



Volume 67, Number 1, January 2009

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An International Journal of Organic Chemistry  
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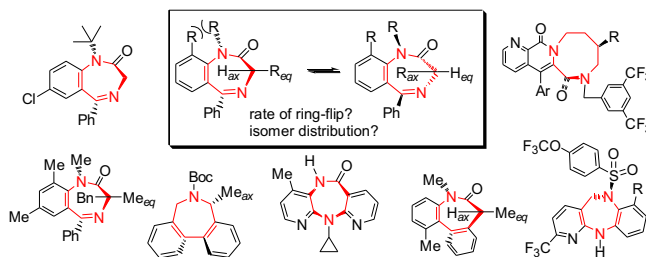
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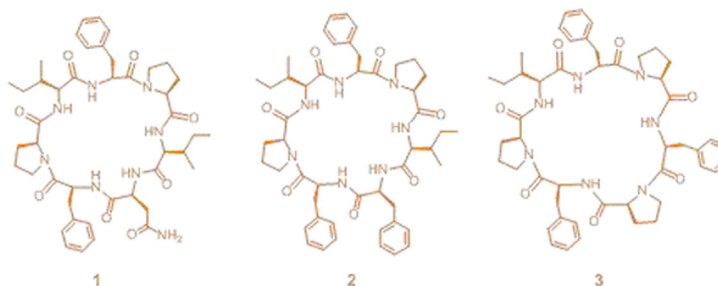
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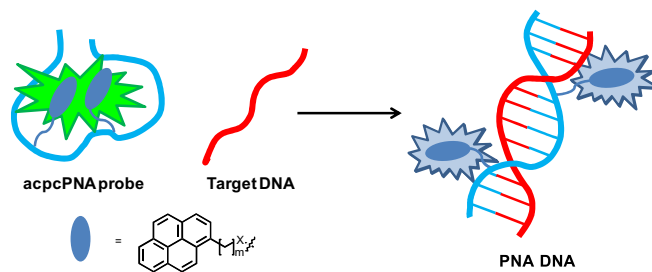
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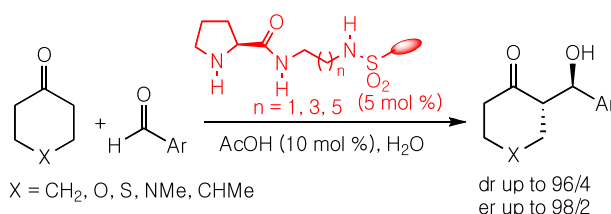
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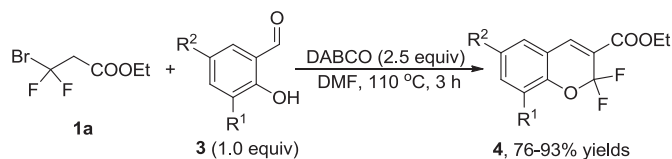
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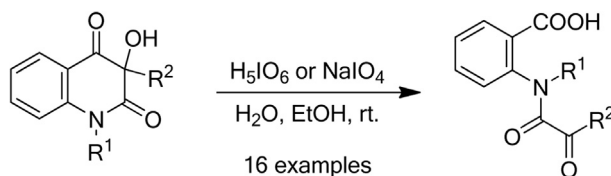
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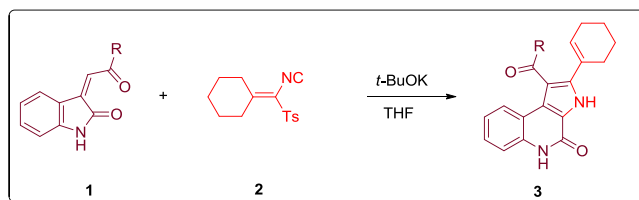
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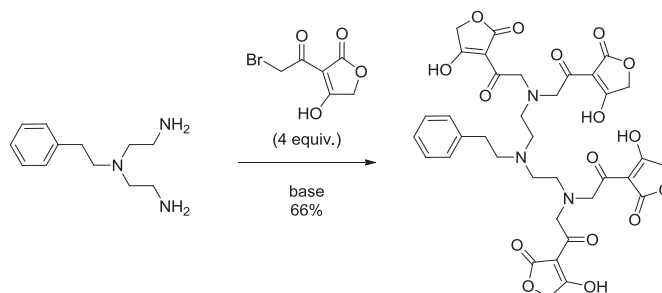
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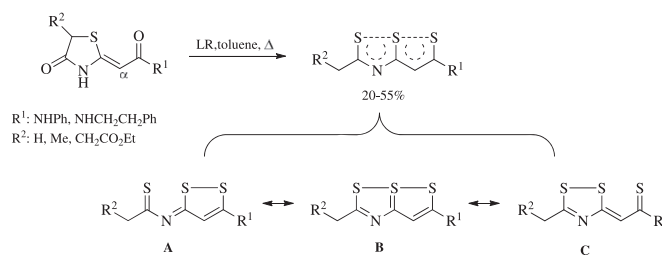
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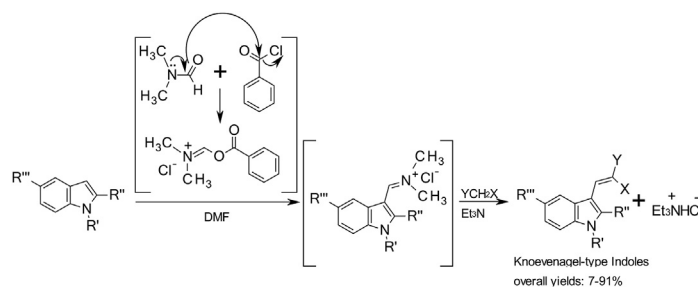
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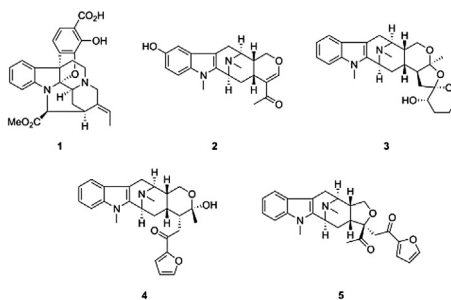
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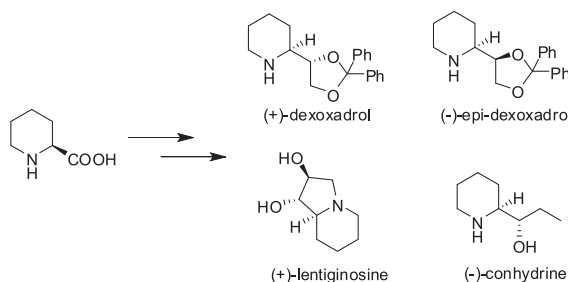
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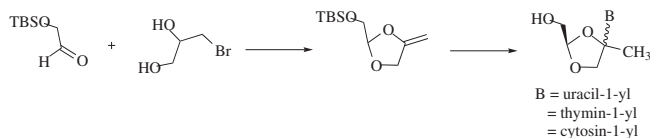
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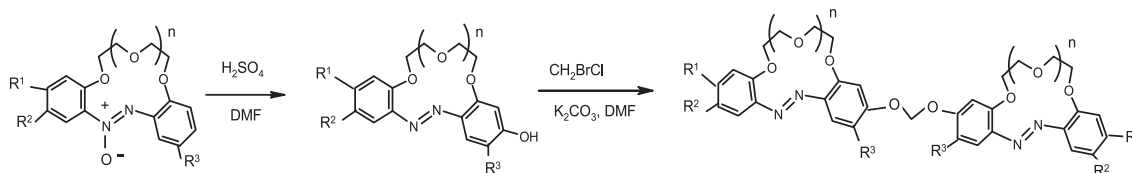
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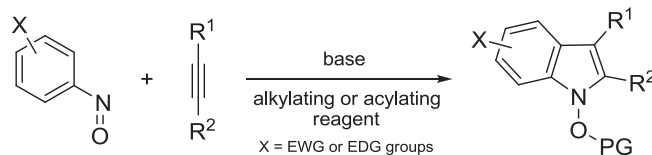
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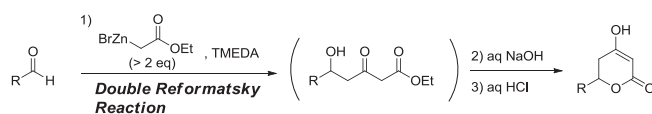
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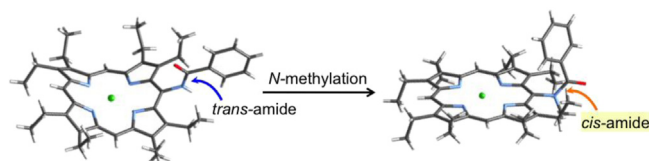
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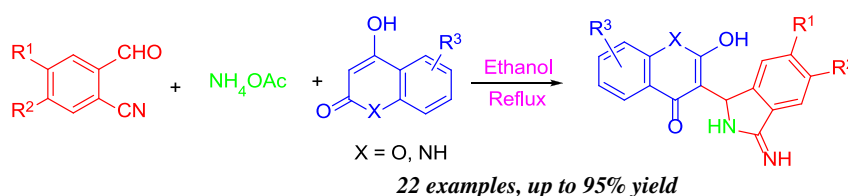
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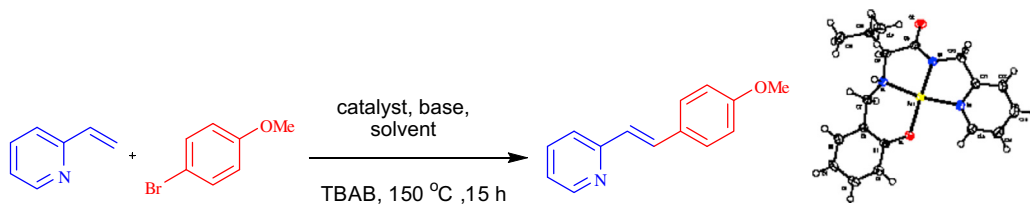
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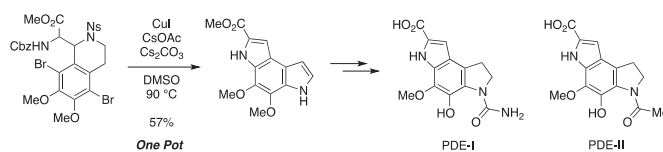
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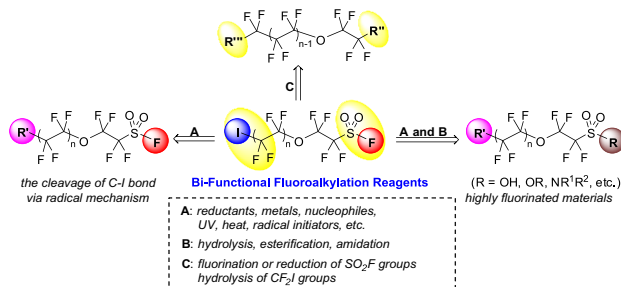
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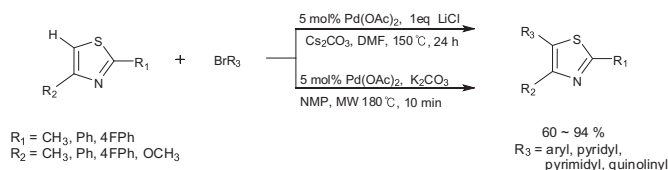
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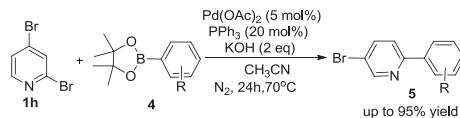




