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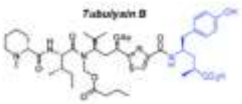

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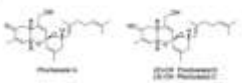

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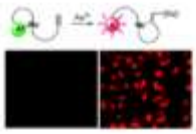

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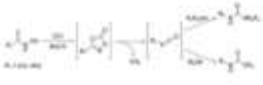

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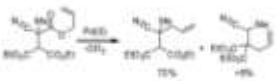

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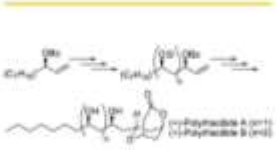

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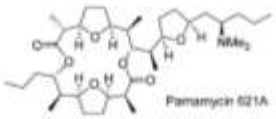

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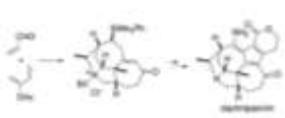

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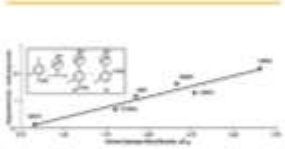

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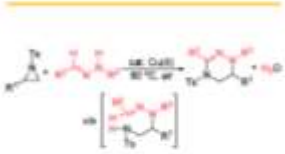

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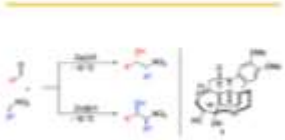

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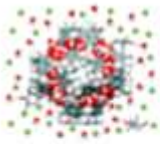

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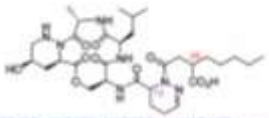

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15 examples, yields: 85-100%

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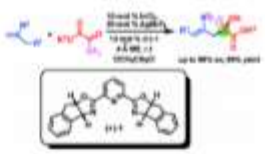

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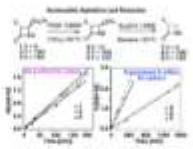

