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TETRAHEDRON

New Picrotoxinin-type and Dendrobine-type Sesquiterpenoids from *Dendrobium* Snowflake 'Red Star'

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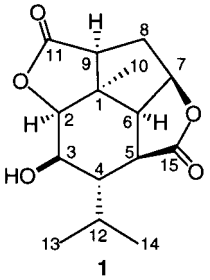
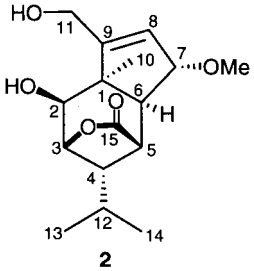
Abstract—Two new picrotoxinin-type sesquiterpenes, flakinins A (**1**) and B (**2**), and three new dendrobine-type sesquiterpene alkaloids, mubironines A (**3**), B (**4**), and C (**5**), have been isolated from the whole plants of *Dendrobium* Snowflake 'Red Star' (Orchidaceae). Their stereostructures were elucidated by 2D NMR data and chemical means. © 2000 Elsevier Science Ltd. All rights reserved.

During our search for structurally interesting compounds from higher plants,[1] we isolated two new picrotoxinin-type sesquiterpenes, flakinins A (**1**) and B (**2**), and three new dendrobine-type alkaloids, mubironines A (**3**), B (**4**), and C (**5**), from the whole plants of *Dendrobium* Snowflake 'Red Star' (Orchidaceae), and its original plant *Dendrobium nobile* is a Chinese herbal medicine[2] used as a tonic in China and Japan, and is known to contain several dendrobine-type alkaloids[3] structurally related to picrotoxinin,[4] a GABA receptor antagonist.[5] Here we describe the isolation and structure elucidation of **1**–**5**.



1



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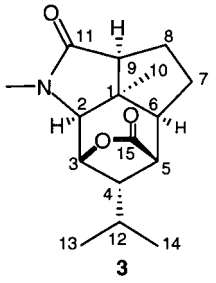

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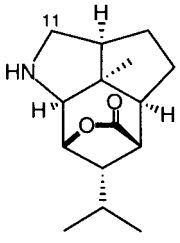

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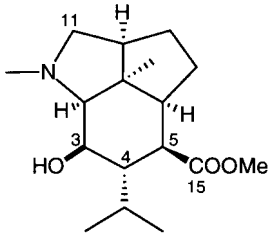

5

The whole plants were extracted with MeOH, and the MeOH extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials adjusted at pH 10 with sat. Na_2CO_3 were partitioned with $CHCl_3$. $CHCl_3$-soluble materials were subjected to a silica gel column ($CHCl_3$/EtOAc/MeOH), in which a fraction eluted with $CHCl_3$/EtOAc/MeOH (9:1:1) was purified by a C_{18} column (MeOH/0.1% TFA, 1:4→4:1) followed by C_{18} HPLC (CH_3CN/0.1% TFA, 1:3) to afford flakinins A (**1**,

Table 1. ^1H and ^{13}C NMR data of flakinin A (**1**) in $CDCl_3$ – CD_3OD (9:1) at 300 K

	δ_H	δ_C	HMBC (^1H)
1		49.15	8β, 5, 7, 10
2	4.35 (1H, d, 1.7)	86.33	3, 10
3	3.55 (1H, dd, 1.7, 9.6)	66.79	2, 4, 5
4	2.03 (1H, m)	42.02	2, 3, 5, 13, 14
5	2.57 (1H, dd, 2.3, 10.5)	38.52	4
6	2.42 (1H, dd, 6.0, 10.5)	47.47	2, 8β, 5, 9, 10
7	4.91 (1H, t, 6.0)	84.21	9, 8α
8α	2.55 (1H, d, 14.9)	34.14	6
8β	2.05 (1H, m)		
9	2.67 (1H, d, 7.6)	52.37	7, 8β, 10
10	1.16 (3H, s)	23.97	2, 6, 9
11		177.00	9, 8α
12	2.09 (1H, m)	28.44	3, 5, 13, 14
13	0.88 (3H, d, 6.8)	20.15	15
14	0.77 (3H, d, 6.8)	17.10	4, 13
15		178.04	4, 5, 6

Keywords: sesquiterpenoids; alkaloids; *Dendrobium*; Orchidaceae.