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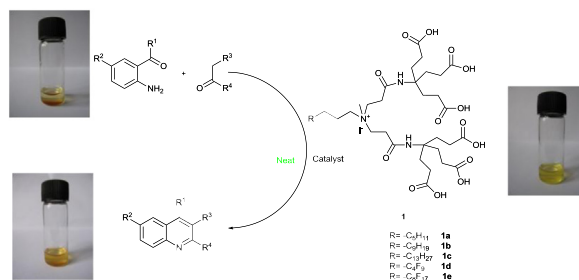
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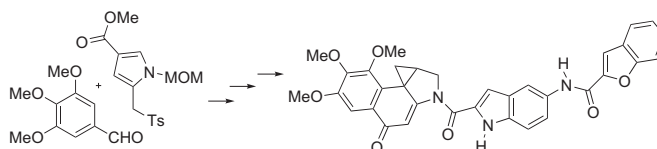
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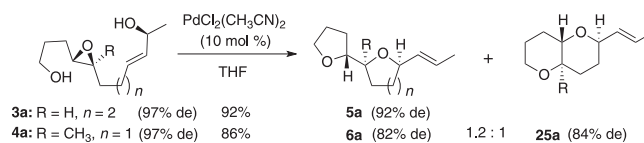
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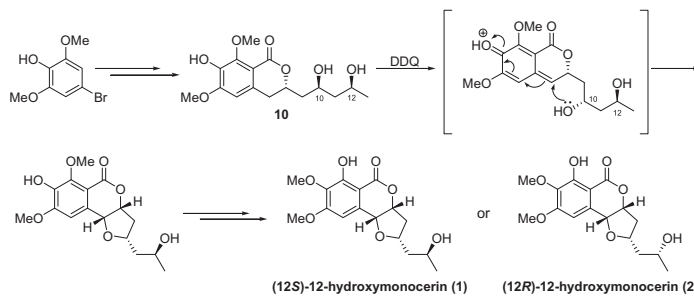
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ISSN 0040-4020



# Voacalgines A–E, new indole alkaloids from *Voacanga grandifolia*



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Noor Cholies Zaini<sup>b</sup>, Osamu Shiota<sup>c</sup>, Hiroshi Morita<sup>a,\*</sup>

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## ARTICLE INFO

### Article history:

Received 29 July 2013

Received in revised form 24 October 2013

Accepted 26 October 2013

Available online 5 November 2013

### Keywords:

Indole alkaloid

*Voacanga grandifolia*

Voacalgine A

Cytotoxicity

## ABSTRACT

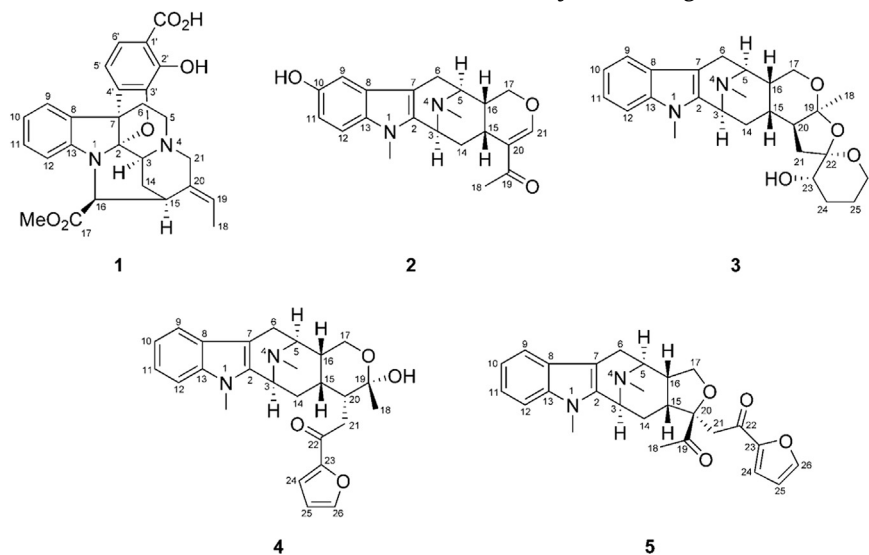
Five new indole alkaloids, voacalgines A–E (**1–5**) consisting of a C-mavacurine type of skeleton with 2,3-dihydroxybenzoate moiety, a macroline-type of skeleton, or a macroline-type of skeleton with C<sub>6</sub> unit, were isolated from the bark of *Voacanga grandifolia*. Their relative structures were determined by means of NMR data. Voacalgine A showed moderate cell growth inhibitory activities against HL-60 and HCT116 cells.

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## 1. Introduction

*Voacanga grandifolia* (Miq.) Rolfe is a member of the Apocynaceae family distributed in Indonesia and India, and is found mostly in Java.<sup>1</sup> The bark and leaves have been known to produce various skeletal alkaloids such as voacinol,<sup>2</sup> vobtusine,<sup>3</sup> vobtusinelactone,<sup>4</sup> and rhazine.<sup>5</sup> In our search for bioactive alkaloids from

tropical plants,<sup>6–14</sup> voacalgines A–E (**1–5**), five new indole alkaloids consisting of a C-mavacurine<sup>15</sup> type of skeleton with fused benzoic acid moiety, a macroline<sup>16</sup> type of skeleton, or a macroline-type of skeleton with another C<sub>6</sub> unit, have been isolated from the bark of *V. grandifolia*. In this paper, we describe the isolation and structure elucidation of **1–5** as well as their *in vitro* cell growth inhibitory activities against three human cell lines.



