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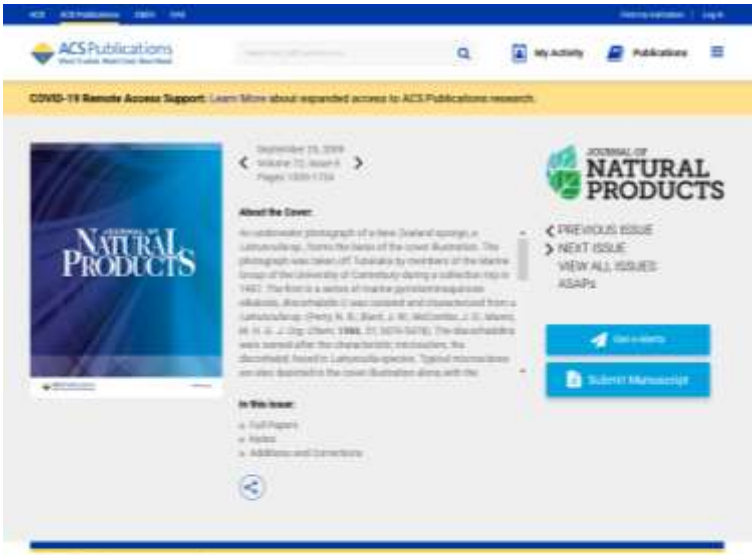

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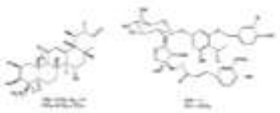

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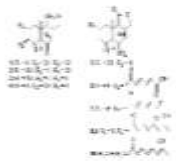

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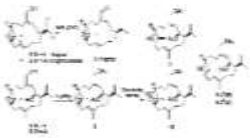

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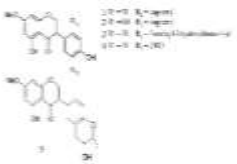

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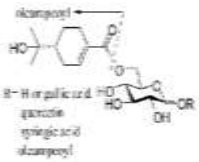

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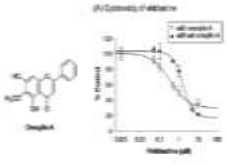

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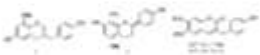

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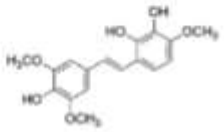

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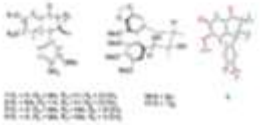

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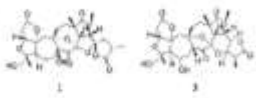

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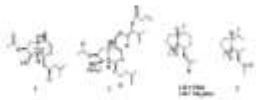

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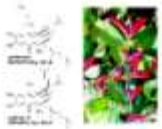

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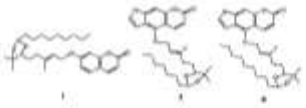

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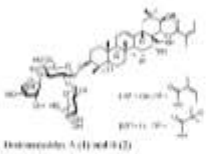

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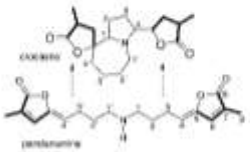

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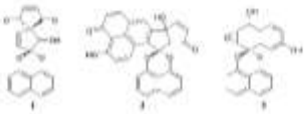

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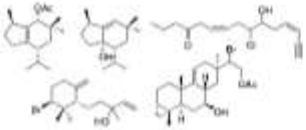

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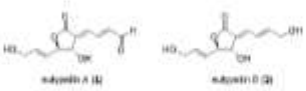

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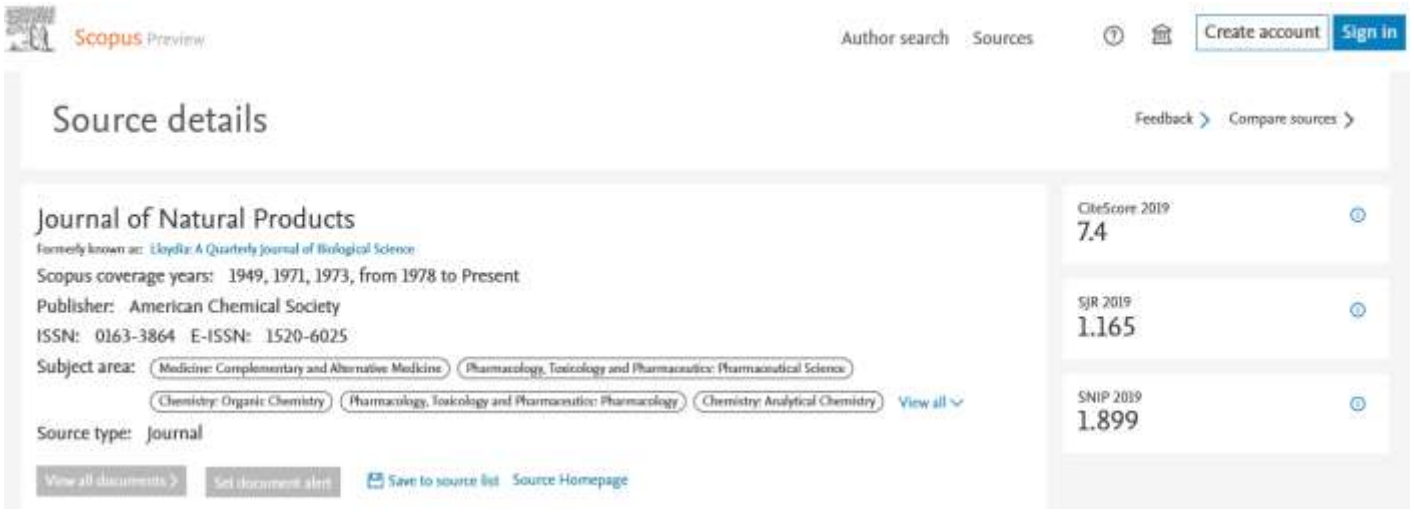

