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Cryptadines A and B, novel $C_{27}N_3$-type pentacyclic alkaloids from *Lycopodium cryptomerinum*

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Abstract—Two novel $C_{27}N_3$-type *Lycopodium* alkaloids, cryptadines A (**1**) and B (**2**) consisting of two octahydroquinoline rings ($C_{11}N$) and a piperidine ring (C_5N), have been isolated from the club moss *Lycopodium cryptomerinum*, and their structures and relative stereochemistry were elucidated on the basis of spectroscopic data, chemical transformations, and computational methods. Cryptadines A (**1**) and B (**2**) exhibited an inhibitory activity against acetylcholinesterase.

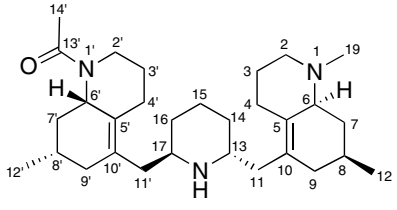
1. Introduction

Lycopodium species are a well-known rich source of unique heterocyclic alkaloids having $C_{11}N$, $C_{16}N$, $C_{16}N_2$, and $C_{27}N_3$ types and have attracted great interest from biogenetic[1,2] and biological[3] points of view. Unique unusual skeletons will offer the challenging targets for total synthesis.[4] Recently we have isolated unique *Lycopodium* alkaloids consisting of a variety of fused cyclic ring system from *Lycopodium* species collected in Japan and Southeast Asia.[5] In our search for structurally and biogenetically interesting *Lycopodium* alkaloids, cryptadines A (**1**) and B (**2**), novel $C_{27}N_3$-type alkaloid consisting of two octahydroquinoline rings ($C_{11}N$) and a piperidine ring (C_5N), were isolated from the club moss *Lycopodium cryptomerinum* collected at Kagoshima in Japan. In this paper we describe the isolation, structure elucidation, and biological activity of **1** and **2**.

2. Results and discussion

2.1. Isolation of cryptadines A (1) and B (2)

The club moss *L. cryptomerinum* was extracted with MeOH, and the extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted at pH 6, 8, and 10, gradually with sat. Na_2CO_3, were stepwise extracted with $CHCl_3$. $CHCl_3$-soluble materials at pH 8 were subjected to a silica gel column ($CHCl_3$/MeOH, 1:0 → 0:1), in which a fraction eluted with MeOH was purified by C_{18} HPLC (24% CH_3CN/0.1% TFA) to afford cryptadines A (**1**, 11.2 mg, 0.004% yield) and B (**2**, 5.1 mg, 0.002% yield) as TFA salts together with known alkaloids, huperzines A[6] (0.001%), J[7] (0.001%), and K[7] (0.001%).



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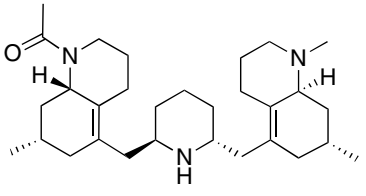

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Keywords: Alkaloids; *Lycopodium*; Cryptadines A and B; Acetylcholinesterase.
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2.2. Structure of cryptadine A (1)

Cryptadine A (**1**) showed the pseudomolecular ion peak at *m/z* 468 $(M+H)^+$ in the FABMS spectrum, and the molecular formula, $C_{30}H_{49}N_3O$, was established by HRFABMS [*m/z* 468.3954, $(M+H)^+$, Δ −0.1 mmu]. IR absorptions implied the presence of amine and amide (3418 and 1673 cm^{-1}) functionalities. ^1H and ^{13}C NMR spectra showed broad signals, because of rotation of its *N*-acetyl moiety. Treatment of **1** with $LiAlH_4$ afforded dihydrodeoxycryptadine A (**3**), which provided sharp signals on the ^1H and ^{13}C NMR spectra.

Dihydrodeoxycryptadine A (**3**) showed the pseudomolecular ion peak at *m/z* 454.4179 $(M+H)^+$, corresponding to the molecular formula, $C_{30}H_{51}N_3$. Analysis of the ^1H and ^{13}C NMR data (Table 1) and the HMQC spectrum of **3** revealed the presence of six sp^3 methines, 16 sp^3 methylenes, four sp^2 quaternary carbons, and four methyl groups. Among them, one sp^3 methyl (δ_C 43.7; δ_H 2.24), three sp^3 methylenes (δ_C 52.6; δ_H 2.19 and 2.95; δ_C 57.9; δ_H 2.13 and 2.82; δ_C 47.3; δ_H 2.44 and 2.86) and four sp^3 methines (δ_C 61.7; δ_H 2.85; δ_C 65.1; δ_H 2.50; δ_C 50.5; δ_H 3.17; δ_C 50.6; δ_H 3.17) were ascribed to those bearing a nitrogen atom.