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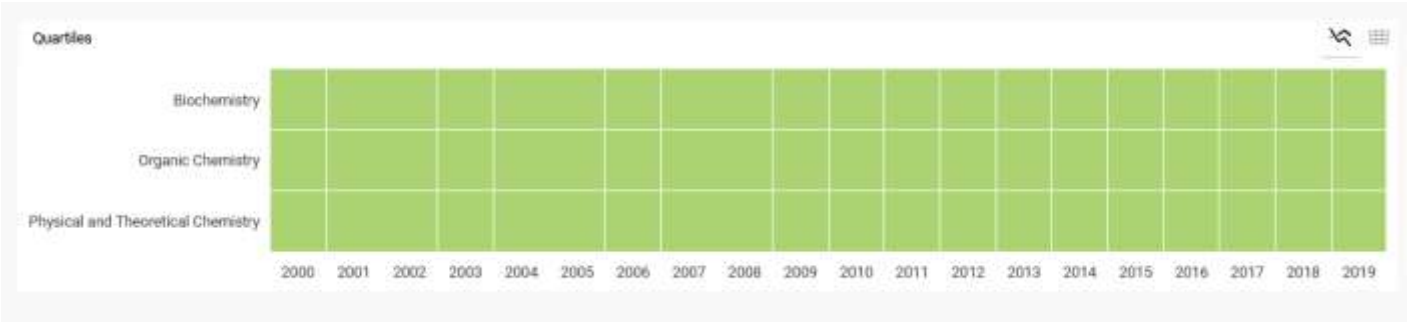
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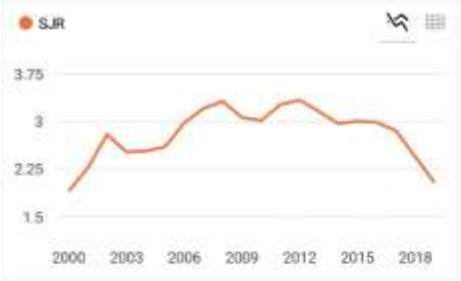
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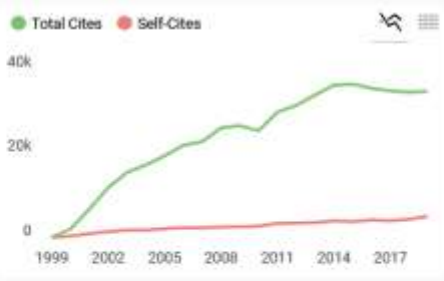
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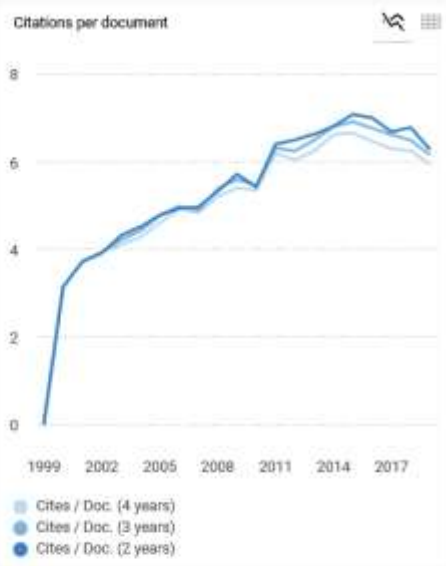
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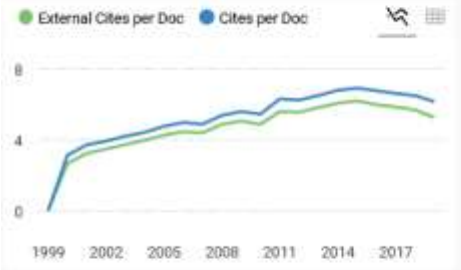
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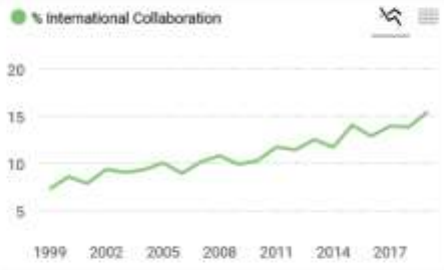
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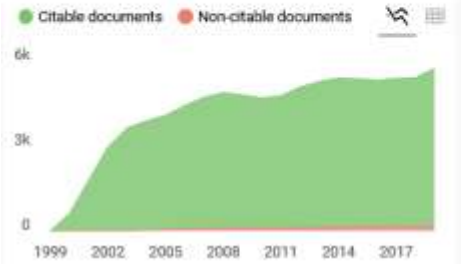
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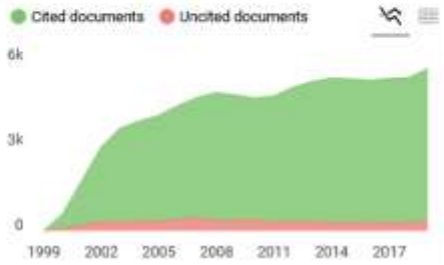
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Alasmontamine A, A First Tetrakis Monoterpene Indole Alkaloid from *Tabernaemontana elegans*

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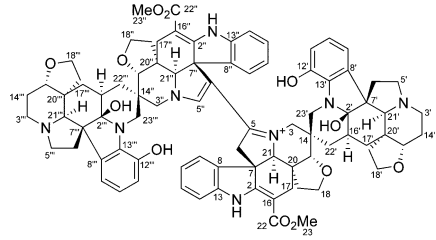
ABSTRACT



alasmontamine A (**1**)

A novel tetrakis monoterpene indole alkaloid, alasmontamine A (1) consisting of bis-vobtusine-type skeletons, was isolated from the leaves of *Tabernaemontana elegans*. The structure including the relative stereochemistry was elucidated on the basis of spectroscopic data. Alasmontamine A (1) exhibited moderate cell growth inhibitory activity against HL-60 cells.

Tabernaemontana elegans Stapf is a member of the Apocynaceae family that occurs in tropical or subtropical regions including Indonesia, Malaysia, and Africa. Traditionally, the roots have been used as a remedy for pulmonary diseases in Africa.[1] *Tabernaemontana* species so far have been shown to produce various skeletal types of indole alkaloids, including iboga-type alkaloids such as ibogamine,[2] aspidosperma-type alkaloids such as taberhanine,[3] and vobasinyl-ibogan bisindole alkaloids such as conodiparine A.[4] Recently, we isolated a new type of bisindole alkaloids as biscarpamontamines A and B from *T. sphaerocarpa*.[5] In our search for structurally and biogenetically interesting alkaloids from tropical plants found in Indonesia, a first tetrakis monoterpene indole alkaloid, alasmontamine A (**1**) consisting of tetrakis aspidosperma-type skeletons, was isolated from the leaves of *T. elegans*, together with vobtusine[6] and vobtusine lactone.[7] In this paper, we describe the isolation and structure elucidation of the new alkaloid, alasmontamine A (**1**).

