Malycorins A—C, New *Lycopodium* Alkaloids from *Lycopodium phlegmaria*

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A novel C_{19}N-type *Lycopodium* alkaloid, malycorin A (1) consisting of a serratinane skeleton with 2-propanol unit has been isolated from the club moss *Lycopodium phlegmaria*, together with two new C_{16}N-type alkaloids, malycorins B (2) and C (3), and the structures and relative stereochemistry were elucidated on the basis of spectroscopic data.

Key words *Lycopodium* alkaloid; malycorin; *Lycopodium phlegmaria*

Lycopodium alkaloids[1] with unique heterocyclic frameworks of C_{16}N-, $C_{16}N_2$-, and $C_{27}N_3$-type skeletons have attracted great interest from biogenetic[1,2] and biological[3] points of view. An interesting feature in all *Lycopodium* alkaloids is to possess polycyclic carbon skeletons with varying levels of oxidation. These unique skeletons have also been challenging targets for total synthesis.[4—8] Among them, huperzine A is a highly specific and potent inhibitor of acetylcholinesterase (AChE).[3] The inherent inhibition of AChE has promoted the pursuit of the total synthesis and structure–activity relationship studies of huperzine A.[9,10] Recently we isolated new types of alkaloids such as sieboldine A,[11] serratezomine A,[12] complanadine A,[13] lyconadin A,[14] senepodine A,[15,16] lyconesidine A,[17] himeradine A,[18] cermizine A,[19] and nankakurine A[20,21] from various *Lycopodium* spp. Our interest has been focused on isolation of structurally interesting alkaloids and biosynthetic intermediates to clarify the biogenetic pathway. Chemical investigation on extracts of *L. phlegmaria* Linnaeus (Lycopodiaceae) resulted in the isolation of a novel C_{19}N-type alkaloid, malycorin A (**1**) and two new C_{16}N-type alkaloids, malycorins B (**2**) and C (**3**) together with huperzine A. This paper describes the isolation and structure elucidation of **1**—**3**.

The club moss *L. phlegmaria* was extracted with MeOH, and the extract was partitioned between EtOAc and 3% tartaric acid. The aqueous layer was adjusted to pH 10 with saturated aq. Na_2CO_3, and extracted with $CHCl_3$. $CHCl_3$-soluble materials were subjected to an amino silica gel column (hexane/EtOAc, 1 : 0→0 : 1, and then $CHCl_3$/MeOH, 1 : 0→0 : 1), in which a fraction eluted with hexane/EtOAc (3 : 2) was purified by C_{18} HPLC (25—35% CH_3CN/0.1% TFA) to afford malycorins A (**1**, 0.0002%), B (**2**, 0.001%), and C (**3**, 0.001%) together with huperzine A (0.001%).

Malycorin A (**1**) was shown to have the molecular formula of $C_{19}H_{31}NO_3$ by High Resolution Electro Spray Ionization Time-of-Flight Mass Spectrometry (HR-ESI-TOF-MS) (*m*/*z* 322.2363, $[M+H]^+$, Δ −1.9 mmu). The IR spectrum was indicative of the presence of five-membered ketone (1740 cm^{-1}) and a hydroxy group (3340 cm^{-1}). Analysis of the ^{1}H- and ^{13}C-NMR data (Table 1) and the HMQC spectrum of **1** revealed the presence of one ketone, five sp^3 methines, nine sp^3 methylenes, two sp^3 quaternary carbons, and two methyl groups. Among them, one sp^3 methylene (δ_C 43.9; δ_H 2.20, 2.90), one sp^3 methine (δ_C 59.6; δ_H 3.38), and one quaternary carbon (δ_C 79.0) were assigned to those bearing a nitrogen atom. The gross structure of **1** was deduced from extensive analyses of the two-dimensional NMR data, including the ^{1}H–^{1}H COSY, homonuclear Hartmann–Hahn (HOHAHA), HMQC, and HMBC spectra in CD_3OD (Fig. 1). The ^{1}H–^{1}H COSY and HOHAHA spectra in CD_3OD revealed connectivities of three partial structures **a** (C-1—C-3 and C-17—C-19), **b** (C-6—C-8 and C-13—C-16), and **c** (C-9—C-11) as shown in Fig. 1.