The gross structure of **3** was deduced from extensive analyses of the two-dimensional NMR data, including the ^1H–^1H COSY, HOHAHA, HMQC, and HMBC spectra in C_6D_6 (Fig. 1). The ^1H–^1H COSY and HOHAHA spectra in C_6D_6 revealed connectivities of seven partial structures **a** (C-6–C-9, C-12), **b** (C-2–C-4), **c** (C-11,

Table 1. ^1H and ^{13}C NMR data of dihydrodeoxycryptadines A (**3**) and B (**4**) in C_6D_6 at 300 K

Compound	δ_H		δ_C	
	3	**4**	**3**	**4**
2a	2.13 (1H, ddd, 14.9, 8.9, 2.1)	2.13 (1H, m)	57.9	58.8
2b	2.82 (1H, m)	2.87 (1H, m)		
3a	1.57 (1H, m)	1.64 (1H, m)	26.6	26.8
3b	1.73 (1H, m)	1.69 (1H, m)		
4a	1.71 (1H, m)	1.74 (1H, m)	29.2	29.7
4b	2.92 (1H, m)	2.97 (1H, m)		
5			128.6	128.6
6	2.50 (1H, m)	2.31 (1H, m)	65.1	63.6
7a	1.26 (1H, m)	1.34 (1H, m)	39.0	35.0
7b	2.00 (1H, m)	1.90 (1H, m)		
8	1.59 (1H, m)	2.06 (1H, m)	28.5	25.1
9a	1.76 (1H, m)	1.61 (1H, m)	40.4	39.5
9b	1.92 (1H, br d, 16.5)	2.18 (1H, m)		
10			131.9	132.2
11a	2.26 (1H, m)	2.02 (1H, m)	39.4	40.6
11b	2.29 (1H, m)	2.40 (1H, m)		
12	0.97 (3H, d, 7.3)	0.99 (3H, d, 6.7)	22.4	21.1
13	3.17 (1H, m)	3.05 (1H, m)	50.6	49.6
14a	1.38 (1H, m)	1.35 (1H, m)	31.5	32.8
14b	1.76 (1H, m)	1.66 (1H, m)		
15	1.56 (2H, m)	1.57 (2H, m)	20.7	20.8
16a	1.38 (1H, m)	1.42 (1H, m)	31.5	30.8
16b	1.76 (1H, m)	1.82 (1H, m)		
17	3.17 (1H, m)	3.29 (1H, m)	50.5	50.9
19	2.24 (3H, s)	2.17 (3H, s)	43.7	43.1
2′a	2.19 (1H, ddd, 14.7, 8.7, 2.4)	2.24 (1H, m)	52.6	52.6
2′b	2.95 (1H, m)	2.95 (1H, m)		
3′a	1.61 (1H, m)	1.63 (1H, m)	26.6	28.0
3′b	1.67 (1H, m)	1.69 (1H, m)		
4′a	1.77 (1H, m)	1.76 (1H, m)	28.9	29.0
4′b	2.87 (1H, m)	2.87 (1H, m)		
5′			128.8	128.7
6′	2.85 (1H, m)	2.86 (1H, m)	61.7	61.6
7′a	1.25 (1H, m)	1.30 (1H, m)	38.7	38.6
7′b	2.05 (1H, m)	2.04 (1H, m)		
8′	1.59 (1H, m)	1.66 (1H, m)	28.3	28.4
9′a	1.75 (1H, m)	1.75 (1H, m)	40.4	39.8
9′b	1.93 (1H, br d, 16.5)	1.95 (1H, br d, 15.6)		
10′			131.5	131.9
11′a	2.26 (1H, m)	2.15 (1H, m)	39.4	37.8
11′b	2.29 (1H, m)	2.44 (1H, m)		
12′	0.97 (3H, d, 7.1)	0.98 (3H, d, 6.3)	22.5	22.5
13′a	2.44 (1H, m)	2.47 (1H, m)	47.3	47.3
13′b	2.86 (1H, m)	2.86 (1H, m)		
14′	1.01 (3H, t, 7.1)	1.02 (3H, t, 7.1)	10.5	10.2