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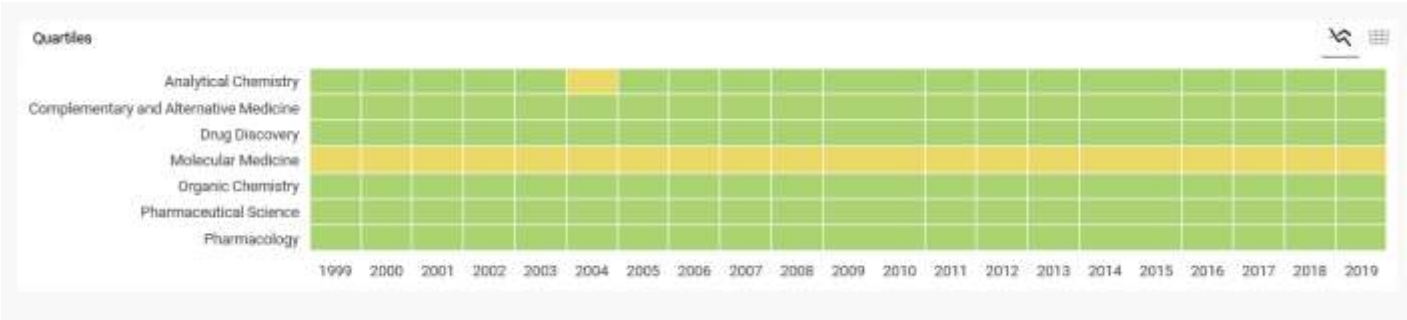
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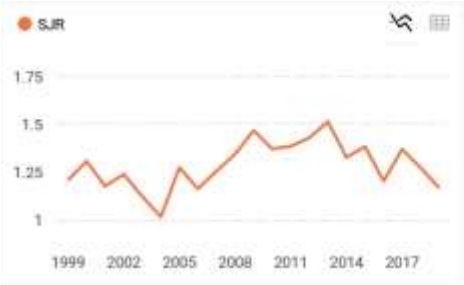
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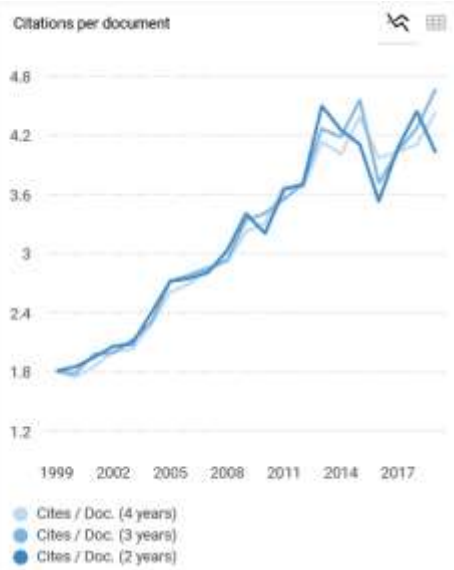
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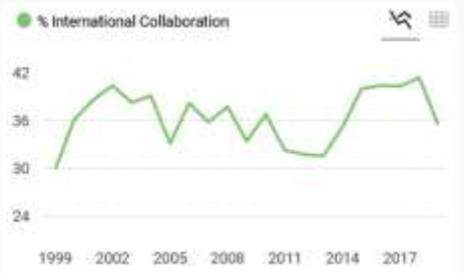
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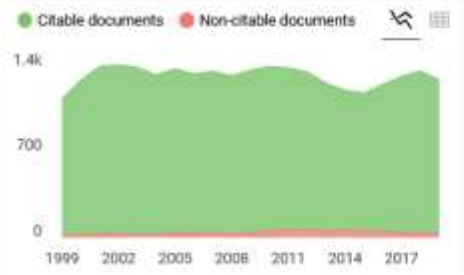
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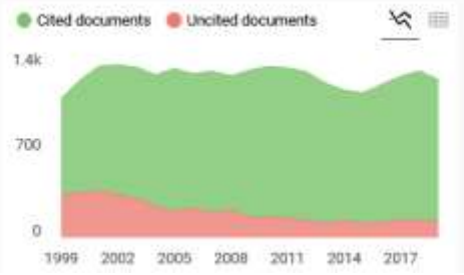
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Biscarpamontamines A and B, an Aspidosperma−Iboga Bisindole Alkaloid and an Aspidosperma−Aspidosperma Bisindole Alkaloid, from *Tabernaemontana sphaerocarpa*

Kazumasa Zaima,[†] Tomoko Hirata,[†] Takahiro Hosoya,[†] Yusuke Hirasawa,[†] Koichiro Koyama,[†] Abdul Rahman,[‡] Idha Kusumawati,[‡] Noor Cholies Zaini,[‡] Motoo Shiro,[§] and Hiroshi Morita*[,†]

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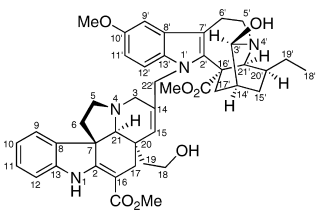
Two new bisindole alkaloids, biscarpamontamine A (**1**), possessing an aspidosperma−iboga-type skeleton, and biscarpamontamine B (**2**), having an aspidosperma−aspidosperma-type skeleton, were isolated from stems of *Tabernaemontana sphaerocarpa*, and their structures were elucidated on the basis of spectroscopic data analysis. The absolute configuration of biscarpamontamine B (**2**) was established by comparison of its CD spectrum and with that of vobtusine (**3**). Biscarpamontamine B (**2**) showed potent cytotoxicity against various human cancer cell lines.