\* Corresponding author. E-mail address: [moritah@hoshi.ac.jp](mailto:moritah@hoshi.ac.jp) (H. Morita).

## 2. Results and discussion

### 2.1. Voacalgine A (1)

Voacalgine A (**1**) showed a molecular formula,  $C_{27}H_{26}N_2O_6$ , which was determined by HRESITOFMS [ $m/z$  475.1842 ( $M+H$ )<sup>+</sup>,  $\Delta$   $-2.7$  mmu]. IR absorption band was characteristic of carbonyl ( $1750$  and  $1670\text{ cm}^{-1}$ ) and hydroxyl ( $3023\text{ cm}^{-1}$ ) groups.  $^1\text{H}$  and  $^{13}\text{C}$  NMR data (Table 1) suggested the presence of two  $\text{sp}^3$  quaternary carbons, four  $\text{sp}^3$  methylenes, three  $\text{sp}^3$  methines, two methyls, seven  $\text{sp}^2$  methines, and nine  $\text{sp}^2$  quaternary carbons. Among them, two  $\text{sp}^3$  methylenes ( $\delta_{\text{C}}$  48.8;  $\delta_{\text{H}}$  2.83 and 2.83, and  $\delta_{\text{C}}$  53.7;  $\delta_{\text{H}}$  3.11 and 4.34) and two  $\text{sp}^3$  methines ( $\delta_{\text{C}}$  52.8;  $\delta_{\text{H}}$  3.38, and  $\delta_{\text{C}}$  58.7;  $\delta_{\text{H}}$  4.67) were attached to the nitrogen atom, and one  $\text{sp}^3$  quaternary carbon ( $\delta_{\text{C}}$  104.7) was ascribed to that bearing both an oxygen and a nitrogen atoms.

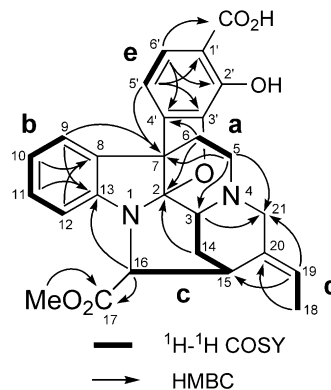
**Table 1**

$^1\text{H}$  ( $J$ , Hz) and  $^{13}\text{C}$  NMR data of voacalgine A (**1**) in  $\text{CD}_3\text{OD}$  at 300 K

Position	$\delta_{\text{H}}$	$\delta_{\text{C}}$
2		104.7
3	3.38 (1H, dd, 2.9, 2.9)	52.8
5	2.83 (2H, m)	48.8
6a	2.32 (1H, ddd, 15.2, 10.6, 6.7)	28.8
6b	2.55 (1H, br d, 15.2)	
7		49.8
8		136.4
9	6.79 (1H, dd, 7.8, 1.8)	123.6
10	6.81 (1H, ddd, 7.8, 7.8, 0.8)	122.0
11	7.10 (1H, ddd, 7.9, 7.8, 1.8)	128.8
12	6.39 (1H, d, 7.9)	111.5
13		146.6
14a	1.82 (1H, ddd, 13.6, 3.4, 3.4)	27.5
14b	2.77 (1H, ddd, 13.6, 3.3, 3.3)	
15	3.55 (1H, m)	32.6
16	4.67 (1H, d, 4.2)	58.7
17		171.3
18	1.65 (3H, dd, 6.8, 2.3)	12.6
19	5.50 (1H, dq, 1.7, 6.8)	122.0
20		135.3
21a	3.11 (1H, d, 12.8)	53.7
21b	4.34 (1H, br d, 12.8)	
1'		108.0
2'		152.9
3'		147.1
4'		128.5
5'	7.30 (1H, d, 8.3)	118.6
6'	7.26 (1H, d, 8.3)	123.1
1'-COOH		170.0
OMe	3.78 (3H, s)	52.9

The gross structure of **1** was deduced from extensive analyses of the two-dimensional NMR data, including the  $^1\text{H}$ – $^1\text{H}$  COSY, HMQC, and HMBC spectra in  $\text{CD}_3\text{OD}$  (Fig. 1). The  $^1\text{H}$ – $^1\text{H}$  COSY and HMQC spectra revealed connectivity of five partial structures **a** (C-5–C-6), **b** (C-9–C-12), **c** (C-3, C-14–C-16), **d** (C-18–C-19), and **e** (C-5'–C-6') as shown in Fig. 1.

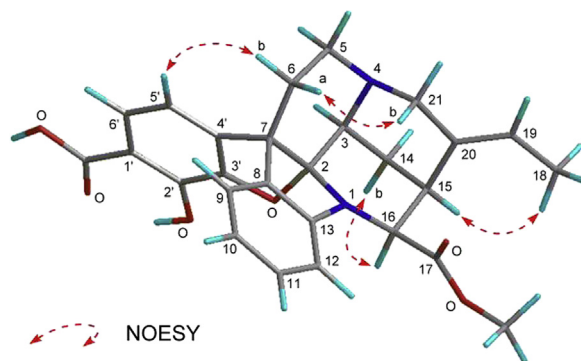
HMBC cross-peaks of  $\text{H}_2$ -5 to C-3 and C-21, and H-3 to C-21 established the connections among C-3, C-5, and C-21 through N-4. The connectivity of partial structures **a**, **c**, and indoline ring (C-2, C-7–C-13 and N-1) was revealed by the HMBC correlations of H-9 and  $\text{H}_2$ -5 to C-7 ( $\delta_{\text{C}}$  49.8), and H-6b and H-14a to C-2 ( $\delta_{\text{C}}$  104.7). HMBC correlations from  $\text{H}_3$ -18 to C-20 and H-19 to C-15 and C-21 established the presence of piperidine ring (C-3, C-14–C-15, C-20–C-21, and N-4) with ethylidene side chain at C-20. HMBC correlations from H-16 to C-13, and H-16 and methoxy protons to C-17 indicated voacalgine A possessed C-mavacurine type skeleton. On the other hand, the presence of 2,3-dihydroxybenzoate including partial structure **e** was presumed from the HMBC correlations from H-5' to C-1' and C-3', and H-6' to C-2', C-4', and carboxyl carbon. In



**Fig. 1.** Selected 2D NMR correlations for voacalgine A (**1**).

addition, the connectivity between this moiety and indole alkaloid moiety at C-4' and C-7 was assigned by the HMBC correlations from H-6a to C-4' and H-5' to C-7. Moreover, the connectivity between C-3' ( $\delta_{\text{C}}$  147.1) and C-2 through an oxygen atom was elucidated by comparison of chemical shifts with bipleiophylline<sup>17</sup> ( $\delta_{\text{C}}$  146.9 and  $\delta_{\text{C}}$  103.2, respectively). Thus, the gross structure of voacalgine A (**1**) was assigned to be a new indole alkaloid consisting of a C-mavacurine type of skeleton and 2,3-dihydroxybenzoic acid.

The relative stereochemistry of **1** was elucidated by the NOESY correlations. A 3,8-diazatricyclo[6.2.2.0<sup>4,9</sup>]dodecane ring (C-2–C-7, C-14–C-16, C-20, C-21, N-1, and N-4) strongly required that both H-3 and H-15 were  $\alpha$ -orientation, and  $\alpha$ -orientation of benzoic acid moiety was supported by the NOESY correlations of H-6b/H-5' and H-6a/H-21b. An  $\alpha$ -configuration of H-16 and *E*-configuration of double bond (C-19–C-20) were elucidated by the correlations of H-14b/H-16 and H-15/H<sub>3</sub>-18, respectively (Fig. 2).