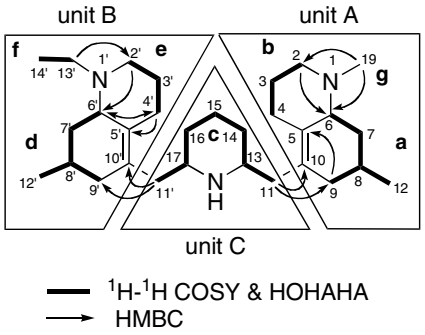


Figure 1. Selected 2D NMR correlations for dihydrodeoxycryptadine A (**3**).

C-13–C-17, C-11′), **d** (C-6′–C-9′, C-12′), **e** (C-2′–C-4′), **f** (C-13′–C-14′), and **g** (C-19) as shown in Figure 1.

In the octahydroquinoline moiety (unit A), the connectivity of partial structures **a** and **b** revealed by the ^{1}H–^{1}H COSY and HOHAHA spectra was analyzed by the HMBC spectrum. HMBC correlations from H_3-19 to C-2 (δ_C 57.9) and C-6 (δ_C 65.1) established the connection among C-2, C-6, and C-19 through a nitrogen atom. HMBC cross peaks of H-9 to C-5 and H-11 to C-9 and C-10 indicated the connection among partial structures **a** and **b**, and four-substituted olefinic carbons assigned to C-5 and C-10, constructing the octahydroquinoline ring (C-2–C-10 and N-1) with two methyl groups (C-12 and C-19) at C-8 and N-1 in unit A. Another octahydroquinoline moiety (C-2′–C-10′ and N-1′) with a methyl group (C-12′) at C-8′ and an ethyl group (C-13′ and C-14′) at N-1′ in unit B was analyzed by the same way as mentioned above. Thus, the gross structure of dihydrodeoxycryptadine A was assigned as **3**.

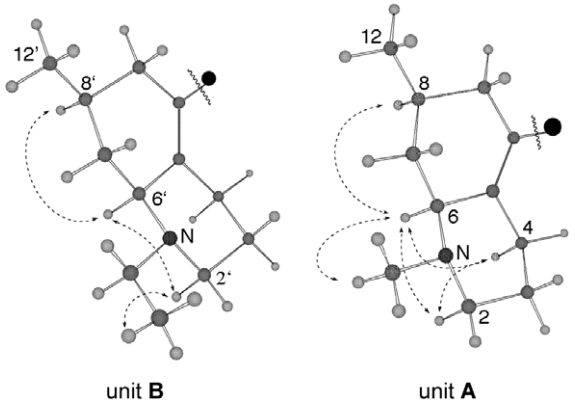


Figure 2. Selected NOESY correlations and relative configurations for units A and B in dihydrodeoxycryptadine A (**3**).

The relative stereochemistry of each octahydroquinoline ring in **3** was assigned by NOESY correlations (Fig. 2). The NOESY correlations of H-6 to H-2, H-4, and H-8 in unit A suggested that these hydrogens were oriented to the same side and took an axial orientation. Similar incident was observed for another octahydroquinoline moiety (C-2′–C-10′ and N-1′) in unit B. Therefore, the relative configurations of the two octahydroquinoline moieties (units A and B) were elucidated to be the same.

The relative stereochemistry of the piperidine ring in **3** was assigned by comparison of chemical shifts with known piperidine derivatives.[8] The ^{1}H signals assigned to the piperidine ring of **3** were observed at δ 3.17 (H-13 and H-17), and the ^{13}C signals at δ 50.59 (C-13), δ 20.72 (C-15), and δ 50.55 (C-17) (see Table 1 and Fig. 3). The ^{13}C signals (C-2, C-4, and C-6) of *trans*-substituted piperidine analogues of andrachamine (**5**) have been reported at higher field than those with a *cis*-substituted piperidine ring.[8] On the other hand, the ^{1}H signals (H-2 and H-6) have been reported at lower field than those with a *cis*-substituted piperidine ring.[8] Dihydrodeoxycryptadine A (**3**) showed similar ^{1}H and ^{13}C chemical shifts to andrachamine analogues with a *trans*-substituted piperidine ring. Thus, stereochemistry of the piperidine ring (C-13–C-17 and N-18) of dihydrodeoxycryptadine A (**3**) was assigned as *trans* configuration. Since **3** possessed almost symmetrical ^{1}H and ^{13}C chemical shifts around the piperidine ring as shown in Figure 3, the absolute configurations of the two octahydroquinoline moieties (units A and B) were deduced to be the same.[8] Therefore, the two proposed relative stereochemistries, *6S*, 8R*, 13R*, 17R*, 6′S*, 8′R**, and *6S*, 8R*, 13S*, 17S*, 6′S*, 8′R**, for **3** were deduced.