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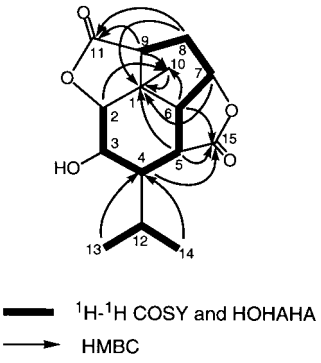
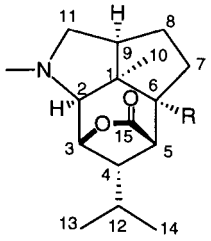
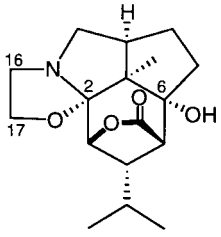
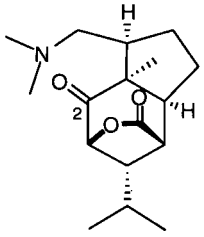


Figure 1. Selected 2D NMR correlations of flakinin A (**1**).

0.0002% yield) and B (**2**, 0.0002% yield), and mubironines B (**4**, 0.0007% yield) and C (**5**, 0.00007% yield) as colorless solids together with known related sesquiterpene alkaloids, dendrobine (**6**, 0.02%), 6-hydroxydendrobine (**7**, 0.001%), 6-hydroxydendroxine (**8**, 0.0002%), and nobilonine (**9**, 0.0007%). The fraction eluted with $CHCl_3$/EtOAc/MeOH (24:1:1) in the previous silica gel column was purified by C_{18} HPLC (CH_3CN/0.1% TFA, 1:3) to give mubironine A (**3**, 0.0001%).







Flakinin A {**1**, $[\alpha]_D^{23}$ +21° (c 0.8, MeOH)} was revealed to have the molecular formula, $C_{15}H_{20}O_5$, by HRESIMS [*m/z* 303.1213 $(M+Na)^+$, Δ +0.5 mmu]. IR absorptions at 3500 and 1770 cm^{-1} were ascribed to hydroxy and ester carbonyl of γ-lactone ring, respectively. The ^{13}C NMR (Table 1) spectrum showed carbon signals due to three methyls, eight sp^3 methines (three of them bearing an oxygen atom), one sp^3 methylene, two ester carbonyls (δ 177.00 and 178.04), and a quaternary carbon. The chemical shifts of C-7 (δ 84.21) and C-2 (δ 86.33) indicated that these carbons were attached to a lactonic oxygen atom, whereas C-3 (δ 66.79) was connected to a hydroxy group, indicating the presence of two γ-lactone rings. The ^1H-^1H COSY and HOHAHA spectra revealed connectivities of C-2~C-9 and C-12 to C-13 and C-14 (Fig. 1). The connection between C-4 and C-12 was derived from HMBC correlations from H_3-13 and H_3-14 to C-4. The presence of a cyclopentane ring (C-1 and C-6~C-9) was implied by HMBC correlations from H-8β, H-7, H-5, and H_3-10 to C-1. HMBC correlations of H-9, H-6, and H-2 to C-10 indicated the presence of a cyclohexane ring (C-1~C-6). The H-9 and H_2-8 showed HMBC correlations for C-11 (δ_C 177.00), and H-6, H-5, and H-4 showed HMBC correlations for C-15 (δ_C 178.04), thus giving rise to the connectivities of C-9 to C-11 and C-5 to C-15. These 2D NMR data led to the complete assignments of ^1H and ^{13}C signals of **1** as shown

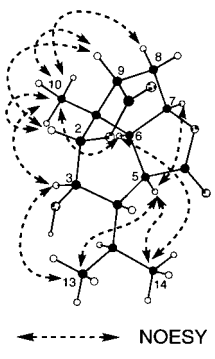


Figure 2. Selected NOESY correlations and relative stereochemistry of flakinin A (**1**).