Tabernaemontana sphaerocarpa Blume is a member of the Apocynaceae family that occurs in Indonesia and is found mostly in Java. Traditionally, the leaves have been used as a laxative, the flowers as a cardiotonic agent, and the latex for removing warts.[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] However, only vobasine-type alkaloids such as tabernaemontanine[5] and dregamine[5] have been isolated from *T. sphaerocarpa*. In our search for structurally and biogenetically interesting alkaloids from tropical plants found in Indonesia, two new bisindole alkaloids, biscarpamontamine A (**1**), having an aspidosperma−iboga-type skeleton, and biscarpamontamine B (**2**), based on an aspidosperma−aspidosperma-type skeleton, were isolated from the stems of *T. sphaerocarpa*, together with vobtusine (**3**),[6] vobtusine lactone (**4**),[7] 3-hydroxyvobtusine (**5**),[8] ibogamine,[2] voacangine,[9] 3-hydroxyvoacangine,[9] and vobasine.[10] In this paper, we describe the isolation and structure elucidation of two new dimeric indole alkaloids, biscarpamontamines A and B (**1** and **2**), and the cytotoxic activity of compounds **1**−**5** against various human cancer cell lines.



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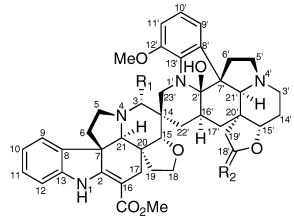

2 R_1=OH, R_2=O
3 R_1=H, R_2=H_2
4 R_1=H, R_2=O
5 R_1=OH, R_2=H_2

The stems of *T. sphaerocarpa* were extracted with MeOH, and a part of the extract was partitioned between EtOAc and 3% aqueous tartaric acid. Water-soluble materials, which were adjusted to pH 9 with saturated Na_2CO_3, were extracted with $CHCl_3$. The $CHCl_3$-soluble materials were subjected to passage over an amino silica gel column (hexane−EtOAc, 9:1→1:1, and $CHCl_3$−MeOH, 1:0 → 0:1) followed by separation over a silica gel column, then purification by ODS HPLC (MeOH−H_2O−TFA) and ODS HPLC (MeCN−H_2O−TFA), giving **1** (5.5 mg, 0.002%) and **2** (13.0 mg, 0.005%), together with seven known alkaloids, which were identified as vobtusine (**3**),[6] vobtusine lactone (**4**),[7] 3-hydroxyvobtusine (**5**),[8] ibogamine,[2] voacangine,[9] 3-hydroxyvoacangine,[9] and vobasine,[10] on the basis of comparison with their spectroscopic data in the literature.

Compound **1**, $[\alpha]^{26}_D$ −127 (*c* 1.0, MeOH), showed a pseudomolecular ion peak at *m/z* 717 $(M - OMe)^+$ in the ESIMS, and the molecular formula, $C_{44}H_{52}N_4O_7$, was established by HRESITOFMS [*m/z* 717.3661 $(M - OMe)^+$, Δ +0.9 mmu]. The IR spectrum implied the presence of hydroxy (3380 cm^{-1}) and ester carbonyl (1730 cm^{-1}) functionalities. Analysis of the ^1H and ^{13}C NMR data (Tables 1 and 2) and the HSQC spectrum of **1** revealed the presence of two ester carbonyls, 10 sp^2 quaternary carbons, three sp^3 quaternary carbons, eight sp^2 methines, five sp^3 methines, 12 sp^3 methylenes, one methyl, and three methoxy groups.

The gross structure of **1** was deduced from extensive analysis of the two-dimensional NMR data, including the $^1H-^1H$ COSY, HSQC, and HMBC spectra in $CD_3OD-CDCl_3$ (9:1) (Figure 1). The $^1H-^1H$ COSY and HSQC spectra revealed connectivities of six partial structures, **a**−**f**, and were classified into two units, A and B, corresponding to aspidosperma- and iboga-type skeletons, respectively, as shown in Figure 1.

In unit A, the HMBC cross-peaks of H-5 and H-9 to C-7 and H-6 to C-8 revealed the attachment of partial structure **a** to the indole moiety (**b**), while the HMBC cross-peaks of H_2-17 to C-2, C-16, and C-21 and H-21 to C-2 indicated the connectivity of the indole moiety and the cyclohexene ring (C-2, C-7, C-16, C-17, C-20, and C-21) through C-2 and C-7. In addition, the HMBC cross-peaks of H_2-3 to C-5 (δ_C 50.3) and C-21 (δ_C 69.4) and H_2-5 to C-21 established the connections between C-3 (δ_C 52.2), C-5, and C-21 through a nitrogen atom (N-4). Another partial structure, **c**, with a hydroxy group at C-18 placed at C-20 and the presence of a methyl carboxylate moiety placed at C-16, was analyzed by the HMBC correlations as shown in Figure 1. The HMBC cross-peaks of H-15 to C-22′ and H_2-22′ to C-3 and C-14 indicated a methylene unit (C-22′) at C-14. These data suggested that unit A possesses an aspidosperma-type skeleton with an extra carbon unit (C-22′), which may be substituted at a nitrogen atom in unit B.