Conformational space for **3** with the proposed stereochemistry was searched by Monte Carlo simulation[9] followed by minimization using MMFF force field[10] implemented in Macromodel program, and the result was consistent with the NOESY data. Each lowest energy conformer belonging to two clusters was represented as **3a** (34.18 kcal/mol) and **3b** (34.46 kcal/mol) (Fig. 4). Conformer **3a** possessed a folding conformation in both octahydroquinoline parts (units A and B), while conformer **3b** adopted an extended conformation. Between the two represented conformers, only

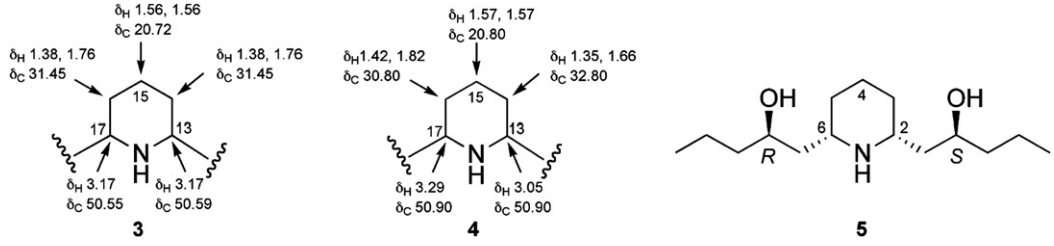


Figure 3. Partial NMR chemical shifts of piperidine ring system for **3** and **4**, and andrachamine (**5**).

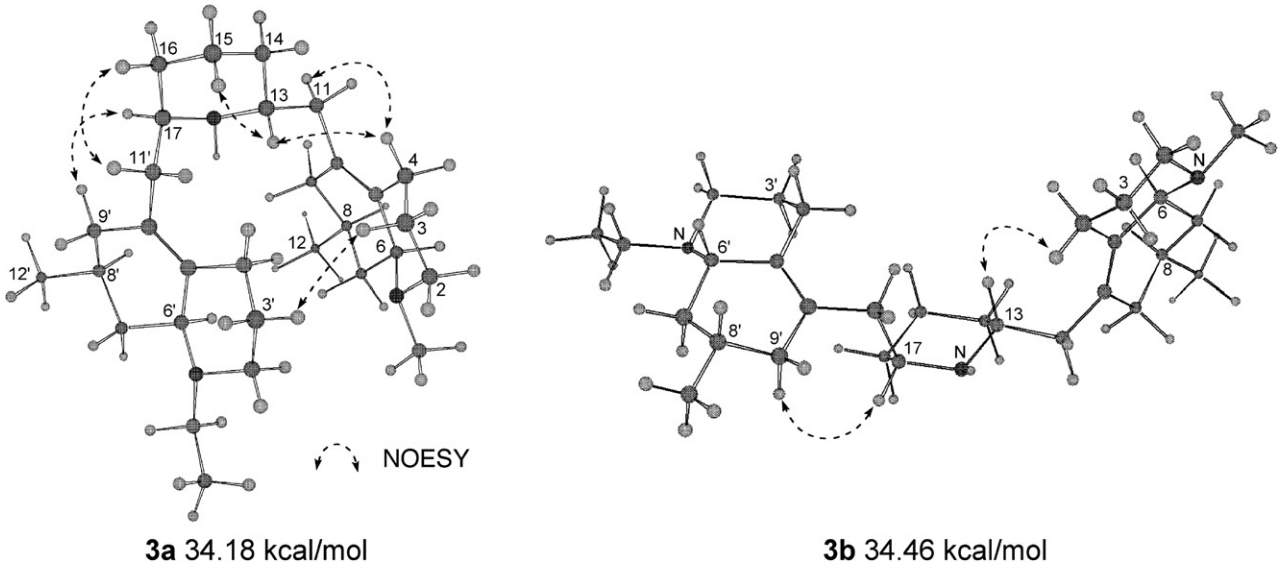


Figure 4. Stable conformers (**3a** and **3b**) for **3** (13*R**, 17*R**) with selected NOESY correlations.

conformer **3a** with *6S*, 8R*, 13R*, 17R*, 6′S*, and 8′R** stereochemistry was consistent with the NOESY data as shown in Figure 4, whereas conformers with *13S*, 17S** were not.