The connectivities of C-7, C-11, and C-13 through a qua-

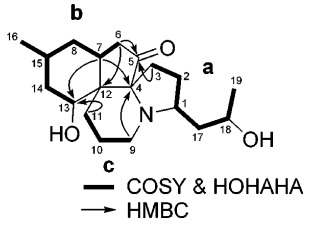
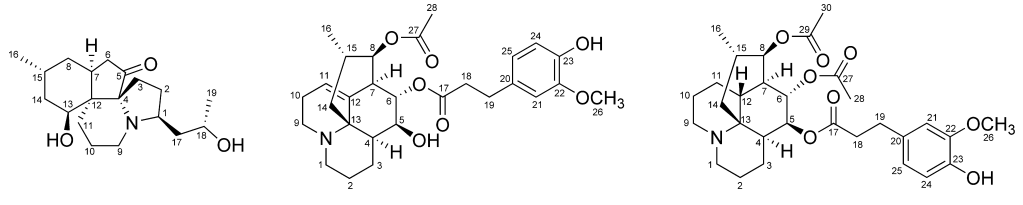


Fig. 1. Selected 2D-NMR Correlations for Malycorin A (**1**)



1 **2** **3**

Chart 1

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Table 1. ^{1}H- and ^{13}C-NMR Data of Malycorin A (**1**) in CD_3OD at 300 K[a)]

	δ_H	δ_C	HMBC (^{1}H)
1	3.38 (1H, m)	59.6	2a, 17
2a	1.65 (1H, m)	28.3	17b
2b	2.06 (1H, m)		
3a	1.96 (1H, m)	23.7	
3b	2.18 (1H, m)		
4		79.0	7, 9b
5		218.8	3a, 6
6a	2.38 (1H, dd, 18.8, 10.3)	40.1	8a
6b	2.53 (1H, dd, 18.8, 11.2)		
7	2.86 (1H, m)	34.0	6a
8a	1.34 (1H, m)	33.0	6b, 16
8b	1.62 (1H, m)		
9a	2.20 (1H, m)	43.9	
9b	2.90 (1H, m)		
10a	1.66 (1H, m)	21.0	
10b	1.79 (1H, m)		
11a	1.16 (1H, m)	26.0	7
11b	1.87 (1H, br d, 13.3)		
12		46.3	6a
13	3.52 (1H, br s)	74.4	7, 11a
14a	1.36 (1H, m)	39.0	16
14b	1.57 (1H, br d, 14.1)		
15	2.04 (1H, m)	21.2	13, 16
16	0.92 (3H, d, 6.6)	22.6	
17a	1.66 (1H, m)	41.7	19
17b	1.74 (1H, m)		
18	3.74 (1H, br q, 6.2)	67.3	17, 19
19	2.80 (3H, d, 6.2)	23.6	17b

a) δ in ppm.

ternary carbon C-12 were implied by HMBC correlations for H-7 and H-11 to C-13, and H-6a to C-12. HMBC cross-peaks for H-3 and H_2-6 to C-5 and H-7 to C-4 indicated that the presence of cyclopentanone ring (C-4—C-7 and C-12) and connectivity of C-3 and C-4. The connection among C-1, C-4 and C-9 through a nitrogen atom was deduced from HMBC correlations of H-9b to C-4 and low field chemical shift of C-1 (δ_C 59.6; δ_H 3.38). Thus, the gross structure of malycorin A was elucidated as **1** possessing a serratinane skeleton with 2-propanol unit at C-1.