Table 2. ^1H and ^{13}C NMR data of flakinin B (**2**) in $CDCl_3$ – CD_3OD (9:1) at 300 K

	δ_H	δ_C	HMBC (^1H)
1		53.01	3, 7, 8, 10, 11
2	3.65 (1H, brs)	73.85	10
3	4.55 (1H, d, 5.5)	85.46	2, 4
4	2.09 (1H, m)	51.51	2, 3, 13, 14
5	2.48 (1H, d, 4.0)	49.94	3, 6, 7
6	2.22 (1H, brd, 6.0, 3.5)	47.19	4, 8, 10
7	4.15 (1H, d, 2.0)	86.08	8, OMe
8	5.74 (1H, d, 2.0)	129.66	11a, 11b
9		154.23	2, 6, 8, 10, 11a, 11b
10	1.41 (3H, s)	29.61	2, 6
11a	4.01 (1H, d, 12.6)	58.87	7, 8
11b	4.20 (1H, d, 12.6)		
12	1.70 (1H, m)	25.34	13, 14
13	0.97 (3H, d, 6.5)	20.85	
14	0.97 (3H, d, 6.5)	19.53	
15		179.81	3, 6
OMe	3.28 (3H, s)	56.66	

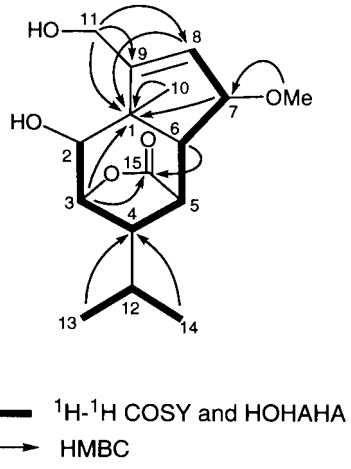


Figure 3. Selected 2D NMR correlations of flakinin B (**2**).

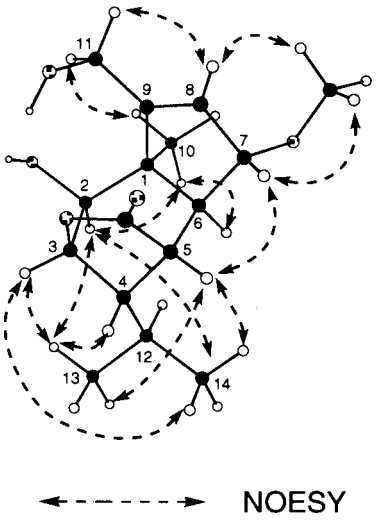


Figure 4. Selected NOESY correlations and relative stereochemistry of flakinin B (**2**).

in Table 1. Thus the gross structure of flakinin A was assigned as **1**.

The NOESY spectrum of **1** showed cross-peaks as shown in computer-generated 3D drawing (Fig. 2). NOESY correlations of H-9/H-10, H-2/H-10, H-7/H-6, H-6/H-10, H-6/H-5, H-5/H-7, H-9/H-2, H-2/H-3, H-2/H-10, H-6/H-14, H-5/H-13, H-5/H-14, and H-3/H-13 indicated that H-2, H-3, H-5, H-6, H-7, H-9, the methyl group at C-1, and the isopropyl group at C-4 were all α-oriented. The cyclohexane ring fused by one cyclopentane and two γ-lactone rings had a twist boat conformation, which was suggested by relatively large proton coupling constants ($J_{3,4}$=9.6 and $J_{5,6}$=10.5 Hz). Thus, the relative stereostructure of flakinin A (**1**) was assigned as shown in Fig. 2. To determine the absolute configuration at C-3, **1** was converted into its (*S*)- and (*R*)-2-methoxy-2-trifluoromethylphenylacetic acid (MTPA) esters. The values of $\Delta\delta$ [δ(*S*-MTPA ester) - δ(*R*-MTPA ester)] obtained from the ^{1}H NMR spectra of the MTPA esters suggested that the absolute configuration at C-3 was *R*.