Alasmontamine A (**1**),[8,9] yellow amorphous solid, $[\alpha]^{27}_{D}$ −311 (*c* 1.0, MeOH), showed molecular formula, $C_{84}H_{91}N_8O_{12}$, which was determined by HRESITOFMS [*m*/*z*

[†] Hoshi University.
[‡] Airlangga University.

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702.3415 (M + H)$^{2+}$, Δ +0.3 mmu]. IR absorptions (3440 and 1670 cm^{-1}) implied the presence of NH and/or OH, and conjugated ester carbonyl functionalities. ^{1}H and ^{13}C NMR, HMQC, and HMBC spectra revealed 84 carbon signals due to 18 sp^2 and 12 sp^3 quaternary carbons, 15 sp^2 and 10 sp^3 methines, 27 sp^3 methylenes, and 2 methyl groups (303 K by 600 MHz cryo probe). Among them, 8 sp^3 methylenes (δ_C 55.0; δ_H 4.11, and 4.26, δ_C 48.6; δ_H 2.37 and 2.88, δ_C 51.6; δ_H 2.31 and 3.09, δ_C 50.7; δ_H 3.71 and 3.83, δ_C 53.5; δ_H 3.82 and 3.92, δ_C 48.6; δ_H 2.37 and 2.88, δ_C 51.6; δ_H 2.31 and 3.09, and δ_C 45.2; δ_H 3.19, and 4.73), 1 sp^2 methine (δ_C 158.7; δ_H 7.68), 4 sp^3 methines (δ_C 76.2; δ_H 4.49, δ_C 64.7; δ_H 2.80, δ_C 72.1; δ_H 4.29, δ_C 64.7; δ_H 2.79), 7 sp^2 quaternary carbons (δ_C 161.4, 144.8, 168.2, 136.1, 158.7, 144.7, and 136.9), and 2 sp^3 quaternary carbons (δ_C 93.6 and 93.2) were ascribed to those bearing a nitrogen atom. Since 18 out of 44 elements of unsaturation were accounted for, **1** was inferred to possess 26 rings.

The gross structure of **1** was elucidated by analyses of 2D NMR data including ^{1}H−^{1}H COSY, HOHAHA, HSQC, and HMBC spectra in CD_3OD at 313 K by using a 920 MHz NMR spectrometer (Figure 1). Each pair of the observed ^{1}H and ^{13}C NMR signals seemed to be due to each half moiety (parts A and B) of a dimeric compound. In part A, connectivities of C-9−C-12, C-18 to C-19, C-3′−C-15′, C-5′ to C-6′, C-9′−C-11′, C-18′−C-19′, and C-17′−C-22′ were deduced from ^{1}H−^{1}H COSY and HOHAHA correlations. In the HMBC spectrum, long-range ^{1}H−^{13}C correlations indicated that part A possessed a 12′-*O*-demethylvobtusine-type framework with an iminium functionality at C-5 (δ_C 168.2). The presence of an iminium carbon (C-5) was elucidated by HMBC correlations for H_2-6 and H-21 to C-5. In addition, the ^{13}C signals at 6- and 21-positions around the iminium functionality were observed at lower field due to deshielding effects (Table 1) compared with those of vobtusine. The relative configurations at C-7, 15, 20, 21, 7′, 15′, 16′, 20′, and 21′ in part A were based on NOESY correlations of H-9 and H-19a/H-21, H-15/H_2-17, H-9′ and H-18′b/H-21′, and H-16′/H-19′b, while the 3,3′-spirobipiperidine (C-3, 14, 15, 20, 21, N, 2′, 16′, 22′, 23′, and N) ring adopted a boat−chair conformation that was supported by NOESY correlations as shown in Figure 2. Furthermore the β-configuration of the OH group at C-2′ was deduced from the upfield chemical shift of C-6′ (δ_C 30.6) by the γ-gauche effect.[6,7]

On the other hand, detailed analyses of the HMBC spectrum of **1** indicated that part B possessed a 12′-*O*-

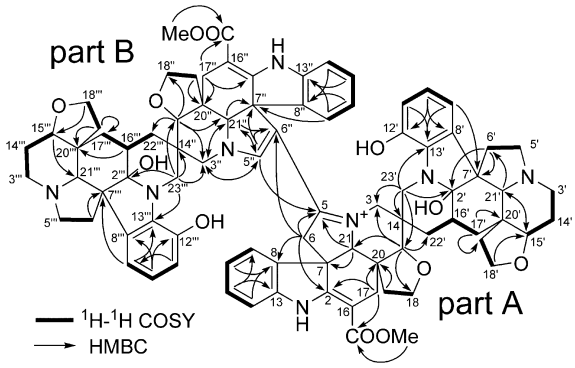


Figure 1. Selected 2D NMR correlations for alasmontamine A (**1**).