The relative configuration of **1** was deduced from NOESY correlations (Fig. 2). The *cis*-junction of bicyclo[4.3.0]-nonane ring (C-4—C-8 and C-12—C-15) and β-configuration of H-15 were deduced by the NOESY correlation of H-6/H-15. NOESY correlations of H-3a and H-11a/H-13 suggested that H-13 and C-3 were oriented to the same side and H-13 was in the α-orientation. Chair conformation of a piperidine ring (C4, C-9—C-12, and N) was supported by a NOESY correlation of H-9a/H-11a. The β-configuration of H-1 was assigned by the NOESY cross-peak of H-1/H-3b. The configuration of C-18 in the 2-propanol moiety at C-1 was deduced from NOESY correlations of H-18/H-2b, H-17/H-9b, and H_3-19/H-1 as shown in Fig. 3. Thus, the structure of malycorin A was elucidated as **1**, possessing a serratinane skeleton with 2-propanol unit at C-1.

HR-ESI-TOF-MS data (**2**: *m/z* 500.2626, $[M+H]^+$, Δ −2.2 mmu; **3**: *m/z* 544.2908, $[M+H]^+$, Δ −0.2 mmu) of malycorin B {**2**, $[\alpha]_D^{24}$ +30° (*c*=1.0, MeOH)} and C {**3**, $[\alpha]_D^{24}$ +28° (*c*=0.3, MeOH)} revealed the molecular formula, $C_{28}H_{37}NO_7$ and $C_{30}H_{41}NO_8$, respectively. The ^{1}H- and ^{13}C-NMR (Table 2) spectra of **2** revealed signals due to seven quaternary carbons (sp^2×6 and sp^3×1), ten methines (sp^2×4

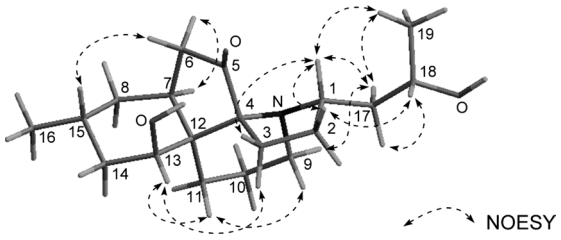

Fig. 2. Selected NOESY Correlations and Relative Configuration for Malycorin A (**1**)

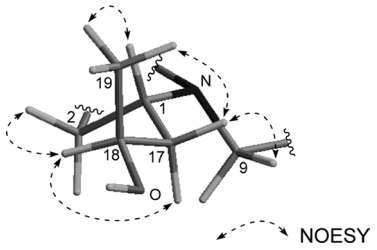

Fig. 3. Selected NOESY Correlations and Relative Configuration around 2-Propanol Unit of Malycorin A (**1**)

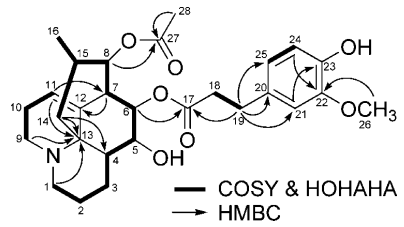

Fig. 4. Selected 2D-NMR Correlations for Malycorin B (**2**)

and sp^3×6), eight methylenes, and three methyls, suggesting that **2** had a similar backbone skeleton to that of lycoposerramine-O[22] with a hydroxyl group. In the ^{13}C-NMR spectrum of **2**, signals due to three oxygen-bearing carbons at δ_C 71.2 (d), 76.1 (d), and 79.0 (d), three nitrogen-bearing carbons at δ_C 45.7 (t), 50.3 (t), and 63.4 (s), and two ester carbonyl carbons at δ_C 172.4 (s) and 173.5 (s) appeared. The structure of **2** was elucidated by 2D-NMR (^{1}H–^{1}H COSY, HOHAHA, HMQC, and HMBC) data (Fig. 4). The ^{1}H–^{1}H COSY and HOHAHA spectra revealed connectivities as shown in Fig. 4. The connectivities of C-1, C-9, and C-13 through a nitrogen atom were implied by HMBC correlations for H-1a and H-9a to C-13. HMBC cross-peaks for H-14a to C-4 and C-13 indicated that C-4 and C-14 were connected to each other through C-13. HMBC cross-peaks of H-11 to C-7 and C-13, and H-7 to C-12 indicated the connection among C-7, C-11, and C-13 through C-12. The presence of a shorbic acid ester at C-6 and acetoxy group at C-8 were revealed by HMBC correlations of H-6 and H_2-19 to C-17, and H-8 and H_3-28 to C-27, respectively.