2.3. Structure of cryptadine B (2)

HRFABMS data [*m/z* 468.3970, $(M+H)^+$, Δ +1.6 mmu] of cryptadine B (**2**) established the molecular formula, $C_{30}H_{49}N_3O$, which was the same as that of **1**. IR absorptions implied the presence of amine and amide (3421 and 1682 cm^{-1}) functionalities. ^1H and ^{13}C NMR spectra gave broad signals for a part of the molecule, which might be due to conformational exchange, like those of **1**. The broadening observed for the NMR spectra of **2** was overcome by measuring dihydrodeoxycryptadine B (**4**) which was provided by reduction of **2** with $LiAlH_4$.

Dihydrodeoxycryptadine B (**4**) showed the pseudomolecular ion peak at *m/z* 454.4168 $(M+H)^+$, corresponding to the molecular formula, $C_{30}H_{51}N_3$. Analysis of the ^1H and ^{13}C NMR data (Table 1) and the HMQC spectrum of **4** revealed the presence of the same carbon origins as those of **3**, such as six sp^3 methines, 16 sp^3 methylenes, four sp^2 quaternary carbons, and four methyl groups. Among them, one sp^3 methyl (δ_C 52.5; δ_H 2.17), three sp^3 methylenes (δ_C 52.6; δ_H 2.24 and 2.95; δ_C 58.8; δ_H 2.13 and 2.87; δ_C 47.3; δ_H 2.47 and 2.86), and four sp^3 methines (δ_C 61.6; δ_H 2.86; δ_C 63.6; δ_H 2.31; δ_C 50.9; δ_H 3.29; δ_C 49.6; δ_H 3.05) were ascribed to those bearing a nitrogen atom.

The structure of **4** was elucidated by 2D NMR (^1H–^1H COSY, HOHAHA, HMQC, and HMBC) data in C_6D_6, which revealed the same connectivities of seven partial structures **a**–**g** as those of **3**. Thus the gross structure dihydrodeoxycryptadine B was assigned as **4**.

The relative stereochemistry of each octahydroquinoline ring in **4** was elucidated by NOESY correlations (Fig. 5). The NOESY correlations of H-6 to H_3-12 and H-2a suggested that H-6 and H_3-12 were α axial orientation in unit A. On the other hand, the NOESY correlations at H-6′/ H-8′ and H-2a′ and H-2a′/ H-4a′ showed H-6′ was α orientation and H_3-12′ was β equatorial orientation in unit B. Therefore, the relative configuration at C-8 of the octahydroquinoline moiety in unit A of dihydrodeoxycryptadine B (**4**) was elucidated to be different from that of dihydrodeoxycryptadine A (**3**).

2.4. Plausible biogenesis of cryptadines A (1) and B (2)

A plausible biogenetic pathway for cryptadines A (**1**) and B (**2**) is proposed as shown in Scheme 1. Cryptadines A (**1**) and B (**2**) might be generated from two octahydroquinoline units (**b**) through unit **a** derived from L-lysine via pelletierine and piperidine units (**c**). Ayer's proposal[11] for lucidine B is also shown in Scheme 1, in which lucidine B is generated from two (enantiomeric) $C_{11}N$ units and a piperidine ring.

