700), 268 (ϵ 4400), 245 (ϵ 5400), and 200 nm (ϵ 25 000); ^1H and ^{13}C NMR, see Tables 1 and 2; ESIMS m/z 607 ($\text{M} + \text{H}^+$); HRESIMS m/z 607.2678 [$\text{M} + \text{H}^+$] (calcd for $\text{C}_{33}\text{H}_{39}\text{N}_2\text{O}_9$, 607.2656).

Conversion of Vincamedine to Alstiphyllanine A (1). To a solution of vincamedine (1.3 mg) in CHCl_3 (0.3 mL) was added *m*-CPBA (1.0 mg) and Na_2CO_3 , and the mixture was kept at 4 °C for 10 min. After evaporation, the residue was applied to a silica gel column ($\text{CHCl}_3/\text{MeOH}$, 9:1) to give a compound (0.7 mg) whose spectroscopic data and $[\alpha]_{\text{D}}$ value were identical with those of natural alstiphyllanine A (**1**).

Conversion of 10-Methoxy-*N*(1)-burnamine-17-*O*-veratrate to Alstiphyllanine B (2). To a solution of 10-methoxy-*N*(1)-burnamine-17-*O*-veratrate (0.7 mg) in acetonitrile (0.2 mL) was added MeI (20 μL), and the mixture was kept at 70 °C for 30 min. After evaporation, a compound (0.4 mg) whose spectroscopic data and $[\alpha]_{\text{D}}$ value were identical with those of natural alstiphyllanine B (**2**) was obtained.

Conversion of 4 to 3. A solution of **4** (1.3 mg) and MeI (0.1 mL) in acetonitrile (0.2 mL) was heated at 70 °C for 30 min. Removal of the solvent afforded the compound **3** (1.4 mg) as a brown, amorphous solid, whose spectroscopic data and $[\alpha]_{\text{D}}$ value were identical with those of natural alstiphyllanine C (**3**).

Antiplasmodial Activity. Human malaria parasites were cultured according to the method of Trager et al.¹¹ The antimalarial activity of the isolated compounds was determined by the procedure described by Budimulya et al.¹² In brief, stock solutions of the samples were prepared in DMSO (final DMSO concentrations of <0.5%) and were diluted to the required concentration with complete medium (RPMI 1640 supplemented with 10% human plasma, 25 mM HEPES, and 25 mM NaHCO_3) until the final concentrations of samples in culture plate wells were 10, 1, 0.1, 0.01, and 0.001 $\mu\text{g}/\text{mL}$. The malarial parasite *P. falciparum* 3D7 clone was propagated in 24-well culture plates. Growth of the parasite was monitored by making a blood smear fixed with MeOH and stained with Geimsa stain. The antimalarial activity of each compound was expressed as an IC_{50} value, defined as the concentration of the compound causing 50% inhibition of parasite growth relative to an untreated control.

The percentage of growth inhibition was expressed according to the following equation: Growth inhibition % = $100 - [(\text{test parasitaemia}/\text{control parasitemia}) \times 100]$. Chloroquine: IC_{50} 0.0061 $\mu\text{g}/\text{mL}$.

Vasodilation Assay.¹⁰ A male Wistar rat weighting 260 g was sacrificed by bleeding from carotid arteries under anesthesia. A section of the thoracic aorta between the aortic arch and the diaphragm was removed and placed in oxygenated, modified Krebs-Henseleit solution (KHS: 118.0 mM NaCl, 4.7 mM KCl, 25.0 mM NaHCO_3 , 1.8 mM CaCl_2 , 1.2 mM NaH_2PO_4 , 1.2 mM MgSO_4 , and 11.0 mM glucose). The aorta was cleaned of loosely adhering fat and connective tissue and cut into ring preparations 3 mm in length. The tissue was placed in a well-oxygenated (95% O_2 , 5% CO_2) bath of 5 mL of KHS solution at 37 °C with one end connected to a tissue holder and the other to a force-displacement transducer (Nihon Kohden, TB-611T). The tissue was equilibrated for 60 min under a resting tension of 1.0 g. During this time the KHS in the tissue bath was replaced every 20 min.

After equilibration, each aortic ring was contracted by treatment with 3×10^{-7} M phenylephrine (PE). The presence of functional endothelial cells was confirmed by demonstrating relaxation to 10^{-5} M acetylcholine (ACh), and aortic ring in which 80% relaxation occurred was regarded as tissue with endothelium. When the PE-induced contraction reached a plateau, each sample was added.

The animal experimental studies were conducted in accordance with the Guiding Principles for the Care and Use of Laboratory Animals, Hoshi University, and under the supervision of the Committee on Animal Research of Hoshi University, which is accredited by the Ministry of Education, Science, Sports Culture, and Technology of Japan.

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