The relative configuration of **2** was deduced from NOESY correlations (Fig. 5). NOESY cross-peaks of H-6/H_3-28 assigned the stereochemistry at C-6 and C-8 as shown in Fig. 5. The NOESY correlation of H-8/H-14a and ^3J coupling constants ($^3J_{H\text{-}14a/H\text{-}15}$=12.6 Hz) indicated that methyl group at C-15 was equatorially oriented. The ^{1}H signal of H-15 (δ_H 3.30) was observed at lower field by anisotropic effect of a β-oriented hydroxyl group at C-5. The α-configuration of H-4

Table 2. ^{1}H- and ^{13}C-NMR Data of Malycorins B (**2**) and C (**3**) in CD_3OD at 300 K[a)]

	2			**3**		
	δ_H	δ_C	HMBC (^{1}H)	δ_H	δ_C	HMBC (^{1}H)
1a	3.19 (1H, m)	50.3	3a	3.02 (1H, dd, 13.7, 1.8)	48.2	3a
1b	3.64 (1H, m)			3.60 (1H, ddd, 13.7, 13.7, 3.5)		
2a	1.86 (1H, m)	20.1		1.73 (1H, m)	18.9	
2b	1.99 (1H, m)			2.01 (1H, m)		
3a	1.44 (1H, m)	21.9		1.31 (1H, m)	20.9	
3b	1.88 (1H, m)			1.38 (1H, m)		
4	2.06 (1H, m)	41.9	6, 14a	3.05 (1H, m)	31.6	6, 14a
5	3.61 (1H, d, 5.4)	71.2	6, 7	5.15 (1H, d, 6.9)	72.1	6, 7
6	4.98 (1H, br s)	76.1	5, 7, 8	4.92 (1H, br s)	71.5	5, 7, 8
7	2.69 (1H, br d, 5.0)	49.9	11	2.27 (1H, br d, 4.7)	44.2	
8	4.40 (1H, dd, 11.3, 5.0)	79.0	6, 7, 16	4.55 (1H, dd, 11.0, 4.7)	78.9	6, 7, 16
9a	3.17 (1H, m)	45.7	11	3.08 (1H, m)	47.3	11
9b	3.63 (1H, m)			3.83 (1H, m)		
10a	2.29 (1H, m)	23.7	11	1.80 (1H, m)	23.8	11
10b	2.53 (1H, m)			2.00 (1H, m)		
11a	5.44 (1H, d, 6.1)	120.4	7, 9a	1.53 (1H, br d, 11.5)	24.0	7, 9a
11b				2.11 (1H, m)		
12		136.8	6, 7, 14b	1.81 (1H, br d, 13.5)	42.5	6, 7, 14b
13		63.4	1a, 3a, 5, 7, 9a, 11, 14		63.4	1a, 3a, 5, 7, 9a, 11, 14
14a	1.21 (1H, dd, 12.6, 12.6)	37.2	16	1.26 (1H, m)	39.0	16
14b	2.75 (1H, m)			2.72 (1H, m)		
15	3.30 (1H, m)	29.8	7, 8, 14, 16	2.69 (1H, m)	31.0	7, 8, 14, 16
16	0.91 (3H, d, 6.3)	19.4	8, 14a	1.04 (3H, d, 6.4)	19.9	8, 14a
17		173.5	6, 18, 19		173.3	6, 18, 19
18a	2.58 (1H, m)	36.9	19	2.68 (1H, m)	36.9	19
18b	2.62 (1H, m)			2.70 (1H, m)		
19a	2.80 (1H, m)	31.8	18, 21, 25	2.87 (1H, m)	31.7	18, 21, 25
19b	2.88 (1H, m)			2.92 (1H, m)		
20		133.3	18, 19, 24		133.3	18, 19, 24
21	6.78 (1H, br s)	113.2	19, 25	6.81 (1H, d, 1.7)	113.2	19, 25
22		148.9	24, 26		149.1	24, 26
23		146.0	21, 25		146.3	21, 25
24	6.71 (1H, d, 7.3)	116.2		6.73 (1H, d, 8.0)	116.0	
25	6.60 (1H, d, 7.3)	121.9	19	6.66 (1H, dd, 8.0, 1.7)	122.0	19
26	3.83 (3H, s)	56.5		3.85 (3H, s)	56.5	
27		172.4	8, 28		172.6	6, 28
28	2.11 (3H, s)	20.9		2.05 (3H, s)	20.6	
29					171.0	8, 30
30				2.03 (3H, s)	20.6	

a) δ in ppm.