**Fig. 2.** Selected NOESY correlations for voacalgine A (**1**).

### 2.2. Voacalgine B (2)

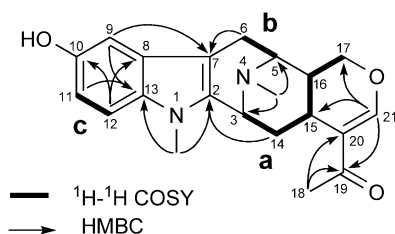
Voacalgine B (**2**) showed a molecular formula,  $C_{21}H_{24}N_2O_3$ , which was determined by HRESITOFMS [ $m/z$  353.1861 ( $M+H$ )<sup>+</sup>,  $\Delta$   $+0.1$  mmu]. IR absorption band was characteristic of  $\alpha,\beta$ -unsaturated ketone ( $1650$  and  $1620\text{ cm}^{-1}$ ) and hydroxyl ( $3300\text{ cm}^{-1}$ ) groups.  $^1\text{H}$  and  $^{13}\text{C}$  NMR data (Table 2) suggested the presence of three  $\text{sp}^3$  methylenes, four  $\text{sp}^3$  methines, three methyls, four  $\text{sp}^2$  methines, and seven  $\text{sp}^2$  quaternary carbons. Among them, two  $\text{sp}^3$  methines ( $\delta_{\text{C}}$  57.5;  $\delta_{\text{H}}$  4.97, and  $\delta_{\text{C}}$  57.7;  $\delta_{\text{H}}$  3.98) and two methyls ( $\delta_{\text{C}}$  29.6;  $\delta_{\text{H}}$  3.68, and  $\delta_{\text{C}}$  40.6;  $\delta_{\text{H}}$  2.92) were attached to the nitrogen atom, and one  $\text{sp}^3$  methylene ( $\delta_{\text{C}}$  65.4;  $\delta_{\text{H}}$  4.27 and 4.35), one  $\text{sp}^2$  methine ( $\delta_{\text{C}}$  160.5;  $\delta_{\text{H}}$  7.83), and one  $\text{sp}^2$  quaternary carbon ( $\delta_{\text{C}}$  152.5) were ascribed to that bearing an oxygen atom.

**Table 2**  
<sup>1</sup>H (J, Hz) and <sup>13</sup>C NMR data of voacalgine B (**2**) in CD<sub>3</sub>OD at 300 K<sup>a</sup>

Position	$\delta_{\text{H}}$	$\delta_{\text{C}}$
2		128.9
3	4.97 (1H, br s)	57.5
5	3.98 (1H, d, 7.4)	57.7
6a	3.10 (1H, d, 18.0)	24.1
6b	3.49 (1H, dd, 18.0, 7.4)	
7		105.5
8		127.2
9	6.90 (1H, d, 2.3)	103.7
10		152.5
11	6.83 (1H, dd, 8.8, 2.3)	113.7
12	7.29 (1H, d, 8.8)	111.2
13		134.5
14a	1.99 (1H, dd, 11.8, 11.8)	31.4
14b	2.42 (1H, m)	
15	2.68 (1H, dt, 11.8, 6.0)	25.0
16	2.45 (1H, m)	39.0
17a	4.27 (1H, dd, 10.7, 10.7)	65.4
17b	4.35 (1H, dd, 10.7, 2.6)	
18	2.13 (3H, s)	25.0
19		198.3
20		119.5
21	7.83 (1H, s)	160.5
N(1)-Me	3.68 (3H, s)	29.6
N(4)-Me	2.92 (3H, s)	40.6

<sup>a</sup> TFA salt.

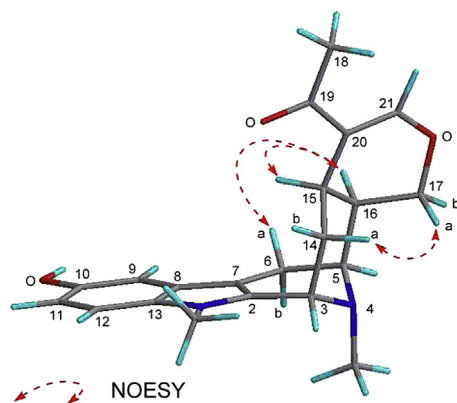
The gross structure of **2** was deduced from extensive analyses of the two-dimensional NMR data, including the <sup>1</sup>H–<sup>1</sup>H COSY, HMQC, and HMBC spectra in CD<sub>3</sub>OD (Fig. 3). The <sup>1</sup>H–<sup>1</sup>H COSY and HMQC spectra revealed connectivity of three partial structures **a** (C-3, C-14–C-17), **b** (C-5–C-6), and **c** (C-11–C-12) as shown in Fig. 3.

**Fig. 3.** Selected 2D NMR correlations for voacalgine B (**2**).

The presence of 5-hydroxy-*N*-methylindole ring was deduced by HMBC correlations of *N*(1)-Me to C-2 and C-13, H-9 to C-7 and C-13, H-12 to C-8 and oxygenated C-10, and H-11 to C-13. HMBC cross-peaks of *N*(4)-Me to C-3 and C-5 established the connection between C-3 and C-5 through *N*-4. The connection among indole ring and partial structures **a** and **b** was indicated by HMBC correlations of H-6 to C-7 and H-14 to C-2. HMBC correlations from H<sub>3</sub>-18 to C-19 and C-20, and H-21 to C-15, C-17, and C-19 established the presence of 3,4-dihydro-2*H*-pyran ring (C-15–C-17, C-20–C-21 and O) with an acetyl group at C-20. Thus, the gross structure of voacalgine B (**2**) was assigned to be a new indole alkaloid with a hydroxyl group at C-10 of alstonerine.<sup>18</sup>

The relative stereochemistry of **2** was elucidated by the NOESY correlations. The correlations of H-14a/H-17a, H-16/H-15 and H-6a indicated the  $\alpha$ -orientation of an *N*-methyl group at *N*-4 and the  $\beta$ -configuration of H-15 and H-16. Thus, the relative stereochemistry of **2** was assigned as shown in Fig. 4.

The CD spectrum of **2** showed a similar pattern to that of alstonerine.<sup>8</sup> Thus, the absolute configurations of **2** were elucidated to be 3*S*, 5*S*, 15*R*, and 16*R*.

**Fig. 4.** Selected NOESY correlations for voacalgine B (**2**).

### 2.3. Voacalgine C (**3**)

Voacalgine C (**3**) showed a molecular formula, C<sub>26</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>, which was determined by HRESITOFMS [*m/z* 439.2618 (M+H)<sup>+</sup>,  $\Delta$  +2.1 mmu]. IR absorption band was characteristic of hydroxyl (3400 cm<sup>-1</sup>) group. <sup>1</sup>H and <sup>13</sup>C NMR data (Table 3) suggested the presence of seven sp<sup>3</sup> methylenes, six sp<sup>3</sup> methines, two sp<sup>3</sup> quaternary carbons, three methyls, four sp<sup>2</sup> methines, and four sp<sup>2</sup> quaternary carbons. Among them, two sp<sup>3</sup> methines ( $\delta_{\text{C}}$  55.5;  $\delta_{\text{H}}$  4.44, and  $\delta_{\text{C}}$  58.0;  $\delta_{\text{H}}$  3.35) and two methyls ( $\delta_{\text{C}}$  29.3;  $\delta_{\text{H}}$  3.68, and  $\delta_{\text{C}}$  41.4;  $\delta_{\text{H}}$  2.59) were attached to the nitrogen atom, and an sp<sup>3</sup> methine ( $\delta_{\text{C}}$  70.5;  $\delta_{\text{H}}$  3.50), two sp<sup>3</sup> methylenes ( $\delta_{\text{C}}$  64.0;  $\delta_{\text{H}}$  3.82 and 4.00, and  $\delta_{\text{C}}$  62.7;  $\delta_{\text{H}}$  3.48 and 3.83), and two sp<sup>3</sup> quaternary carbon ( $\delta_{\text{C}}$  107.2 and 107.3) were ascribed to that bearing an oxygen atom.

**Table 3**  
<sup>1</sup>H (J, Hz) and <sup>13</sup>C NMR data of voacalgine C (**3**) in CD<sub>3</sub>OD at 300 K<sup>a</sup>

Position	$\delta_{\text{H}}$	$\delta_{\text{C}}$
2		131.0
3	4.44 (1H, br s)	55.5
5	3.35 (1H, m)	58.0
6a	2.70 (1H, br d, 16.1)	23.8
6b	3.34 (1H, m)	
7		106.9
8		127.2
9	7.46 (1H, d, 7.6)	119.0
10	7.06 (1H, dd, 7.6, 7.4)	120.3
11	7.17 (1H, dd, 7.4, 7.9)	122.7
12	7.36 (1H, d, 7.9)	110.1
13		139.0
14a	1.78 (1H, m)	32.3
14b	2.48 (1H, ddd, 14.7, 14.7, 3.5)	
15	1.78 (1H, m)	27.4
16	2.23 (1H, ddd, 10.0, 5.1, 5.1)	37.7
17a	3.82 (1H, m)	64.0
17b	4.00 (1H, dd, 11.9, 10.0)	
18	1.58 (3H, s)	26.0
19		107.3
20	2.07 (1H, dd, 11.8, 7.6)	44.2
21a	1.78 (1H, m)	38.8
21b	2.02 (1H, dd, 12.3, 12.3)	
22		107.2
23	3.50 (1H, br t, 3.0)	70.5
24a	1.62 (1H, m)	28.2
24b	1.97 (1H, dddd, 12.8, 12.6, 3.0, 3.0)	
25a	1.29 (1H, m)	20.9
25b	1.87 (1H, dddd, 12.6, 12.6, 12.4, 3.4, 3.4)	
26a	3.48 (1H, m)	62.7
26b	3.83 (1H, m)	
N(1)-Me	3.68 (3H, s)	29.3
N(4)-Me	2.59 (3H, s)	41.4

<sup>a</sup> formic acid salt.