The structure of unit B was also analyzed using the HMBC correlations as shown in Figure 1. The HMBC cross-peaks of H_2-6′ to C-2′ and C-8′ and H-9′ to C-7′ revealed the attachment of

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Table 1. ^{1}H NMR Data (*J*, Hz) of Biscarpamontamines A (**1**) and B (**2**) at 300 K

position	**1**[a]	**2**[b]
3a	3.11 (d, 15.6)	4.47 (d, 10.4)
3b	2.88 (d, 15.6)	
5a	2.75 (m)	3.14 (m)
5b	2.48 (m)	2.78 (d, 8.3)
6a	1.80 (m)	2.05 (m)
6b	1.56 (dd, 4.0, 11.8)	1.79 (dd, 3.8, 11.0)
9	7.02 (d, 7.6)	7.27 (d, 7.5)
10	6.63 (t, 7.6)	6.89 (t, 7.5)
11	6.88 (t, 7.6)	7.17 (t, 7.5)
12	6.61 (d, 7.6)	6.83 (d, 7.5)
15	5.28 (s)	3.34 (s)
17a	2.21 (d, 15.3)	2.84 (brd, 14.5)
17b	2.25 (d, 15.3)	2.43 (d, 14.5)
18a	3.16 (m)	3.59 (m)
18b	3.22 (m)	3.70 (m)
19a	0.97 (m)	1.37 (m)
19b	0.97 (m)	1.48 (m)
21	2.49 (s)	2.49 (s)
CO_2Me	3.52 (s)	3.46 (s)
NH		8.95 (s)
3′a	3.76 (d, 1.7)	2.93 (brd, 10.6)
3′b		2.30 (brd, 10.6)
5′a	3.30 (m)	3.07 (d, 10.4)
5′b	2.81 (m)	2.24 (d, 10.4)
6′a	2.82 (m)	3.16 (m)
6′b	2.75 (m)	1.35 (m)
9′	6.69 (d, 2.4)	6.74 (d, 7.9)
10′		6.70 (t, 7.9)
11′	6.50 (dd, 2.4, 8.7)	6.65 (d, 7.9)
12′	6.92 (d, 8.7)	
14′a	1.77 (brs)	2.05 (m)
14′b		2.15 (m)
15′a	1.26 (m)	4.19 (brd, 8.0)
15′b	1.16 (m)	
16′		1.92 (brs)
17′a	2.57 (dd, 2.4, 13.8)	2.78 (d, 8.2)
17′b	1.63 (ddd, 3.1, 3.1, 13.8)	1.20 (brs)
18′	0.64 (t, 7.4)	
19′a	1.24 (m)	2.32 (brd, 4.8)
19′b	1.35 (m)	2.84 (brd, 4.8)
20′	1.08 (m)	
21′	3.57 (s)	2.61 (brs)
22′a	2.54 (s)	2.00 (brd, 3.7)
22′b	2.54 (s)	2.02 (brd, 3.7)
23′a		5.04 (d, 14.2)
23′b		3.10 (d, 14.2)
OMe	3.58 (s)	3.58 (s)
CO_2Me	3.41 (s)	

[a] $CD_3OD-CDCl_3$, 9:1. [b] $CDCl_3$.

partial structure **e** to the indole moiety with a methoxy group at C-10′, which was indicated by the HMBC correlations of methoxy protons (δ_H 3.58) to C-10′. The 2-aza-6-ethylbicyclo[2.2.2]octan-3-ol ring with a methyl carboxylate moiety at C-16′ consisting of the partial structure **d** was located between the indole moiety and unit **e** by HMBC correlations as shown in Figure 1. Thus, unit B was revealed to be an iboga-type skeleton as in 3-hydroxyvoacangine.[9] Finally, judging from the chemical shift of C-22′ (δ_C 40.9), C-14 in unit A and N-1′ in unit B were concluded to be linked through C-22′. Thus, the gross structure of biscarpamontamine A was assigned as **1**, as shown in Figure 1.

The relative configuration of **1** was elucidated by NOESY correlations, as shown in a computer-generated 3D drawing (Figure 2). The NOESY correlations of H-21/H-9 and H-19a in unit A indicated that H-21 and the hydroxyethyl side chain at C-20 are α-orientated. The α-orientation of H-14′, H-20′, and H-21′, and the hydroxy group at C-3′, was elucidated by the NOESY correlations of H-20′/H-15′a and H-21′, H-14′/H-17′a, and H-17′b/H-3′.

Compound **2**, $[\alpha]^{30}_D$ −142 (*c* 1.0, MeOH), showed a pseudomolecular ion peak at *m*/*z* 731 $(M - H_2O + H)^+$ in the ESIMS,

Table 2. ^{13}C NMR Data of Biscarpamontamines A (**1**) and B (**2**) at 300 K

position	**1**[a]	**2**[b]
2	166.2	166.6
3	52.2	82.0
5	50.3	47.8
6	44.3	44.1
7	54.9	54.4
8	137.3	137.7
9	121.0	121.8
10	120.3	120.9
11	127.4	127.9
12	108.9	109.3
13	142.7	143.0
14	133.9	39.7
15	129.1	88.6
16	91.2	94.0
17	29.6	26.9
18	57.4	64.4
19	36.9	34.8
20	39.2	47.4
21	69.4	58.3
CO_2Me	168.6	168.5
CO_2*Me*	50.4	51.2
2′	137.2	93.4
3′	96.3	48.3
5′	52.5	52.0
6′	21.3	31.4
7′	109.0	54.5
8′	127.7	133.5
9′	99.9	114.9
10′	153.2	119.8
11′	111.0	112.0
12′	111.0	145.2
13′	130.9	136.3
14′	29.4	24.9
15′	24.5	82.3
16′	54.8	31.1
17′	34.3	31.2
18′	11.0	175.8
19′	26.0	41.6
20′	37.1	43.5
21′	57.0	64.1
22′	40.9	33.9
23′		46.0
O*Me*	55.5	55.5
CO_2Me	174.4	
CO_2*Me*	51.9	

[a] $CD_3OD-CDCl_3$, 9:1. [b] $CDCl_3$.