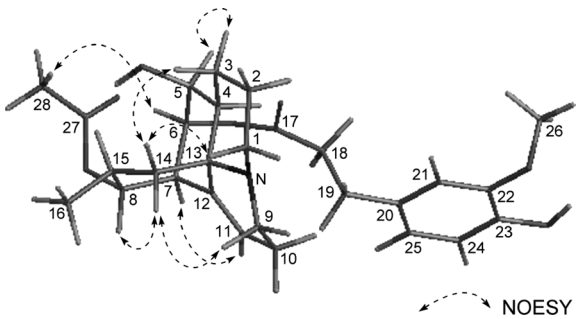

Fig. 5. Selected NOESY Correlations and Relative Configuration for Malycorin B (**2**)

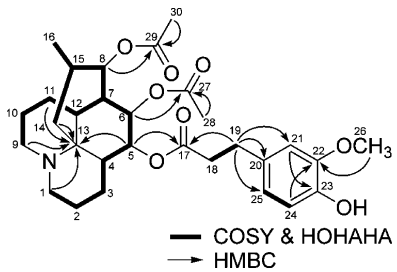

Fig. 6. Selected 2D-NMR Correlations for Malycorin C (**3**)

was supported by the NOESY correlation of H-3a/H-5. Thus, the structure of malycorin B was assigned as **2**.

The molecular formula of malycorin C (**3**) was larger than that of malycorin B (**2**) by 44 mmu. ^{1}H- and ^{13}C-NMR data (Table 2) of **3** were analogous to those of **2** with two acetoxy groups at C-6 and C-8, and a shorbic acid ester at C-5 although signals of trisubstituted olefin carbons (δ_H 5.44; δ_C 120.4, 136.8) at C-11 and C-12 of **2** were not observed for **3**. The gross structure of **3** was elucidated by 2D-NMR (^{1}H–^{1}H COSY, HOHAHA, HMQC, and HMBC) data.

The ^{1}H–^{1}H COSY and HOHAHA spectra revealed connectivities as shown by the bold line (Fig. 6). The partial unit in mother skeleton was connected to C-13 on the basis of HMBC correlations of H-1a, H-5, H-9a, H-11a, and H-14a to

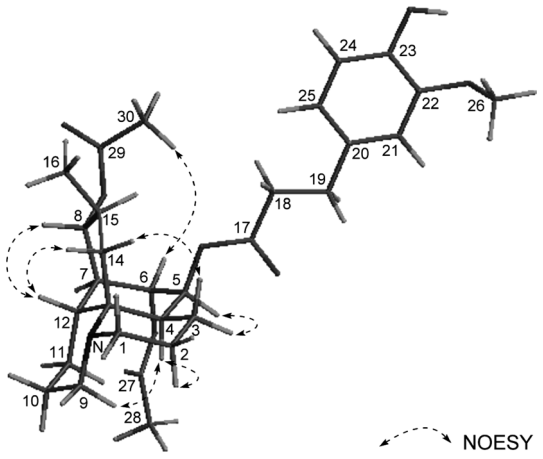

Fig. 7. Selected NOESY Correlations and Relative Configuration for Malycorin C (**3**)

C-13. The presence of two acetoxy groups at C-6 and C-8 were revealed by HMBC correlations of H-6 and H_3-28 to C-27, and H-8 and H_3-30 to C-29. The relative configuration of **3** was deduced from NOESY correlations (Fig. 7). Chair conformation of cyclohexane ring (C7, C-8, and C-12—C-15) was suggested by NOESY correlations of H-12 to H-8 and H-14a. NOESY correlations of H-4 to H-2b and H-9b indicated an α-configuration of H-4. H-6 was assigned as β-orientation by the NOESY cross-peak of H-6 and H_3-30. The α-configuration of H-5 was supported by the NOESY correlation of H-3a/H-5. Thus, the structure of malycorin C was assigned as **3**.