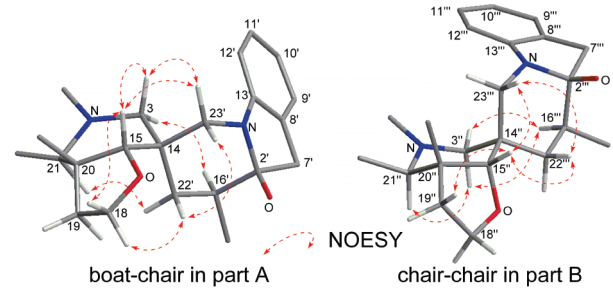


Figure 2. Selected NOESY correlations around two spiro carbons (C-14 and C-14′) in parts A and B of **1**.

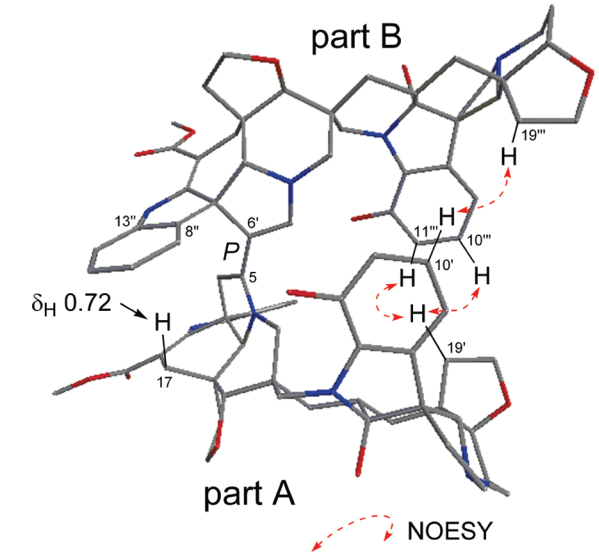


Figure 3. Selected NOESY correlations and the relative stereochemistry for alasmontamine A (**1**).

(8) The leaves of *T. elegans* collected at Alas Purwo, Indonesia in 2007 were extracted with MeOH, and the extract was partitioned between EtOAc and 3% tartaric acid. The aqueous layer was adjusted at pH 9 with saturated Na_2CO_3 aq and extracted with $CHCl_3$. $CHCl_3$-soluble alkaloidal materials were subjected to a silica gel column ($CHCl_3$/MeOH) twice followed by an LH-20 column ($CHCl_3$/MeOH) to afford alasmontamine A (**1**, 0.0005%) together with known alkaloids, vobtusine[6] and vobtusine lactone.[7]

(9) Alasmontamine A (**1**): yellow amorphous solid; $[\alpha]^{27}_{D}$ −311 (*c* 1.0, MeOH); IR (KBr) ν_{max} 3440, 2940, 1670, and 1630 cm^{-1}; UV (MeOH) λ_{max} 365 (ε 17 800), 329 (20 400), 295 (19 700), 259 (17 700), and 218 (55 400) nm; CD (MeOH) λ_{max} 373 (θ −22 100), 338 (−13 100), 325 (−17 900), 295 (4 500), 280 (4 100), 265 (13 600), 250 (5 600), and 225 (33 100) nm; ^{1}H and ^{13}C NMR (Table 1); ESIMS (pos.) *m*/*z* 702 (M + H)$^{2+}$; HRESITOFMS *m*/*z* 702.3415 (M + H)$^{2+}$, calcd for $C_{84}H_{92}N_8O_{12}$ 1404.6824.