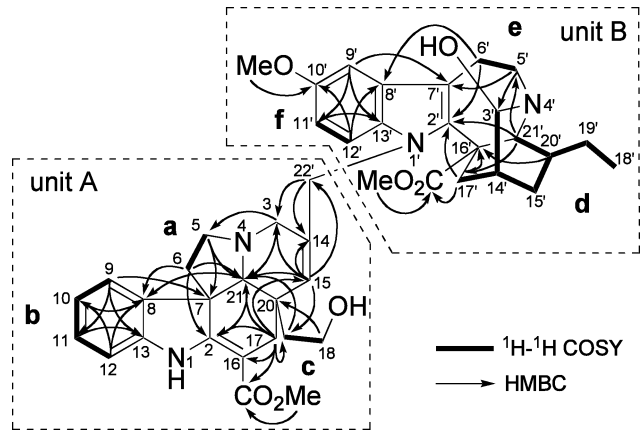


Figure 1. Selected 2D NMR correlations for biscarpamontamine A (**1**).

and the molecular formula, $C_{43}H_{48}N_4O_8$, was established by HRESITOFMS [*m*/*z* 731.3450 $(M - H_2O + H)^+$, Δ +0.5 mmu]. IR absorptions implied the presence of hydroxy (3440 cm^{-1}) and carbonyl (1780 cm^{-1}) functionalities. Analysis of the ^{1}H and ^{13}C NMR data (Tables 1 and 2) and the HSQC spectrum of **2** revealed

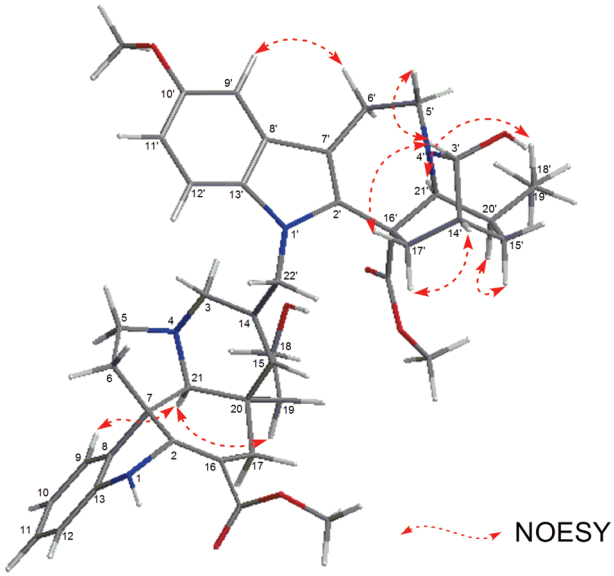


Figure 2. Selected NOESY correlations for biscarpamontamine A (**1**).

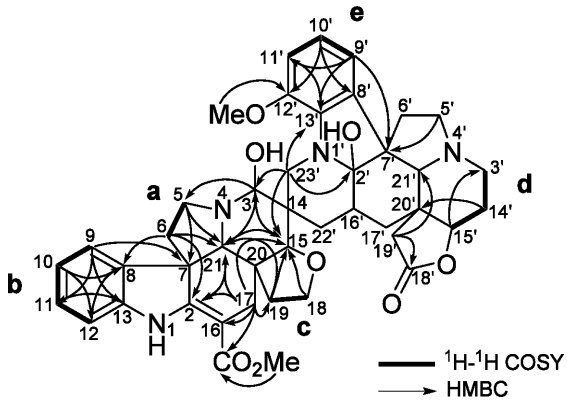


Figure 3. Selected 2D NMR correlations for biscarpamontamine B (**2**).

the presence of two esters, eight sp^2 quaternary carbons, five sp^3 quaternary carbons, eight sp^2 methines, five sp^3 methines, 13 sp^3 methylenes, and two methoxy groups.

The gross structure of **2** was deduced from NMR data in $CDCl_3$ (Table 1). The ^1H and ^{13}C NMR data of **2** were highly similar to those of vobtusine lactone (**4**). The noticeable difference of the chemical shifts of H-3 (δ_H 4.47) and C-3 (δ_C 82.0) was due to the presence of a hydroxy group at C-3, consistent with the HMBC correlations of H-3 to C-5 and C-15, and H-21 and H_2-23′ to C-3 (Figure 3). Thus, the gross structure of **2** was elucidated as the 3-hydroxy derivative of vobtusine lactone (**4**)[7] and was named as biscarpamontamine B.

The relative configuration of **2** was elucidated by NOESY correlations, as shown in Figure 4. The NOESY correlations of H-5a/H-9 and H-5b/H-3 indicated that the hydroxy group at C-3 is α-oriented. Additionally, H-23′a/H-17a and H-23′b/H-15 showed the configuration of the spiro center at C-14 to be the same as that in vobtusine lactone (**4**).[7]

X-ray analysis of a crystal of vobtusine (**3**) obtained from MeOH confirmed the proposed absolute structure for the unique fused-polycyclic ring system of **3**, through the Flack parameter,[11] $x = 0.03(16)$ (Figure 5). The absolute configuration of **2** was assigned by comparison of its CD spectrum with that of vobtusine (**3**).[6] The CD spectrum of **2** showed a similar pattern to that of **3** without a ketone at C-18′ and a hydroxy at C-3 (Figure 6). Thus, **2** was

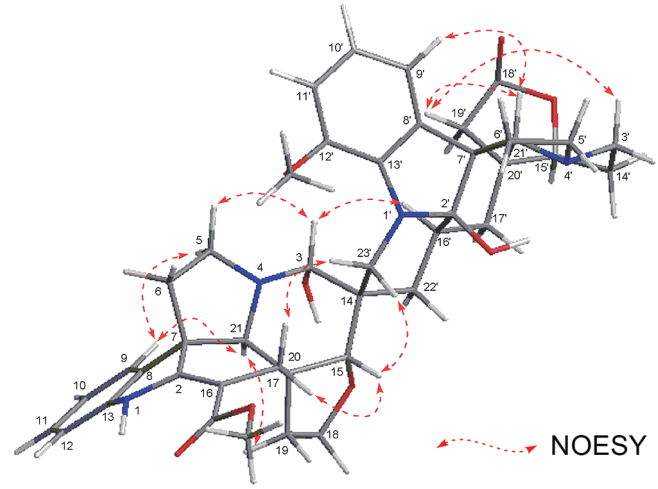


Figure 4. Selected NOESY correlations for biscarpamontamine B (**2**).

revealed to have 3*R*, 7*S*, 14*S*, 15*R*, 20*R*, 21*S*, 2′*R*, 7′*R*, 15′*S*, 16′*R*, 20′*R*, and 21′*R* configurations.