Flakinin B (**2**) had the molecular formula, $C_{16}H_{24}O_5$, by HRESIMS [*m/z* 319.1525 $(M+Na)^+$, Δ +0.3 mmu]. IR absorptions at 3350 and 1780 cm^{-1} indicated the presence of hydroxyl and lactonic carbonyl group, respectively. ^{1}H and ^{13}C NMR data (Table 2) disclosed the existence of four methyls (one of them bearing an oxygen atom), one sp^3 methylene bearing an oxygen atom, seven sp^3 methines (three of them bearing an oxygen atom), one sp^2 methine, one sp^3 quaternary carbon, one sp^2 carbon, and one ester carbonyl carbon. Interpretation of the ^{1}H-^{1}H COSY and HOHAHA spectra (Fig. 3) revealed proton connectivities from H-2 to H-8, and from H-12 to H_3-13 and H_3-14. The connection between C-4 and C-12 was assigned on the basis of ^{1}H-^{13}C long-range correlations from H_3-13 and H_3-14 to C-4 in the HMBC spectrum. Connections among C-2, C-6, C-9, and C-10 through C-1 were deduced from HMBC correlations of H-3, H-7, H-8, and H_3-10 to C-1. The existence of an allylic hydroxy methylene was implied by HMBC correlations of H_2-11 to C-1, C-8, and C-9. In addition, the γ-lactone ring indicated by IR absorption (1780 cm^{-1}) was substantiated by HMBC correlations of H-3 and H-6 to C-15. Thus the gross structure of flakinin B was elucidated to be **2**.

NOESY correlations were observed for H-6/H_3-10, H-2/H_3-10, H-2/H_3-13, H-2/H_3-14, H-3/H_3-13, H-3/H_3-14, H-5/H_3-13, and H-5/H_3-14, indicating that the methyl group at C-1, H-6, H-2, and the isopropyl group at C-4 were all α-oriented. The NOE correlation between H-5 and H-7 implied that the methoxy at C-7 was α-oriented. Thus, the relative stereostructure of flakinin B (**2**) was assigned as shown in Fig. 4. To determine the absolute configuration at C-2, **2** was converted into its (*S*)- and (*R*)- MTPA esters. The values of $\Delta\delta$ obtained from the ^{1}H NMR spectra suggested that the absolute configuration at C-2 of **2** was *S*.

Mubironines A (**3**), B (**4**), and C (**5**) were revealed to possess the molecular formulae, $C_{16}H_{23}O_3N$, $C_{15}H_{23}O_2N$, and $C_{17}H_{29}O_3N$, respectively, by HRESIMS and HRFABMS. Detailed analysis of ^{1}H and ^{13}C NMR data revealed that compounds **3**, **4**, and **5** were new sesquiterpene alkaloids related to dendrobine (**6**). IR absorptions for **3** implied the presence of amide carbonyl (1680 cm^{-1}) and γ-lactonic carbonyl (1780 cm^{-1}). The *N*-methyl amide moiety was indicated by NMR data (*N*-methyl: δ_H 2.87; δ_C 27.74, amide carbonyl: δ_C 177.64) of **3**. Oxidation of dendrobine (**6**)[6] with $KMnO_4$ afforded the amide derivative, whose spectral data and $[\alpha]_D$ value were identical with those of

Table 3. ^{1}H NMR data of mubironines A (**3**), B (**4**), and C (**5**) in $CDCl_3$-CD_3OD (9:1) at 300 K