Table 1. ^{1}H and ^{13}C NMR Data of Alasmontamine A (**1**) in CD_3OD

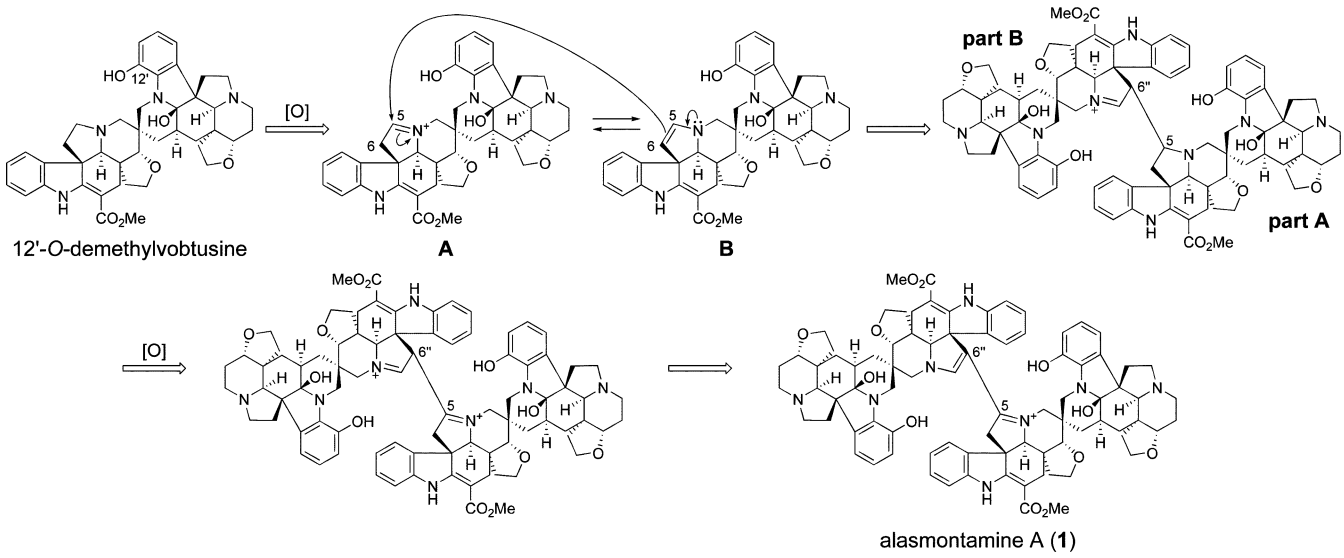
unit A				unit B			
position	δ_H[a]	δ_C[b]	HMBC[a]	position	δ_H[a]	δ_C[b]	HMBC[a]
2		161.4	6b, 17b	2″		158.7	17″
3a	4.11 (1H, d, 13.6)	55.0	22′b, 23′ [b]	3″a	3.82 (1H, m)	53.5	5″, 15″, 22‴,[b] 23‴
3b	4.26 (1H, d, 13.6)			3″b	3.92 (1H, m)		
5		168.2	6a,[b] 6b, 21, 5″ [b]	5″	7.68 (1H, s)	158.7	3″,[b] 21″
6a	2.76 (1H, m)	48.7		6″a		104.6	6a,[b] 5″, 21″ [b]
6b	2.95 (1H, d, 18.6)			6″b			
7		52.4[a,c]	6, 21	7″		60.9	5″, 9″, 21″ [b]
8		134.9	6a,[b] 6b, 10, 12, 21	8″		135.4	10″, 12″, 21″
9	7.56 (1H, m)	122.6[a,c]	11	9″	7.26 (1H, d, 7.3)	124.4	11″
10	6.91 (1H, dd, 7.5, 7.2)	122.8	12	10″	7.11 (1H, dd, 7.3, 7.3)	123.4	12″
11	7.19 (1H, dd, 7.4, 7.2)	130.0	9	11″	7.33 (1H, dd, 7.6, 7.3)	131.2	9″
12	6.96 (1H, d, 7.4)	111.1	10	12″	7.02 (1H, d, 7.6)	111.6	10″
13		144.8	9, 11	13″		144.7	9″, 11″
14		41.8[a,c]	22′b, 23′b[b]	14″		39.8	3″,[b] 15″,[b] 22‴b,[b] 23‴b[b]
15	2.79 (1H, s)	87.3	17,[b] 18b, 19b,[b] 22′b[b]	15″	3.46 (1H, s)	87.1	3″b, 18″, 22‴b,[b] 23‴a
16		92.6	17	16″		98.4	17″
17a	0.72 (1H, d, 16.2)	31.1		17″a	2.36 (1H, d, 14.5)	28.2	15″,[b] 19″b,[b] 21″ [b]
17b	2.51 (1H, d, 16.2)			17″b	2.66 (1H, dd, 14.5, 1.6)		
18a	3.83 (1H, m)	69.2	15[b]	18″a	3.75 (1H, m)	64.3	19″b[b]
18b	4.05 (1H, dd, 8.4, 8.4)			18″b	3.75 (1H, m)		
19a	1.56 (1H, 11.7, 11.7, 11.7)	35.8	15,[b] 17,[b] 21[b]	19″a	1.43 (1H, ddd, 12.8, 8.5, 4.3)	37.0	17″b,[b] 18″,[b] 21″ [b]
19b	1.62 (1H, m)			19‴b	1.60 (1H, m)		
20		50.8	15,[b] 17, 18b, 19b,[b]21[b]	20″		49.1	17″, 19″ [b]
21	4.49 (1H, s)	76.2	3b, 15,[b] 17	21″	4.29 (1H, s)	72.1	3″b, 5″, 15″, 17″, 19″ [b]
22		169.1	17b, 23	22″		168.6	17″, 23″
23	3.78 (3H, s)	51.7		23″	3.69 (3H, s)	51.9	