A plausible biogenetic pathway for biscarpamontamines A and B (**1** and **2**) is proposed as shown in Scheme 1. Biogenetically, biscarpamontamine A (**1**) might be derived by coupling between C-14 in aspidospermidine-3-methylcarboxylate (**6**)[12] and the corresponding formate such as *N*-formyl-12-methoxyechitamidine (**7**)[13] through Aldol-type fragmentation. On the other hand, biscarpamontamine B (**2**) might be derived by coupling between C-14 in aspidospermidine-3-methylcarboxylate (**6**)[12] and an *N*-substituted ibogamine such as *N*-formylcoronaridine (**8**)[14] to form a C-14−C-23′ connectivity, followed by formation of a C-14−C-22′ connectivity, as shown in Scheme 1.

Dimeric alkaloids **1**−**5** were evaluated for cytotoxicity against five human cancer cell lines, HL60, RPMI8226, NCI-H226, HCT116, and MCF7, as shown in Table 3. Biscarpamontamine B (**2**), with a hydroxy group at C-3, and 3-hydroxyvobtusine (**5**), with a carbonyl moiety at C-18, showed the most potent cytotoxicity. The presence of these functional groups might be important for cytotoxicity. Efforts are currently underway to elucidate the mode of action for the cytotoxicity of these dimeric alkaloids.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a JASCO DIP-1000 automatic digital polarimeter. UV spectra were obtained on an Ultrospec 2100 pro spectrophotometer, CD spectra were measured on a JASCO J-820 spectropolarimeter, and IR spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. High-resolution ESIMS were obtained on a LTQ Orbitrap XL (Thermo Scientific). HPLC was carried out using a JASCO PU-2089 Plus pump equipped with a UV-2075 Plus detector (λ 254 nm) and CAPCELL PAK C-18 MG-II columns (for analytical HPLC, 250 × 4.6 mm i.d., 5 μm particle size, and for preparative HPLC, 250 × 10 mm i.d., 5 μm particle size, Shiseido, Tokyo, Japan). ^1H and 2D NMR spectra were recorded on a Bruker AV 600 spectrometer, and chemical shifts are referenced to the residual solvent peaks (δ_H 3.31 and δ_C 49.0 for methanol-d_4 and δ_H 7.26 and δ_C 77.0 for $CDCl_3$). 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 HSQC spectra in the phase-sensitive mode and HMBC spectra, 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.

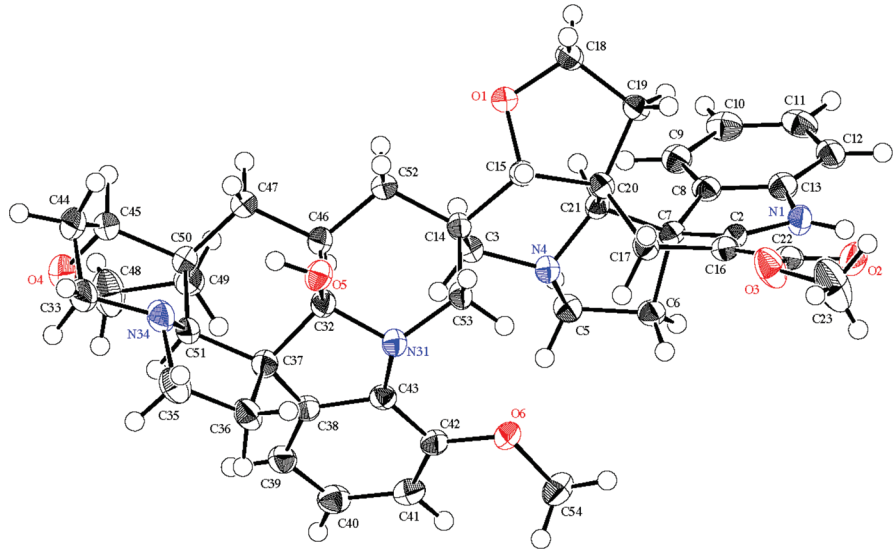


Figure 5. Molecular structure of vobtusine (**3**) obtained by X-ray analysis. [Flack parameter: $x = 0.03(16)$].

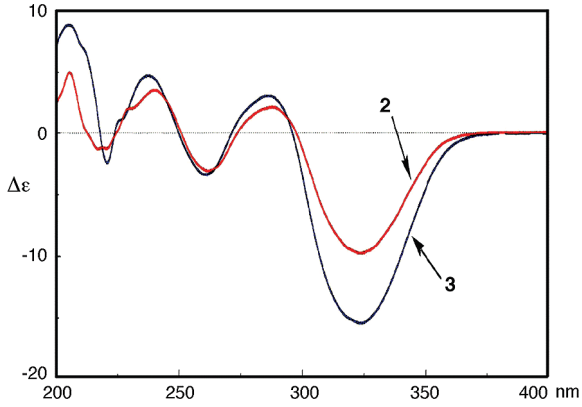


Figure 6. CD spectra of biscarpamontamine B (**2**) and vobtusine (**3**).

Plant Material. The stems of *Tabernaemontana sphaerocarpa* were collected in Java, Indonesia, in 2007. The botanical identification was made by Ms. Sri Wuryanti, Purwodadi Botanical Garden, Indonesia. A voucher specimen (no. AP070902) has been deposited at Purwodadi Botanical Garden, Pasuruan, Indonesia.