	3	**4**	**5**
2	3.24 (1H, d, 3.4)	3.47 (1H, s)	3.35 (1H, s)
3	4.72 (1H, dd, 5.4, 3.4)	4.77 (1H, d, 2.4)	3.92 (1H, m)
4	2.28 (1H, m)	2.10 (1H, m)	2.17 (1H, m)
5	2.52 (1H, m)	2.45 (1H, t, 5.0)	2.50 (1H, m)
6	2.17 (1H, t, 7.0)	2.00 (1H, m)	1.88 (1H, m)
7	2.06 and 2.01 (each 1H, m)	2.15 and 2.03 (each 1H, m)	1.97 and 1.43 (each 1H, m)
8	1.76 and 2.10 (each 1H, m)	1.90 and 1.42 (each 1H, m)	1.70 and 1.64 (each 1H, m)
9	2.55 (1H, m)	2.49 (1H, m)	2.49 (1H, m)
10	1.43 (3H, s)	1.32 (3H, s)	1.33 (3H, s)
11		3.15 and 2.93 (each 1H, t, 10.0)	3.45 and 3.40 (each 1H, m)
12	1.88 (1H, m)	1.58 (1H, m)	1.78 (1H, m)
13	1.01 (3H, d, 6.5)	0.87 (3H, d, 6.4)	0.87 (3H, d, 7.0)
14	1.03 (3H, d, 6.5)	0.89 (3H, d, 6.4)	1.01 (3H, d, 7.0)
NMe	2.87 (3H, s)		3.03 (3H, s)
OMe			3.63 (3H, s)

natural mubironine A (**3**). Thus mubironine A (**3**) was concluded to be the 11-oxodendrobine. The ^{13}C NMR spectrum of mubironine B (**4**) containing one sp^2 carbon, one quaternary carbon, seven sp^3 methines, three methylenes, and three methyls implied that **4** was structurally related to dendrobine (**6**). Detailed analyses of 2D NMR data (Table 3) revealed that **4** was *N*-demethyl dendrobine. On the other hand, in the NMR spectra of mubironine C (**5**), ^1H and ^{13}C signals due to a methoxy at δ_H 3.63 and δ_C 51.85 were observed and the signal due to a lactonic methine proton (δ_H 4.83) of dendrobine (**6**) was shifted at δ_H 3.92 for **5**, implying cleavage of the γ-lactone ring. Alkaline hydrolysis of dendrobine (**6**) with 10% $NaOCH_3$, followed by methylation with trimethylsilyldiazomethane afforded the methyl ester derivative of the hydrolysate, whose spectral data and $[\alpha]_D$ value were identical with those of natural mubironine C (**5**). Thus mubironine C (**5**) was determined to be the methyl ester of *seco*-dendrobine.

Flakinin A (**1**) is a unique sesquiterpene containing a fused tetracyclic ring system with faced two γ-lactonic rings. This is the first isolation of picrotoxinin-type sesquiterpenes such as flakinins A (**1**) and B (**2**) together with structurally related alkaloids such as dendrobine (**6**) and nobilonine (**9**) from *Dendrobium* plants, although picrotoxinin is considered to be a plausible biogenetic precursor of dendrobine-type alkaloids. Flakinins A (**1**) and B (**2**), and mubironine C (**5**) exhibited moderate cytotoxicity against murine leukemia L1210 cells (IC_{50}, 4.0, 8.5, and 2.6 μg/ml, respectively) in vitro.

Experimental Section

General Methods. ^1H and 2D NMR spectra were recorded in $CDCl_3$ and/or $CDCl_3$ /CD_3OD (9:1) on a 600 MHz spectrometer at 300K, while ^{13}C NMR spectra were measured on a 125 MHz spectrometer. Chemical shifts were reported using residual $CDCl_3$ (δ_H 7.26 and δ_C 77.03) as internal standards. Standard pulse sequences were employed for the 2D NMR experiments. HMBC spectra were recorded using a 50 ms delay time for long-range C-H coupling with Z-axis PFG. NOESY spectra were measured with a mixing time of 800 ms. FABMS was measured by using glycerol matrix.