The gross structure of **3** was deduced from extensive analyses of the two-dimensional NMR data, including the  $^1\text{H}$ – $^1\text{H}$  COSY, HMQC, and HMBC spectra in  $\text{CD}_3\text{OD}$  (Fig. 5). The  $^1\text{H}$ – $^1\text{H}$  COSY and HMQC spectra revealed connectivity of four partial structures **a** (C-3, C-14–C-17, and C-20–C-21), **b** (C-5–C-6), **c** (C-9–C-12), and **d** (C-23–C-26) as shown in Fig. 5.

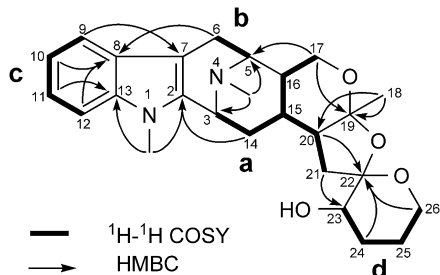


Fig. 5. Selected 2D NMR correlations for voacalgine C (**3**).

By analysis of HMBC spectrum as shown in Fig. 5, three partial structures **a–c** composed of a macroline-type skeleton at C-2–C-17. The HMBC correlations for  $\text{H}_3$ -18 to C-19 ( $\delta_{\text{C}}$  107.3) and C-20 ( $\delta_{\text{C}}$  44.2), and  $\text{H}_2$ -17 to C-19 indicated the presence of 2-methyltetrahydropyran ring (C-15–C-20 and O). Furthermore, correlations of H-20, H-24a, and H-26a to C-22 ( $\delta_{\text{C}}$  107.2) and H-21b to C-23 ( $\delta_{\text{C}}$  70.5) suggested the presence of tri-cyclic polyether structure on C-15–C-26. Thus, the gross structure of voacalgine C (**3**) was elucidated to be possessing a macroline-type skeleton with tetrahydropyran-2-spiro-2'-tetrahydrofuran ring as 25-deoxy form of macrodasine E.<sup>19</sup>

The relative stereochemistry of **3** was mainly elucidated by the NOESY correlations. In the 2-methyltetrahydropyran ring (C-15–C-20), the NOESY correlations of  $\text{H}_3$ -18/H-14b, H-17b, and H-20, and a large  $^3J$  coupling constant (10.0 Hz) between H-16 and H-17b suggested that  $\text{CH}_3$ -18 and H-20 were  $\alpha$ -oriented and H-15 and H-16 were  $\beta$ -oriented. The correlations of H-5/H-17a and H-6a/H-16 indicated the  $\alpha$ -orientation of an *N*-methyl group at N-4 (Fig. 6).

On the other hand, the NOESY correlations of H-24b/H-26b and large  $^3J$  coupling constants between H-24b/H-25b (12.4 Hz) and H-25b/H-26 (12.4 Hz) indicated that the tetrahydropyran ring (C-22–C-26) took chair conformation. And an  $\alpha$ -oriented hydroxy group at C-23 was deduced from a small  $^3J$  coupling constant

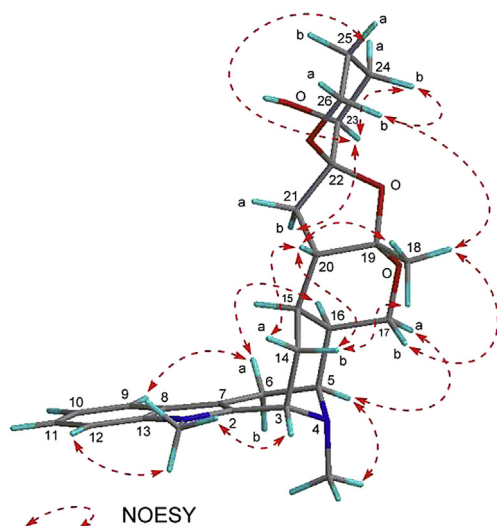


Fig. 6. Selected NOESY correlations for voacalgine C (**3**).

(3.0 Hz) between H-23/H-24b. Finally, the relative configuration of a spiro carbon at C-22 was elucidated by the NOESY correlation of  $\text{H}_3$ -18/H-26b.

The stable conformer corresponding to the axial orientation of OH-23 was generated after conformational searching by computer modeling (MMFF force field energy minimization) and the result was consistent with the coupling constants of H-23 (br t, 3.0 Hz).

## 2.4. Voacalgine D (**4**)

Voacalgine D (**4**) showed a molecular formula,  $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_4$ , which was determined by HRESITOFMS [ $m/z$  435.2299 ( $\text{M}+\text{H}$ )<sup>+</sup>,  $\Delta$  +1.6 mmu]. IR absorption band was characteristic of  $\alpha,\beta$ -unsaturated ketone ( $1670\text{ cm}^{-1}$ ) and hydroxyl ( $3400\text{ cm}^{-1}$ ) groups. By analysis of 1D and 2D NMR spectra (Table 4), voacalgine D possessed a macroline-type skeleton as well as voacalgine C.

Table 4  
 $^1\text{H}$  ( $J$ , Hz) and  $^{13}\text{C}$  NMR data of voacalgine D (**4**) in  $\text{CD}_3\text{OD}$  at 300 K<sup>a</sup>

Position	$\delta_{\text{H}}$	$\delta_{\text{C}}$
2		132.3
3	4.20 (1H, br s)	55.6
5	3.13 (1H, m)	57.0
6a	2.54 (1H, d, 16.6)	23.6
6b	3.24 (1H, m)	
7		107.1
8		127.3
9	7.38 (1H, d, 7.6)	118.8
10	7.00 (1H, dd, 7.6, 7.4)	119.9
11	7.12 (1H, dd, 7.4, 7.9)	122.1
12	7.24 (1H, d, 7.9)	109.8
13		138.7
14a	1.68 (1H, m)	27.2
14b	2.87 (1H, m)	
15	1.65 (1H, m)	28.5
16	1.97 (1H, ddd, 11.8, 3.4, 3.4)	44.8
17a	3.46 (1H, m)	61.0
17b	4.49 (1H, dd, 11.7, 11.7)	
18	1.32 (3H, s)	28.4
19		98.3
20	2.21 (1H, ddd, 10.6, 5.3, 5.3)	43.6
21a	2.82 (1H, m)	37.9
21b	2.90 (1H, m)	
22	7.09 (1H, br d, 3.6)	190.6
23	6.54 (1H, dd, 3.6, 1.7)	153.9
24	7.66 (1H, dd, 1.7, 0.5)	119.2
25	3.44 (3H, s)	113.5
26	2.42 (3H, s)	148.7
N(1)-Me		29.1
N(4)-Me		41.5

<sup>a</sup> Formic acid salt.

The HMBC correlations from  $\text{H}_3$ -18 to C-19 ( $\delta_{\text{C}}$  98.3) and C-20 ( $\delta_{\text{C}}$  43.6), and H-17a to C-15 ( $\delta_{\text{C}}$  28.5) and C-19, and H-21a to C-15 indicated the presence of 2-hydroxy-2-methyltetrahydropyran ring (C-15–C-20 and O). And, the correlations of H-26/C-23 and C-24, and H-24/C-23 and 26 suggested the presence of a 2-furyl group on C-23–C-26. Furthermore, the connectivity of C-21 and C-23 through C-22 ketone was deduced from the HMBC correlation of H-21a to C-22 and the NOESY correlation of H-24/H-21a. Thus, the gross structure of voacalgine D (**4**) was assigned to be a new indole alkaloid consisting of a macroline-type skeleton with a 2-furyloyl group at C-21 (Fig. 7).

The relative stereochemistry of **4** was elucidated by the NOESY correlations. The correlations of H-14b/H-17b, H-15/H-16, H-16/H-20, and H-6a/H-16 indicated the  $\alpha$ -orientation of an *N*-methyl group at N-4 and the  $\beta$ -configuration of H-15, H-16, and H-20. The

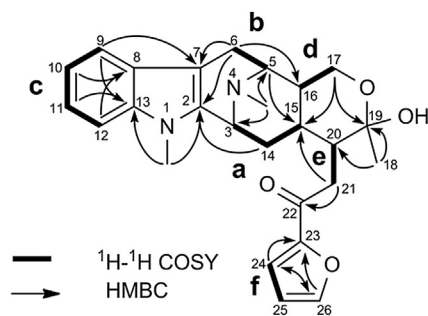


Fig. 7. Selected 2D NMR correlations for voacalgine D (4).

configuration of a methyl group at C-19 was assigned as equatorial by the NOESY correlation of H-20/H<sub>3</sub>-18 and no correlation of H<sub>3</sub>-18/H-17b (Fig. 8).