2′		93.6[a,c]	6′b, 22′b,[b] 23′b	2‴		93.2[a,c]	17‴a, 22‴a, 22‴b,[b] 23‴b
3′a	2.37 (1H, m)	48.6[a,c]	15′	3‴a	2.37 (1H, m)	48.6[a,c]	15‴
3′b	2.88 (1H, m)			3‴b	2.88 (1H, m)		
5′a	2.31 (1H, m)	51.6[a,c]	6′b	5‴a	2.31 (1H, m)	51.6[a,c]	6‴b
5′b	3.09 (1H, m)			5‴b	3.09 (1H, m)		
6′a	1.20 (1H, m)	30.6[a,c]		6‴a	1.21 (1H, m)	31.4[a,c]	
6′b	2.74 (1H, m)			6‴b	2.75 (1H, m)		
7′		57.0	6′b, 9′	7‴		56.0[a,c]	6‴b, 9‴
8′		136.6	10′	8‴		135.9	10‴
9′	6.65 (1H, d, 7.7)	116.3	11′	9‴	6.83 (1H, d, 7.5)	115.9	11‴
10′	5.85 (1H, dd, 7.9, 7.7)	121.6		10‴	6.35 (1H, dd, 7.6, 7.5)	120.9	
11′	6.22 (1H, d, 7.9)	116.5	9′	11‴	6.41 (1H, d, 7.6)	118.9	9‴
12′		142.0	10′	12‴		142.0	10‴
13′		136.1	9′, 11′, 23′a, 23′b[b]	13‴		136.9	9‴, 11‴, 23‴a, 23‴b[b]
14′a	1.95 (1H, m)	25.5[a,c]		14‴a	1.95 (1H, m)	25.5[a,c]	
14′b	1.99 (1H, m)			14‴b	1.99 (1H, m)		
15′	3.54 (1H, brt, 2.6)	80.5[a,c]	18′b	15‴	3.51 (1H, brt, 2.7)	80.5[a,c]	18‴b
16′	2.28 (1H, m)	31.2[a,c]		16‴	1.99 (1H, m)	32.3[a,c]	22‴[b]
17′a	1.07 (1H, brd, 12.9)	31.6[a,c]		17‴a	0.97 (1H, d, 11.6)	32.1[a,c]	
17′b	1.90 (1H, dd, 12.9, 12.9)			17‴b	2.00 (1H, m)		
18′a	4.01 (1H, ddd, 10.1, 8.6, 3.6)	65.1[a,c]		18‴a	3.94 (1H, ddd, 9.9, 8.6, 3.2)	64.8[a,c]	
18′b	4.23 (1H, ddd, 10.1, 8.1, 8.0)			18‴b	4.16 (1H, ddd, 9.9, 8.2, 7.9)		
19′a	2.07 (1H, m)	36.8[a,c]	18′b[b]	19‴a	1.74 (1H, ddd, 10.5, 9.2, 9.4)	36.2[a,c]	18‴b[b]
19′b	2.59 (1H, ddd, 11.8, 8.0, 3.6)			19‴b	2.56 (1H, ddd, 10.5, 7.9, 3.2)		
20′		46.3[a,c]		20‴		46.1[a,c]	16‴,[b] 19‴b[b]
21′	2.80 (1H, s)	64.7[a,c]		21‴	2.79 (1H, s)	64.7[a,c]	
22′a	1.49 (1H, brd, 13.0)	29.3[a,c]		22‴a	1.67 (1H, brd, 14.4)	36.0	3″,[b] 23‴b[b]
22′b	2.15 (1H, dd, 13.0, 12.8)			22‴b	2.20 (1H, dd, 14.8, 14.4)		
23′a	3.71 (1H, d, 14.2)	50.7	15, 22′a	23‴a	3.19 (1H, dd, 14.5, 1.6)	45.2	15″, 22‴a[b]
23′b	3.83 (1H, m)			23‴b	4.73 (1H, m)		