Material. The whole plants of *Dendrobium* Snowflake 'Red Star' were purchased from Shiroishi-ene in Sapporo in 1999. The botanical identification was made by Mr N. Yoshida, Faculty of Pharmaceutical Sciences, Hokkaido University. A voucher specimen has been deposited in the herbarium of Hokkaido University.

Extraction and Isolation. The whole plants (1.8 kg) of *Dendrobium* Snowflake 'Red Star' were crashed and extracted with MeOH (10 L×3). The MeOH extract was treated with 3% tartaric acid to adjust at pH 2 and then partitioned with EtOAc. The aqueous layer was treated with sat. Na_2CO_3 aq. to adjust at pH 10 and extracted with $CHCl_3$ to give a crude alkaloidal fraction (1.45 g), which was subjected to silica gel column chromatography ($CHCl_3$/EtOAc/MeOH 24:1:1, 9:1:1, and 5:1:1). The fraction eluted by $CHCl_3$/EtOAc/MeOH (9:1:1) was subjected to a C_{18} column chromatography (20~80% MeOH/0.1% TFA) followed by C_{18} HPLC (CH_3CN/0.1% TFA 1:3) to afford flakinins A (**1**, 3.6 mg, 0.0002%) and B (**2**, 3.6 mg, 0.0002%), and mubironines B (**4**, 12.6 mg, 0.0007%) and C (**5**, 1.3 mg, 0.00007%) as colorless solids. The fraction eluted by $CHCl_3$/EtOAc/MeOH (24:1:1) in the silica gel column was subjected to C_{18} HPLC (CH_3CN/0.1% TFA 1:3) to afford mubironine A (**3**, 1.8 mg, 0.0001%), dendrobine (**6**, 360 mg, 0.02%), 6-hydroxydendroxine (**8**, 3.6 mg, 0.0002%), and nobilonine (**9**, 108 mg, 0.006%). The fraction eluted by $CHCl_3$/EtOAc/MeOH (9:1:1) in the silica gel column was subjected to C_{18} HPLC (25% CH_3CN/0.1% TFA) to afford 6-hydroxydendrobine (**7**, 180 mg, 0.001%).

Flakinin A (1). Colorless solid; $[\alpha]_D^{23}$ +21° (c 0.8, MeOH); ^1H and ^{13}C NMR (Table 1); ESIMS *m/z* 303 $(M+Na)^+$; HRESIMS *m/z* 303.1213 (M+Na; calcd for $C_{15}H_{20}O_5Na$, 303.1208); IR (neat) ν_{max} 3500, 2960, 1770, and 1190 cm^{-1}.

Flakinin B (2). Colorless solid; $[\alpha]_D^{23}$ +103° (c 1.2, MeOH);^1H and ^{13}C NMR (Table 2); ESIMS *m/z* 319 $(M+Na)^+$; HRESIMS *m/z* 319.1525 (M+Na; calcd for $C_{16}H_{24}O_5Na$, 319.1522); IR (neat) ν_{max} 3350, 2960, 1780, 1088, and 1063 cm^{-1}.

Mubironine A (3). Colorless solid; $[\alpha]_D^{23}$ −9° (c 0.4, MeOH); ESIMS *m/z* 300 $(M+Na)^+$; HRESIMS *m/z* 300.1567 (M+Na; calcd for $C_{16}H_{23}O_3NNa$, 300.1558); IR (neat) ν_{max} 2910, 1780, and 1680 cm^{-1}. ^{13}C NMR data ($CDCl_3$-CD_3OD, 9:1) δ_C 54.22 (C-1), 64.97 (C-2), 75.46 (C-3), 50.91 (C-4), 43.36 (C-5), 42.96 (C-6), 31.84 (C-7), 28.51 (C-8), 57.63 (C-9), 32.25 (C-10), 177.64 (C-11), 24.57 (C-12), 20.55 (C-13), 21.23 (C-14), 174.81 (C-15), and 27.74 (NMe).