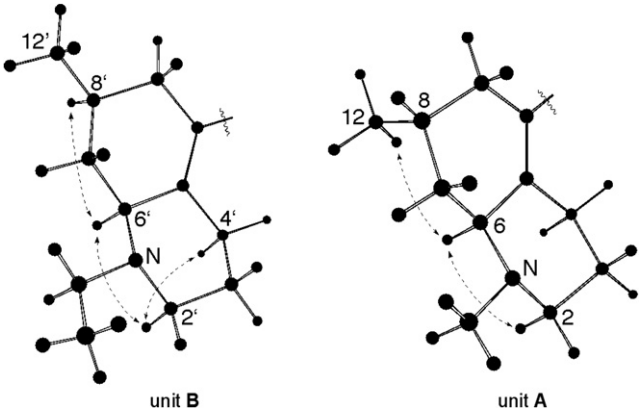
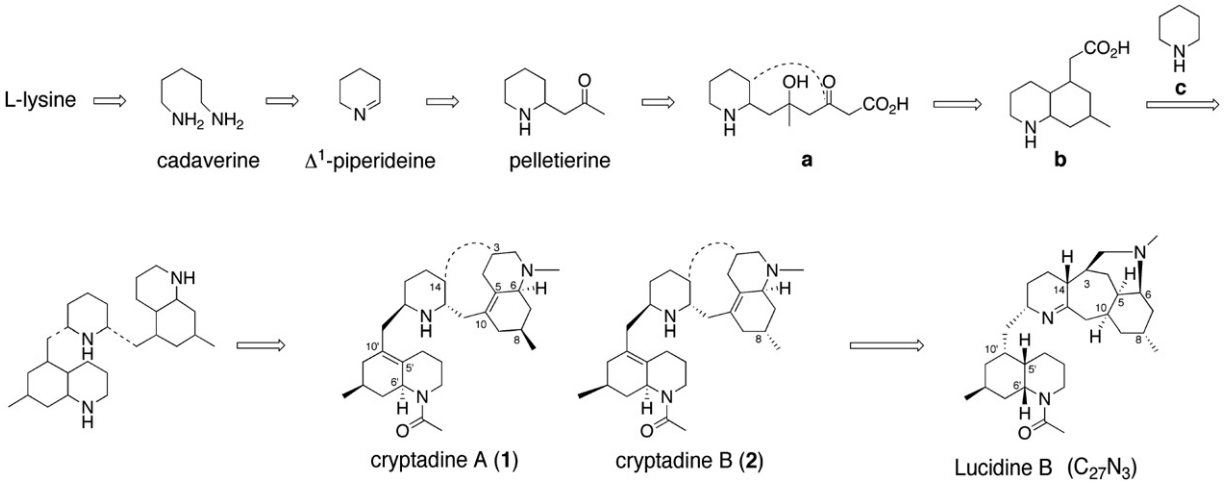


Figure 5. Selected NOESY correlations and relative configurations for units A and B in dihydrodeoxycryptadine B (**4**).



Scheme 1. Plausible biogenesis of cryptadines A (**1**) and B (**2**), and $C_{27}N_3$ type *Lycopodium* alkaloids.

2.5. Bioactivity of cryptadines A (1) and B (2)

Cryptadines A (**1**) and B (**2**) inhibited acetylcholinesterase (from bovine erythrocyte) with IC_{50} 106.3 and 18.5 μM, respectively,[12] in comparison with that (IC_{50}, 53 nM) of (−)-huperzine A.

3. Experimental

3.1. General methods

^1H and 2D NMR spectra were recorded on a 600 MHz spectrometer at 300 K, while ^{13}C NMR spectra were measured on a 150 MHz spectrometer. The NMR sample of cryptadines A (**1**) and B (**2**), and dihydrodeoxycryptadines A (**3**) and B (**4**) was prepared by dissolving 1.0 mg in 30 μL of CD_3OD in 2.5 mm microcells (Shigemi Co. Ltd) and chemical shifts were reported using residual CD_3OD (δ_H 3.31 and δ_C 49.0) as internal standards. 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 and HOHAHA spectra in the phase sensitive mode were measured with a mixing time of 800 and 30 ms, respectively. 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. FABMS was measured by using glycerol as a matrix.

3.2. Material

The club moss *L. cryptomerinum* was collected at Kagoshima in 2003. The botanical identification was made by Mr. N. Yoshida, Health Sciences University of Hokkaido. A voucher specimen has been deposited in the herbarium of Hokkaido University.