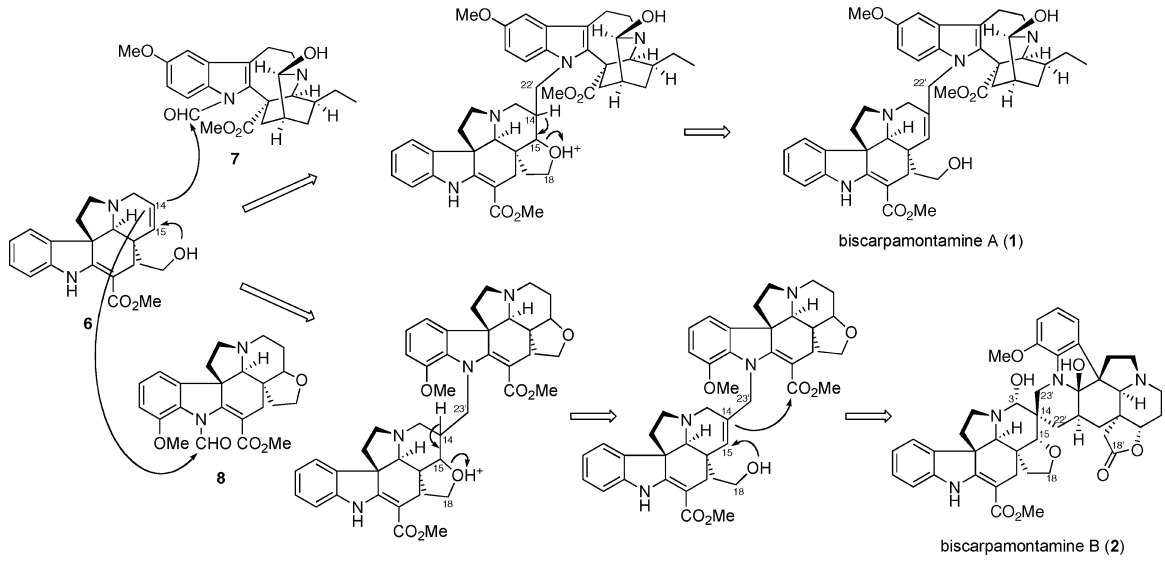
Extraction and Isolation. The stems (3.0 kg) of *T. sphaerocarpa* were extracted with MeOH, and a part (20 g) of the extract (240 g) was treated with 3% tartaric acid (pH 2) and then partitioned with EtOAc. The aqueous layer was treated with saturated aqueous Na_2CO_3 to pH 9 and extracted with $CHCl_3$ to give an alkaloidal fraction (2.94 g). The alkaloidal fraction was subjected to passage over an amino silica gel column (hexane−EtOAc, 9:1 → 1:1, $CHCl_3$−MeOH, 1:0 → 0:1, Chromatorex, Fuji Silysia Ltd., Japan) to give 21 fractions. Fractions 8 and 11 were recrystallized to give vobtusine (**3**) in $CHCl_3$−MeOH (9:1) and vobtusine lactone (**4**) in $CHCl_3$−MeOH (20:1), respectively. The residue of fraction 8 was subjected to ODS HPLC (45 → 80% MeOH−0.1% TFA(aq), 35 min) to give vobasine, and then the fourth eluted fraction was also subjected to ODS HPLC (32% MeCN−0.1% TFA(aq)) to give 3-hydroxyvobtusine (**5**). Fraction 5 was subjected to ODS HPLC (38% MeCN−0.1% TFA(aq)) to give ibogamine, voacangine, and 3-hydroxyvoacangine. Fraction 10 was subjected to ODS HPLC (40 → 80% MeOH−0.1% TFA(aq), 40 min)

Table 3. Cytotoxicity of **1**−**5** against Human Cancer Cell Lines

	IC_{50} (μM)[a]				
compound	HL60	RPMI8226	NCI-H226	HCT116	MCF7
1	12.2	27.9	16.9	14.0	25.3
2	0.5	1.9	2.4	0.8	1.8
3	15.8	38.7	20.2	37.4	36.5
4	8.0	18.0	7.6	17.6	22.5
5	0.8	2.3	2.4	1.0	1.6

[a] IC_{50}, 50% inhibition concentration.

Scheme 1. Plausible Biogenetic Pathway of Biscarpamontamines A (**1**) and B (**2**)



followed by ODS HPLC (58% MeOH−0.1% TFA(aq)) to give biscarpamontamine B (**2**, 13.0 mg, 0.005%). Fraction 12 was subjected to separation over a silica gel column ($CHCl_3$−MeOH, 50:1 → 0:1, silica gel 60, Merk Ltd., Japan) followed by ODS HPLC (50% MeOH−0.1% TFA(aq)) to give 16 fractions, and then fraction 8 was subjected to passage over an amino silica gel column (hexane−EtOAc, 8:2 → 1:1, $CHCl_3$−MeOH, 1:0 → 0:1) to give biscarpamontamine A (**1**, 5.5 mg, 0.002%).

Biscarpamontamine A (1): yellow, amorphous solid; $[\alpha]^{26}_D$ −127 (*c* 1.0, MeOH); UV (MeOH) λ_{max} 330 (ϵ 12 000), 295 (15 600), 220 (33 500) nm; CD (MeOH) λ_{max} 327 ($\Delta\epsilon$ −12.39), 291 ($\Delta\epsilon$ 1.19), 271 ($\Delta\epsilon$ −1.41), 237 ($\Delta\epsilon$ 8.97), 220 ($\Delta\epsilon$ 6.30), 205 ($\Delta\epsilon$ 17.28); IR (KBr) ν_{max} 3380, 2950, 1730 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; ESIMS *m*/*z* 717 $(M - OMe)^+$; HRESITOFMS *m*/*z* 717.3661 [calcd for $C_{43}H_{49}N_4O_6$ $(M - OMe)^+$, 717.3652].