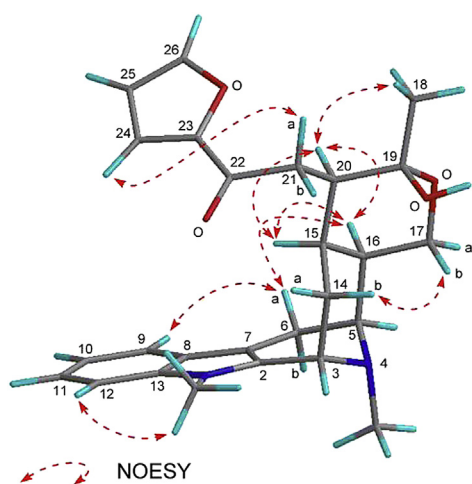


Fig. 8. Selected NOESY correlations for voacalgine D (4).

## 2.5. Voacalgine E (5)

Voacalgine E (5) showed molecular formula, C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>, which was determined by HRESITOFMS [*m/z* 433.2144 (M+H)<sup>+</sup>, Δ +1.7 mmu]. IR absorption band was characteristic of ketone (1710 cm<sup>-1</sup>) and α,β-unsaturated ketone (1670 cm<sup>-1</sup>) groups. By analysis of 1D and 2D NMR spectra (Table 5), voacalgine E possessed a macroline-type skeleton and a 2-furyloyl group as well as voacalgine D.

The gross structure of 5 was deduced from extensive analyses of the two-dimensional NMR data. The <sup>1</sup>H–<sup>1</sup>H COSY and HMQC spectra revealed connectivity of four partial structures **a** (C-3, C-14–C-17), **b** (C-5–C-6), **c** (C-9–C-12), and **d** (C-24–C-26) as shown in Fig. 9. Since, the left-half of the structure of voacalgine E in Fig. 9 showed similar HMBC correlations as well as voacalgine D (4), 5 was presumed to have a macroline-type skeleton. The HMBC correlations of H<sub>2</sub>-17 to C-20 (δ<sub>C</sub> 92.9), H<sub>3</sub>-18 to C-19 (δ<sub>C</sub> 214.9) and C-20, and H-15 to C-19 revealed the presence of 2-acetyltetrahydrofuran ring (C-15–C-20). On the other hand, the presence of a 2-furyloyl group was elucidated by the HMBC correlations from H-25 and H-26 to C-23 (δ<sub>C</sub> 153.6), and H-24 to C-22 ketone (δ<sub>C</sub> 186.6). And the connection of this moiety and C-20 through C-21 methylene was deduced by the HMBC correlations of

Table 5  
<sup>1</sup>H (J, Hz) and <sup>13</sup>C NMR data of voacalgine E (5) in CD<sub>3</sub>OD at 300 K<sup>a</sup>

Position	δ <sub>H</sub>	δ <sub>C</sub>
2		126.8
3	5.09 (1H, br s)	56.0
5	4.01 (1H, br s)	55.6
6a	3.08 (1H, d, 17.6)	24.0
6b	3.42 (1H, dd, 17.6, 6.0)	
7		105.4
8		126.8
9	7.54 (1H, d, 7.7)	119.5
10	7.13 (1H, dd, 7.7, 7.6)	121.0
11	7.27 (1H, dd, 7.9, 7.6)	123.9
12	7.46 (1H, d, 7.9)	110.6
13		139.6
14a	2.28 (1H, ddd, 12.1, 11.8, 0.8)	27.6
14b	2.40 (1H, br d, 11.8)	
15	2.14 (1H, ddd, 12.1, 7.1, 5.9)	38.0
16	2.74 (1H, ddd, 8.2, 8.2, 7.1)	44.3
17a	4.23 (1H, dd, 9.9, 9.7)	69.4
17b	4.34 (1H, dd, 9.7, 9.4)	
18	2.24 (3H, s)	27.0
19		214.9
20		92.9
21a	3.36 (1H, m)	43.8
21b	3.49 (1H, m)	
22		186.6
23		153.6
24	7.36 (1H, br d, 3.4)	120.0
25	6.64 (1H, dd, 3.4, 1.2)	113.8
26	7.78 (1H, br s)	149.1
N(1)-Me	3.78 (3H, s)	29.7
N(4)-Me	2.94 (3H, s)	40.3

<sup>a</sup> Formic acid salt.

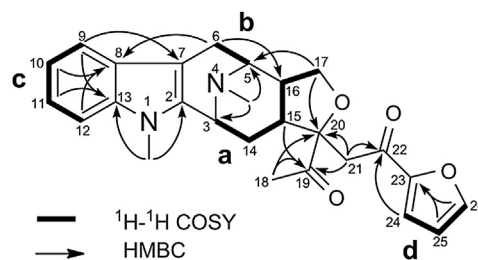


Fig. 9. Selected 2D NMR correlations for voacalgine E (5).

H<sub>2</sub>-21 to C-19, C-20, and C-22. Thus, the gross structure of voacalgine E was assigned to be a new indole alkaloid consisting of a macroline-type skeleton that E-ring is transformed to five-membered ring with a 2-furyloyl group at C-21 and an acetyl group at C-20.

The relative stereochemistry of 5 was elucidated by the NOESY correlations. The correlations of H-15/H-16, H-16/H<sub>3</sub>-18, and H-6a/H-16 indicated the α-orientation of an N-methyl group at N-4 and the β-configuration of H-15, H-16, and an acetyl group (Fig. 10).

## 3. Plausible biogenetic pathway

A plausible biogenetic pathway of voacalgines A, D, and E (1, 4, and 5) with rare skeletons was proposed as shown in Fig. 11. Voacalgine A (1) is the second example combined with C-mavacurine type of skeleton (6) and 2,3-dihydroxybenzoic acid (7). Voacalgines D (4) and E (5) might be derived from the ring-opened form of alstonerine (8)<sup>20</sup> through introduction of C<sub>6</sub> unit<sup>21</sup> to C-20 followed by cyclization.

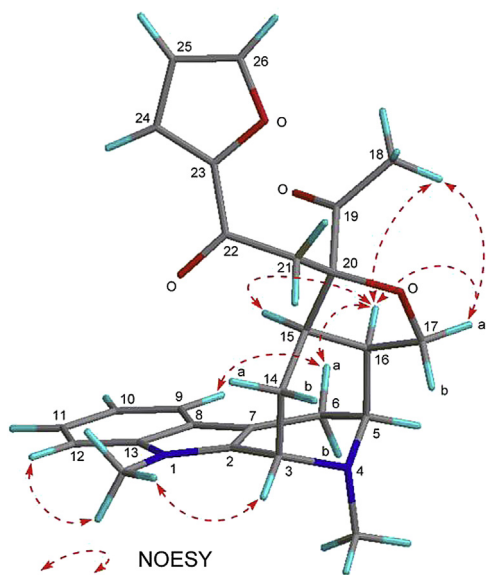


Fig. 10. Selected NOESY correlations for voacalgine E (5).