[a] Recorded at 313 K by 920 MHz NMR. [b] Recorded at 303 K by 600 MHz cryo probe NMR. [c] Assigned by HSQC or HMBC.

demethylvobtusine type framework with an enamine on C-5″ and C-6″. HMBC correlations for H-3″b and H-5″ to C-21″ (δ_C 72.1), H_2-3″ and H-21″ to C-5″ (δ_C 158.7), and H-5″ and H-21″ to C-3″ (δ_C 53.5) supported connections among C-3″, 5″, and 21″ through a nitrogen atom. And H-5″, H-9″, and H-21″ to C-7″ (δ_C 60.9), and H-5″ and H-21″ to C-6″ (δ_C 104.6) revealed the presence of an enamine on C-5″ and C-6″. The relative configurations at C-7″, 14″, 15″, 20″, 21″, 7‴, 15‴, 16‴, 20‴, and 21‴ in part B were the same as corresponding ones of part A. However, the conformation of the 3,3′-spirobipiperidine (C-3″, 14″, 15″, 20″, 21″, N, 2‴, 16‴, 22‴, 23‴, and N) ring in part A was different from that in part B. NOESY correlations of H_2-3″/H-16‴, H-3″a/H-21″, H-15″/H-22‴b and H-23‴a, and H-22‴b/H-23‴a suggested the chair−chair conformation of a 3,3′-spirobipiperidine ring in part B. The ^{13}C NMR chemical shifts of part B except for an enamine moiety were in good agreement with those of vobtusine which also possessed a chair−chair conformation assigned by X-ray analysis.[5] The connection of C-5 and C-6″ between parts A and B was provided by HMBC correlations for H-5″ to C-5 and H-6a to C-6″.

Finally, the relative stereochemistry between parts A and B in **1** was elucidated by the combination of Monte Carlo (MC) search[10] in MacroModel program[11] and NOESY correlations. A total of 3000 MC steps were performed to confirm the reproducibility of calculation results. After the MC conformational search, each of the resulting conforma-

Scheme 1. Plausible Biogenetic Path for Alasmontamine A (**1**)



tions was subjected to the energy-minimization calculation by MMFF94s force field.[12] Low-energy conformers belonged to two separate clusters.

The lowest energy one (1234.59 kJ/mol) had an *M* rotation at the C-5−C-6″ axis, and the other one had a *P* rotation (1251.76 kJ/mol) that corresponded with the solution conformer as shown below. Since the latter only satisfied the NOESY correlations of H-10′/H-19‴, H-19′/H-10‴, and H-19′/H-11‴, the relative stereochemistry of **1** was assigned as Figure 3. The allylic proton signal for H-17a was shifted to higher field (δ_H 0.72) as compared with that of H-17″a (δ_H 2.36). This can be explained by the anisotropic effect of the benzene ring (C-8″ − C-13″) as shown in a computer generated 3D drawing (Figure 3).

Alasmontamine A (**1**) consisting of bis-vobtusine type skeletons is a novel tetrakis monoterpene indole alkaloid from nature. A plausible biogenetic pathway for alasmontamine A (**1**) is proposed as shown in Scheme 1. Tetrakis monoterpene indole skeleton might be formed through an iminium-enamine coupling (C-5−C-6) of two vobtusine-type skeletons **A** and **B**, which might be produced through Polonovski-type reaction[13] from the *N*-oxide of 12′-*O*-demethylvobtusine. Formation of alasmontamine A (**1**) might occur through further oxidation, which was accompanied by enamine formation as shown in Scheme 1.

Alasmontamine A (**1**) showed moderate cell growth inhibitory activity against HL-60 cells (IC_{50} 31.7 μM).

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Supporting Information Available: 1D and 2D NMR spectra for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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