Biscarpamontamine B (2): colorless solid; $[\alpha]^{30}_D$ −142 (*c* 1.0, MeOH); UV (MeOH) λ_{max} 330 (ϵ 6000), 300 (5400), 260 (5400), 220 (15 600) nm; CD (MeOH) λ_{max} 324 ($\Delta\epsilon$ −9.75), 288 ($\Delta\epsilon$ 2.13), 262 ($\Delta\epsilon$ −3.11), 240 ($\Delta\epsilon$ 3.53), 217 ($\Delta\epsilon$ −1.29), 206 ($\Delta\epsilon$ 4.96); IR (KBr) ν_{max} 3440, 2930, 1780 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; ESIMS *m*/*z* 731 $(M - H_2O + H)^+$; HRESITOFMS *m*/*z* 731.3450 [calcd for $C_{43}H_{47}N_4O_7$ $(M - H_2O + H)^+$, 731.3445].

X-ray Analysis of 3. Vobtusine (**3**) was crystallized from MeOH to give colorless needles (mp >300 °C). Crystal data: $C_{43}H_{52}N_4O_7$, space group $P2_1$ (#4), $a = 11.2730(2)$ Å, $b = 12.2662(2)$ Å, $c = 13.8488(7)$ Å, $\beta = 110.9121(7)°$, $V = 1788.82(10)$ $Å^3$, $Z = 2$, $D_{calc} = 1.368$ g/cm^3, Cu Kα radiation ($\lambda = 1.54187$ Å), T −180 (1) °C. The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F^2 was based on 6376 observed reflections and converged with unweighted and weighted agreement factors of $R_1 = 0.0394$ [$I > 2.00\sigma(I)$] and $wR_2 = 0.1053$. The absolute configuration was determined on the basis of Flack parameter 0.03(16),[11] refined using 3002 Friedel pairs. Complete crystallographic data of **3** have been deposited at the Cambridge Crystallographic Data Centre (CCDC 736222).[15]

Cytotoxic Activity. Each cell line [HL60 (human blood premyelocytic leukemia), RPMI8226 (multiple myeloma), NCI-H226 (non-small cell lung carcinoma), HCT116 (human colon cancer), and MCF7 (human breast adenocarcinoma) cells] was seeded onto 96-well microtiter plates at 1×10^4 cells per well for HL60 and RPMI8226 and 5×10^3 cells per well for NCI-H226, HCT116, and MCF7, respectively. Cells were preincubated for 24 h at 37 °C in a humidified atmosphere of 5% CO_2. Different concentrations of each compound (10 μL) were added to the cultures, and then the cells were incubated at 37 °C for 48 h. On the third day, 15 μL MTT solution (5 mg/mL) were added into each well of the cultured medium. After a further 2 h of incubation, 100 μL of 10% SDS−0.01 N HCl solution was added to each well and the formazan crystals in each well were dissolved by stirring with a pipet. The optical density measurements were made using a micropipet reader (Benchmark Plus microplate spectrometer; Bio-Rad) equipped with a two-wavelengths system (550 and 700 nm). In each experiment, three replicates of wells were prepared for each sample. The ratio of the living cells was determined on the basis of the difference of the absorbance between those of samples and controls. These differences are expressed in percentage, and cytotoxic activity was indicated as an IC_{50} value. Vincristine and vinblastine, bisindole alkaloids, were used as a positive control, and their IC_{50} values against HL60 cells were 0.87 and 1.6 nM, respectively.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra of biscarpamontamines A and B are available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Heyne, K. *Tumbuhan Berguna Indonesia*, Vol. III; Yayasan Sarana Wana Jaya; Jakarta, 1987; p 1635.
(2) Wenkert, E.; Cochran, D. W.; Gottlieb, H. E.; Hagaman, E. W.; Braz Filho, R.; Matos, F. J. A.; Madruga, M. I. L. M. *Helv. Chim. Acta* **1976**, *59*, 2437–2442.
(3) Kam, T. S.; Pang, H. S.; Lim, T. M. *Org. Biomol. Chem.* **2003**, *1*, 1292–1297.
(4) Kam, T. S.; Sim, K. M.; Pang, H. S. *J. Nat. Prod.* **2003**, *66*, 11–16.
(5) Chatterjee, A.; Banerji, A.; Majumder, P. L. *Indian J. Chem.* **1968**, *6*, 545–546.
(6) Schuler, B. O. G.; Verbeek, A. A.; Warren, F. L. *J. Chem. Soc.* **1958**, 4776–4777.
(7) (a) Kunesch, N.; Das, B. C.; Poisson, J. *Bull. Soc. Chim. Fr.* **1970**, 4370–4375. (b) Rolland, Y.; Kunesch, N.; Poisson, J.; Hagaman, E. W.; Schell, F. M.; Wenkert, E. *J. Org. Chem.* **1976**, *41*, 3270–3275.
(8) Bruno, D.; Giordano, L.; Giovanni, P. *Heterocycles* **1980**, *14*, 201–203.
(9) Beek, T. A.; Verpoorte, R.; Baerheim-Svendsen, A. *Planta Med.* **1983**, *47*, 83–86.
(10) Renner, U. *Experientia* **1959**, *15*, 185–186.
(11) Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881.
(12) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598–2610.
(13) Oguakwa, J. U.; Galeffi, C.; Messana, I.; Patamia, M.; Nicoletti, M.; Marini-Bettolo, G. B. *Gazz. Chim. Ital.* **1983**, *113*, 533–535.
(14) Verkey, E. T.; Pillay, P. P.; Bose, A. K.; Das, K. G. *Indian J. Chem.* **1966**, *4*, 332–334.
(15) CCDC 736222 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/deposit, or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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