3.2.1. Extraction and isolation. The club moss *L. cryptomerinum* (300 g) was extracted with MeOH (1 L × 3), and the extract (6.5 g) was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted at pH 6, 8, and 10, gradually with satd Na_2CO_3, were stepwise extracted with $CHCl_3$. $CHCl_3$-soluble materials at pH 8 (191 mg) were subjected to a silica gel column ($CHCl_3$/MeOH, 1:0 → 0:1), in which a fraction eluted with MeOH was purified by C_{18} HPLC (Phenomenex LUNA C_{18}(2), 5 μm, Shimadzu, 10 × 250 mm; eluent, 24% CH_3CN/0.1% TFA; flow rate, 3 mL/min; UV detection at 210 nm) to afford cryptadines A (**1**, 11.2 mg, 0.004% yield) and B (**2**, 5.1 mg, 0.002% yield) as TFA salts together with known alkaloids, huperzines A[6] (0.001%), J[7] (0.001%), and K[7] (0.001%).

*Cryptadine A (**1**):* Colorless solid; $[\alpha]_D^{19}$ −50° (*c* 0.8, MeOH); IR (film) ν_{max} 3418, 2953, 2871, and 1673 cm^{-1}; FABMS *m/z* 468 $(M+H)^+$; HRFABMS *m/z* 468.3953 [calcd for $C_{30}H_{50}N_3O$ $(M+H)^+$, 468.3954]; CD (MeOH) (1.2 mg/2 ml) $[\theta]_{225}$ +133.6, $[\theta]_{218}$ −9.1.

*Cryptadine B (**2**):* Colorless solid; $[\alpha]_D^{20}$ −69° (*c* 0.2, MeOH); IR (film) ν_{max} 3421, 2953, 2874, and 1682 cm^{-1}; FABMS *m/z* 468 $(M+H)^+$; HRFABMS *m/z* 468.3970 [calcd for $C_{30}H_{50}N_3O$ $(M+H)^+$, 468.3954]; CD (MeOH) (0.6 mg/0.4 ml) $[\theta]_{224}$ +54.7, $[\theta]_{208}$ −6.9.

3.2.2. Reduction of cryptadine A (1). To a solution of **1** (1.0 mg) in THF (300 μl) was added $LiAlH_4$ (5 mg). The mixture was allowed to stand at 80 °C for 5 h. After cooling, the mixture was extracted with $CHCl_3$. After evaporation of solvent, the residue was applied to an amino silica gel column (hexane/EtoAc, 1:0 → 4:6, $CHCl_3$/MeOH, 1:0 → 0:1) to give a compound **3** (0.7 mg). Colorless solid; $[\alpha]_D^{19}$ −26° (*c* 0.1, MeOH); IR (film) ν_{max} 3418, 2925, and 2852 cm^{-1}; ^1H and ^{13}C NMR data (Table 1); FABMS *m/z* 454 $(M+H)^+$; HRFABMS *m/z* 454.4179 [calcd for $C_{30}H_{52}N_3$

$(M+H)^+$, 454.4161]; CD (MeOH) (0.3 mg/0.4 ml) $[\theta]_{294}$ +0.7, $[\theta]_{259}$ −0.5, $[\theta]_{228}$ −0.2.

3.2.3. Reduction of cryptadine B (2). To a solution of **2** (1.3 mg) in THF (500 μl) was added $LiAlH_4$ (7 mg). The mixture was allowed to stand at 80 °C for 5 h. After cooling, the mixture was extracted with $CHCl_3$. After evaporation of solvent, the residue was applied to a amino silica gel column (hexane/EtoAc, 1:0 → 4:6, $CHCl_3$/MeOH, 1:0 → 0:1) to give a compound **4** (0.9 mg). Colorless solid; $[\alpha]_D^{20}$ −21° (*c* 0.1, MeOH); IR (film) ν_{max} 3421, 2925, and 2856 cm^{-1}; ^1H and ^{13}C NMR data (Table 1); FABMS *m*/*z* 454 $(M+H)^+$; HRFABMS *m*/*z* 454.4168 [calcd for $C_{30}H_{52}N_3$ $(M+H)^+$, 454.4161]; CD (MeOH) (0.3 mg/0.4 ml) $[\theta]_{250}$ −0.2, $[\theta]_{234}$ −0.3, $[\theta]_{223}$ +0.2.

3.3. Computational methods

Conformational searching was carried out using Pseudo Monte Carlo simulation in Macromodel program for **3** with two stereochemistries. The closure bond was chosen at C-14–C-15 with the closure limit from 1 to 4 Å. A thousand Monte Carlo steps were performed and could be classified into two clusters. Each conformer was finally minimized by molecular mechanics calculation of MMFF force field. Conformational searching for **4** was performed by the same procedure as **3**.

Acknowledgments

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References and notes

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