Mubironine B (4). Colorless solid; $[\alpha]_D^{23}$ −15° (c 1.6, MeOH); FABMS *m/z* 250 $(M+H)^+$; HRFABMS *m/z* 250.1794 (M+H; calcd for $C_{15}H_{24}O_2N$, 250.1807); IR (neat) ν_{max} 3370, 2960, 1780, 1190, and 1130 cm^{-1}. ^{13}C NMR data ($CDCl_3$-CD_3OD, 9:1) δ_C: 52.09 (C-1), 62.03 (C-2), 77.88 (C-3), 50.67 (C-4), 42.82 (C-5), 42.78 (C-6), 32.80 (C-7), 30.42 (C-8), 53.09 (C-9), 30.71 (C-10), 51.71 (C-11), 24.27 (C-12), 19.67 (C-13), 20.54 (C-14), and 177.75 (C-15).

Mubironine C (5). Colorless solid; $[\alpha]_D^{23}$ −5° (c 0.6, MeOH); ESIMS *m/z* 296$(M+H)^+$; HRESIMS *m/z* 296.2217 (M+H; calcd for $C_{17}H_{30}O_3N$, 296.2225); IR (neat) ν_{max} 3330, 2920, 1730, 1460, 1200, and 1140 cm^{-1}. ^{13}C NMR data ($CDCl_3$-CD_3OD, 9:1) δ_C: 51.97 (C-1), 77.50 (C-2), 67.50 (C-3), 39.24 (C-4), 44.34 (C-5), 47.59 (C-6), 28.77 (C-7), 31.38 (C-8), 48.63 (C-9), 29.57 (C-10), 65.00 (C-11), 29.27 (C-12), 17.06 (C-13), 21.15 (C-14), 174.80 (C-15), 31.80 (NMe), and 51.85 (OMe).

Oxidation of Dendrobine (6).[6] $KMnO_4$ (1.3 mg) in acetone/H_2O (2:3, 0.2 ml) was added to a stirred solution of dendrobine (**6**, 1.0 mg) and $MgSO_4$ in acetone/H_2O (5:1, 0.3 ml) at 5°C. The mixture was stirred at room temperature for 1.5 h, and washed with sat. $Na_2S_2O_3$ (2 mL) and then extracted with $CHCl_3$ (3 mL×3). The solvent was evaporated in vacuo to give a pale oil (1.9 mg), whose spectral data

and $[\alpha]_D$ value were identical with those of mubironine A (**3**).

Hydrolysis and methylation of Dendrobine (6). 10% $NaOCH_3$ in MeOH (0.2 ml) was added to dendrobine (**6**, 3.0 mg) at 50°C and stirred overnight. The mixture was extracted with $CHCl_3$ and after evaporation of the organic solvent, trimethylsilyldiazomethane (2.0 M hexane solution, 100 μl) was added to a stirred solution of the residual oil (2.2 mg) in methanol (0.2 ml) at room temperature. The mixture was stirred for 30 min, and after evaporation the residue was subjected to a silica gel column to give the methyl ester of the hydrolysate of **6**, whose spectral data and $[\alpha]_D$ value were identical with those of mubironine C (**5**).

(*R*)- and (*S*)-MTPA esters of flakinins A (1) and B (2). To a solution of **1** (0.3 mg) in CH_2Cl_2 (40 μl) was added (−)- or (+)-MTPACl (1.0 μl), triethylamine (1.1 μl) and *N*,*N*-dimethylamino pyridine (0.1 mg). Each mixture was stood at room temperature for 4 h. *N*,*N*-Dimethylamino-1,3-propandiamine (1.0 μl) was added, and after evaporation of solvent, each residue was applied to a silica gel column (Hexane-AcOEt, 8:2) to give the (*R*)- and (*S*)-MTPA esters of **1** (0.3 mg each). The (*S*)- and (*R*)-MTPA esters of **2** were prepared according to the same procedure as described above.

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