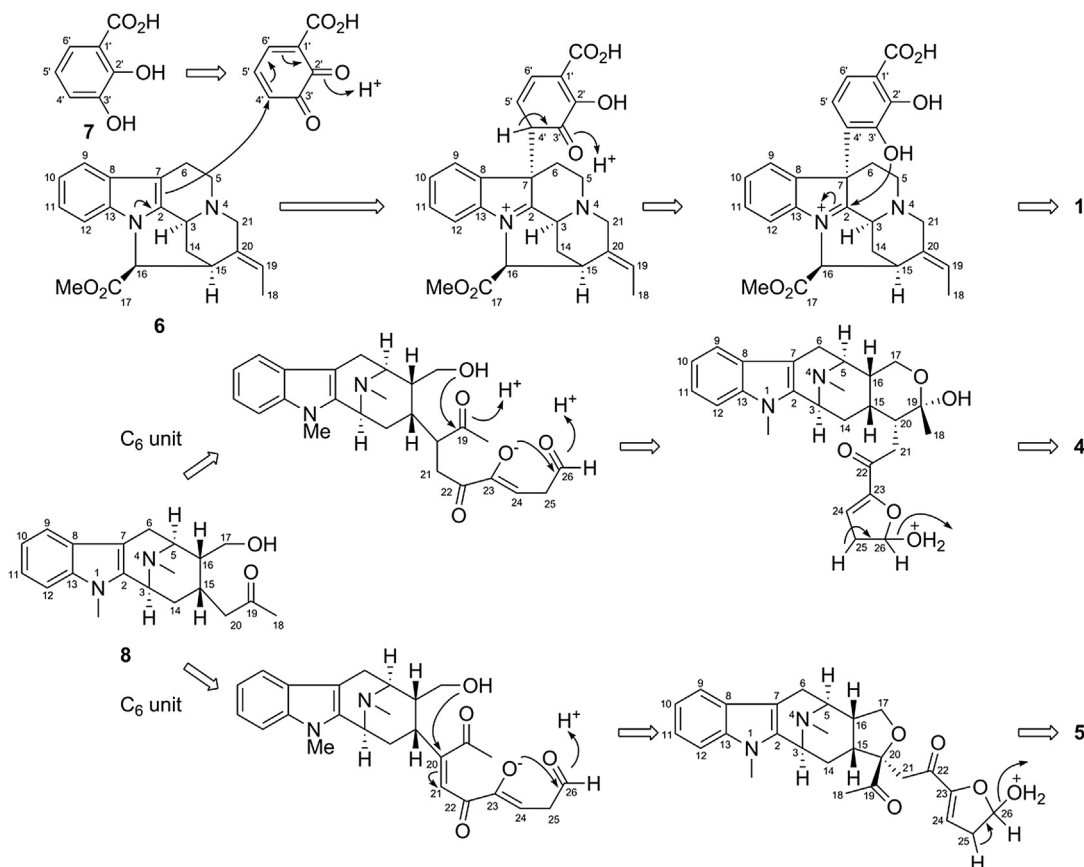


Fig. 11. Plausible biogenetic pathway of voacalgines A (1), D (4), and E (5).

moderate cell growth inhibitory activities against HL-60 and HCT116 cells ( $IC_{50}$  for **1**: 12.1  $\mu$ M for HL-60, and 45.7  $\mu$ M for HCT116).

## 5. Experimental section

### 5.1. General experimental details

**5.1.1. General methods.** 1D and 2D NMR spectra were recorded on a Bruker AV700 spectrometer, and chemical shifts were referenced to the residual solvent peaks ( $\delta_H$  3.31 and  $\delta_C$  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 1 K 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 1 K 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 1 K for  $F_1$  and multiplication with squared cosine-bell windows shifted in both dimensions were performed prior to 2D Fourier transformation.

## 4. Conclusion

In this work, five new indole alkaloids, voacalgines A–E (**1**–**5**) were isolated from the bark of *V. grandifolia*. The structures and stereochemistry of **1**–**5** were elucidated by 2D NMR analysis.

Voacalgines A–E (**1**–**5**) were tested for cytotoxic activity against HL-60, HCT116, and MCF7 cell line. Voacalgine A only showed

## 5.2. Material

The bark of *V. grandifolia* was collected at Purwodadi Botanical Garden, Indonesia in 2006. The botanical identification was made by Ms. Sri Wuryanti, Purwodadi Botanical Garden, Indonesia. A voucher specimen (no. AP070910) has been deposited in the herbarium at Purwodadi Botanical Garden, Pasuruan, Indonesia.



### 5.3. Extraction and isolation

The bark of *V. grandifolia* (444 g) was extracted with MeOH, the extract (32 g) was treated with 3% tartaric acid (pH 2) and then partitioned with EtOAc. The aqueous layer was treated with saturated Na<sub>2</sub>CO<sub>3</sub> (aq) to pH 10 and extracted with CHCl<sub>3</sub> to give an alkaloidal fraction (4.3 g). The alkaloidal fraction was subjected to an amino SiO<sub>2</sub> column in hexane/EtOAc (1:0→0:1) and then CHCl<sub>3</sub>/MeOH (1:0→0:1).

The CHCl<sub>3</sub>/MeOH (50:1) eluted fraction was chromatographed over a SiO<sub>2</sub> column in CHCl<sub>3</sub>/MeOH (1:0→0:1) and the CHCl<sub>3</sub>/MeOH (50:1) eluted fraction was applied to an amino SiO<sub>2</sub> column in CHCl<sub>3</sub>/MeOH (1:0→0:1) to afford voacalgine A (**1**, 4.0 mg, 0.0009%).

The CHCl<sub>3</sub>/MeOH (1:0) eluted fraction of the first amino SiO<sub>2</sub> column was chromatographed over a SiO<sub>2</sub> column in CHCl<sub>3</sub>/MeOH (1:0→0:1) and the CHCl<sub>3</sub>/MeOH (50:1) eluted fraction was separated by an ODS HPLC (47% MeOH aq with 0.1% TFA, 2.0 mL/min, 254 nm) to afford voacalgine B (**2**, 3.7 mg, 0.0008%, *t*<sub>R</sub>=15 min).

The hexane/EtOAc (2:1) eluted fraction of the first amino SiO<sub>2</sub> column was chromatographed over a SiO<sub>2</sub> column in CHCl<sub>3</sub>/MeOH (1:0→0:1) and the CHCl<sub>3</sub>/MeOH (80:1) eluted fraction was separated by an ODS HPLC (42% MeOH aq with 0.1% formic acid, 2.0 mL/min, 254 nm) to afford voacalgine E (**5**, 1.3 mg, 0.0003%, *t*<sub>R</sub>=15 min), whereas the CHCl<sub>3</sub>/MeOH (50:1) eluted fraction was chromatographed over an amino SiO<sub>2</sub> column in hexane/EtOAc (1:0→0:1) and the hexane/EtOAc (2:1) eluted fraction was separated by an ODS HPLC (40% MeOH aq with 0.1% formic acid, 2.0 mL/min, 254 nm) to afford voacalgine C (**3**, 0.9 mg, 0.0002%, *t*<sub>R</sub>=20 min).

The CHCl<sub>3</sub>/MeOH (100:1) eluted fraction of the first amino SiO<sub>2</sub> column was separated by an ODS HPLC (48% MeOH aq with 0.1% formic acid, 2.0 mL/min, 254 nm) to afford voacalgine D (**4**, 2.6 mg, 0.0006%, *t*<sub>R</sub>=16 min).

### 5.4. Characterization of natural products

**5.4.1. Voacalgine A (1).** Brown amorphous solid;  $[\alpha]_D^{26} +110$  (c 1.0, CHCl<sub>3</sub>); IR (KBr)  $\nu_{\max}$  3023, 1750, and 1670 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{\max}$  201 ( $\epsilon$  34,600), 229 (15,600), and 334 (3100) nm; ESIMS *m/z* 475 (M+H)<sup>+</sup>; HRESITOFMS *m/z* 475.1842 [(M+H)<sup>+</sup>,  $\Delta$  -2.7 mmu, calcd for C<sub>27</sub>H<sub>27</sub>N<sub>2</sub>O<sub>6</sub>, 475.1869].

**5.4.2. Voacalgine B (2).** Brown amorphous solid;  $[\alpha]_D^{27} -67$  (c 1.0, CHCl<sub>3</sub>); IR (KBr)  $\nu_{\max}$  3300, 1650, and 1620 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{\max}$  201 ( $\epsilon$  19,000) and 232 (19,900) nm; CD (MeOH)  $\lambda_{\max}$  301 ( $\Delta\epsilon$  -6.63), 259 (+7.68), 229 (-9.35), and 205 (+5.34); ESIMS *m/z* 353 (M+H)<sup>+</sup>; HRESITOFMS *m/z* 353.1861 [(M+H)<sup>+</sup>,  $\Delta$  +0.1 mmu, calcd for C<sub>21</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub>, 353.1860].

**5.4.3. Voacalgine C (3).** Brown amorphous solid;  $[\alpha]_D^{22} -22$  (c 0.5, MeOH); IR (KBr)  $\nu_{\max}$  3400 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{\max}$  201 ( $\epsilon$  12,100), 229 (18,600), and 336 (3800) nm; ESIMS *m/z* 439 (M+H)<sup>+</sup>; HRESITOFMS *m/z* 439.2618 [(M+H)<sup>+</sup>,  $\Delta$  +2.1 mmu, calcd for C<sub>26</sub>H<sub>35</sub>N<sub>2</sub>O<sub>4</sub>, 439.2597].