Experimental

General Experimental Procedures Optical rotations were measured on a JASCO P-1030 polarimeter. UV spectra were recorded on a Shimadzu UV-250 spectrophotometer and IR spectra on a JASCO FTIR-230 spectrometer. Mass spectra were obtained with a Micromass LCT spectrometer. ^{1}H- 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. Each NMR sample of malycorins was prepared by dissolving in 30 ml of CD_3OD in 2.5 mm micro cells (Shigemi Co., Ltd.) and chemical shifts were reported using residual CD_3OD (δ_H 3.31 and δ_C 49.0) as internal standard. Standard pulse sequences were employed for the 2D-NMR experiments. 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.

Plant Material The club moss *Lycopodium phlegmaria* was collected at Kagoshima in Japan. The botanical identification was made by Mr. N. Yoshida, Health Sciences University of Hokkaido. A voucher specimen has been deposited in the herbarium of Hoshi University.

Extraction and Isolation The club moss *L. phlegmaria* (150 g) was extracted with MeOH, and the extract was partitioned between EtOAc and 3% tartaric acid. The aqueous layer was adjusted to pH 10 with saturated aq. Na_2CO_3, and extracted with $CHCl_3$. $CHCl_3$-soluble materials were subjected to an amino silica gel column (hexane/EtOAc, 1 : 0→0 : 1, and then $CHCl_3$/MeOH, 1 : 0→0 : 1), in which a fraction eluted with hexane/EtOAc (3 : 2) was purified by a silica gel column ($CHCl_3$/MeOH→MeOH) and then C_{18} HPLC (Phenomenex LUNA C_{18}, 5 μm, Shimadzu GLC Ltd., 10×250 mm; eluent, 25—35% CH_3CN/0.1% TFA; flow rate 2 ml/min; UV detection at 210 nm) to afford malycorins A (**1**, 0.3 mg, 0.0002%), B (**2**, 1.5 mg, 0.001%), C (**3**, 1.7 mg, 0.001%), and huperzine A (0.001%).

Malycorin A (**1**): Colorless amorphous solid, $[\alpha]_D^{27}$ +38° (c=0.2, MeOH); IR (KBr) ν_{max} 3340, 2920, 1740, 1460, and 1260 cm^{-1}; ^{1}H- and ^{13}C-NMR (Table 1); ESI-MS (pos.) m/z: 322 $(M+H)^+$; HR-ESI-TOF-MS m/z: 322.2363 $(M+H)^+$, Calcd for $C_{19}H_{32}NO_3$ 322.2382.

Malycorin B (**2**): Colorless amorphous solid; $[\alpha]_D^{24}$ +30° (c=1.0, MeOH); UV (MeOH) λ_{max} 293 (ε 2400), 228 (5100), and 203 (21600) nm; IR (KBr) ν_{max} 3440, 2940, and 1720 cm^{-1}; ^{1}H- and ^{13}C-NMR (Table 2); ESI-MS (pos.) m/z: 500 $(M+H)^+$; HR-ESI-TOF-MS m/z: 500.2626 $(M+H)^+$, Calcd for $C_{28}H_{38}NO_7$ 500.2648.

Malycorin C (**3**): Colorless amorphous solid; $[\alpha]_D^{24}$ +28° (c=0.3, MeOH); UV (MeOH) λ_{max} 282 (ε 2600), 230 (7600), and 203 (24800) nm; IR (KBr) ν_{max} 3440, 2940, and 1740 cm^{-1}; ^{1}H- and ^{13}C-NMR (Table 2); ESI-MS (pos.) m/z: 544 $(M+H)^+$; HR-ESI-TOF-MS m/z: 544.2908 $(M+H)^+$, Calcd for $C_{30}H_{42}NO_8$ 544.2910.

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