**5.4.4. Voacalgine D (4).** Brown amorphous solid;  $[\alpha]_D^{24} -6$  (c 1.0, MeOH); IR (KBr)  $\nu_{\max}$  3400, 1670, and 1630 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{\max}$  229 ( $\epsilon$  30,400) and 273 (14,500) nm; ESIMS *m/z* 435 (M+H)<sup>+</sup>; HRESITOFMS *m/z* 435.2299 [(M+H)<sup>+</sup>,  $\Delta$  +1.6 mmu, calcd for C<sub>26</sub>H<sub>31</sub>N<sub>2</sub>O<sub>4</sub>, 435.2234].

**5.4.5. Voacalgine E (5).** Brown amorphous solid;  $[\alpha]_D^{22} -14$  (c 0.5, MeOH); IR (KBr)  $\nu_{\max}$  1710 and 1670 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{\max}$  201 ( $\epsilon$

14,900), 228 (20,400), and 374 (10,300) nm; ESIMS *m/z* 433 (M+H)<sup>+</sup>; HRESITOFMS *m/z* 433.2144 [(M+H)<sup>+</sup>,  $\Delta$  +1.7 mmu, calcd for C<sub>26</sub>H<sub>29</sub>N<sub>2</sub>O<sub>4</sub>, 433.2127].

### 5.5. Cytotoxicity

HL-60, human promyelocytic leukemia cells were maintained in RPMI-1640 medium; MCF7, human breast adenocarcinoma; and HCT116, human colorectal adenocarcinoma cells were maintained in Dulbecco's modified Eagle's medium (DMEM) medium. Both growth media were supplemented with 10% fetal calf serum and 1% penicillin–streptomycin. The cells (5×10<sup>3</sup> cells/well) were cultured in Nunc disposable 96-well plates containing 90  $\mu$ L of growth medium per well and were incubated at 37 °C in a humidified incubator of 5% CO<sub>2</sub>. Ten microliters of serially diluted samples (50  $\mu$ M, 25  $\mu$ M, 12.5  $\mu$ M, and 6.25  $\mu$ M) were added to the cultures at 24 h of incubation. After 48 h of incubation with the samples, 15  $\mu$ L of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (5 mg/mL) was added to each of the wells. The cultures were incubated for another 3 h before the cells supernatant are removed. After the removal of the cells supernatant, 50  $\mu$ L of dimethyl sulfoxide (DMSO) was added to each well. The formed formazan crystal was dissolved by re-suspension by pipette. The optical density was measured using a microplate reader (Bio-Rad) at 550 nm with reference wavelength at 700 nm. In all experiments, three replicates were used. Cisplatin was used as positive control (IC<sub>50</sub>: 0.87  $\mu$ M for HL-60, 27.7  $\mu$ M for MCF7, and 16.0  $\mu$ M for HCT116).


### Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research from Japan Society for the Promotion of Science, The Open Research Center Project, and Takeda Science Foundation.

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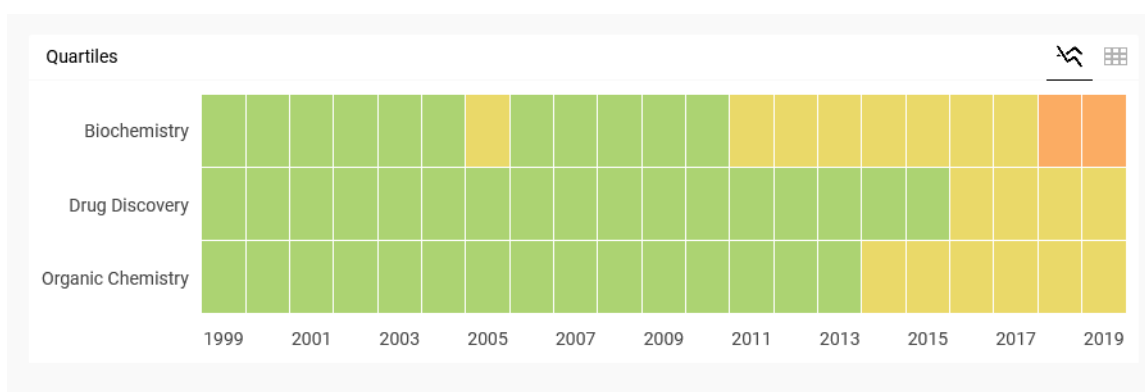
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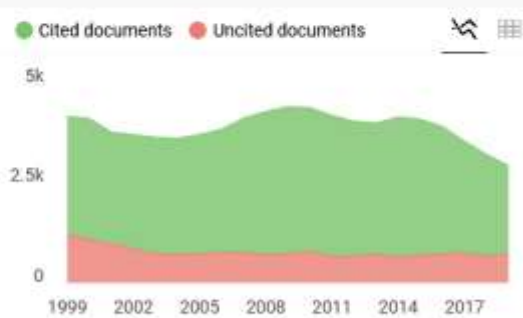
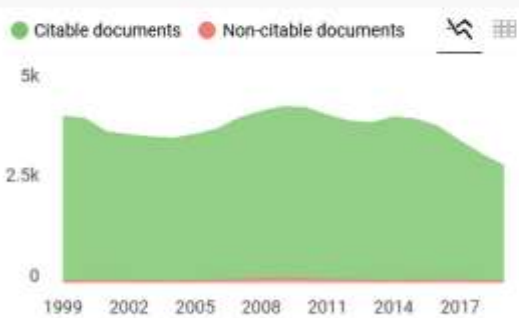
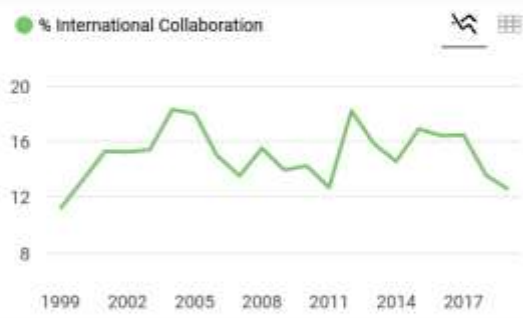
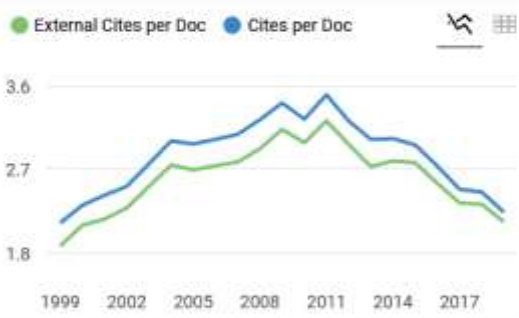
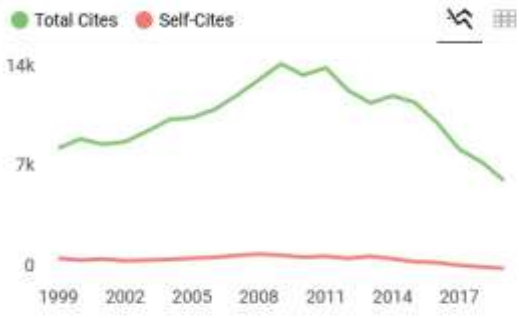
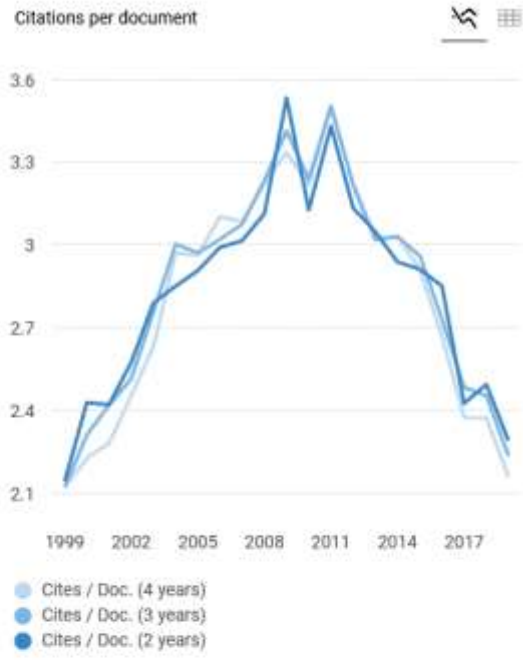
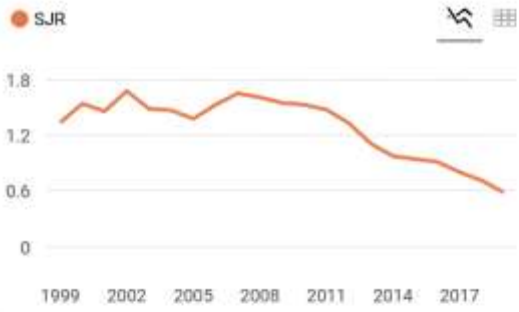
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