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Structure Elucidation and Synthesis of Lycoposerramine-B, a Novel Oxime-Containing *Lycopodium* Alkaloid from *Lycopodium serratum* Thunb.

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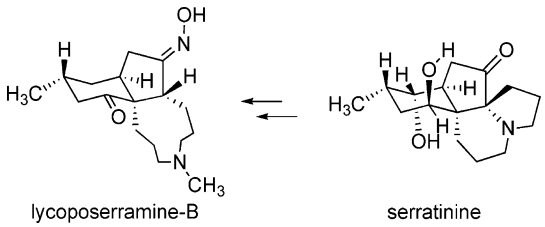

A new alkaloid, lycoposerramine-B (**1**), containing an oxime function, was isolated from the club moss *Lycopodium serratum* Thunb. The structure of **1** was elucidated by spectroscopic analysis, including *J*-resolved HMBC spectroscopy, and confirmed by its synthesis from the known alkaloid, serratinine (**3**).

Introduction

The genus *Lycopodium*, which produces structurally complex alkaloids[1] and potent acetylcholine esterase inhibitors,[2] has been extensively studied by many groups.[3] In our continuing chemical studies on the structurally unique alkaloids of *Lycopodium*, we have isolated a number of new alkaloids from *L. serratum*.[4−6] Further purification of the alkaloidal fraction of this plant has led to the isolation of a new base named lycoposerramine-B (**1**), which was the first example of a *Lycopodium* alkaloid having an oxime function in the molecule. In this paper, we describe structure elucidation by means of spectroscopic analysis and the chemical transformation from a known alkaloid, serratinine (**3**).

Results and Discussion

1. Isolation and Structure Elucidation of Lycoposerramine-B by Spectroscopic Analysis. The crude base fraction obtained by means of a previously reported procedure[6] was purified by repeated chromatography over SiO_2 gel to afford a new alkaloid, lycoposerramine-B (**1**, 0.07% yield based on the crude base).

Compound **1**, named lycoposerramine-B, was obtained as a colorless amorphous powder. High-resolution FAB-

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TABLE 1. ^{1}H and ^{13}C Data of Lycoposerramine-B (1) in $CDCl_3$

	δ_H	δ_C	HMBC (H to C)
1a	2.03 (1H, m)	48.5	C-2, 9
1b	2.66 (1H, dd, 13.4, 13.4)		
2a	1.46 (1H, m)	27.5	
2b	1.69 (1H, m)		
3a	1.28 (1H, br d, 14.4)	25.5[a]	
3b	2.00 (1H, m)		C-2, 4, 12
4	3.18 (1H, d-like, 2.8)	42.9	C-2, 3, 5, 6, 11, 12, 13
5		169.6	
6a	2.20 (1H, m)	28.7	C-4, 5, 7, 8, 12
6b	2.54 (1H, ddd, 1.1, 9.5, 19.0)		C-4, 5, 7, 12
7	2.41 (1H, m)	42.9	C-5, 6, 12, 13
8	1.73 (2H, m)	31.6	C-6, 7, 12, 14, 15, 16
9a	2.27 (1H, m)	55.1	
9b	2.31 (1H, m)		
10a	1.20 (1H, m)	21.4	
10b	1.36 (1H, m)		
11a	2.00 (1H, m)	25.6[a]	C-4, 7, 9, 10, 12, 13
11b	2.20 (1H, m)		C-9, 10, 12, 13
12		61.7	
13		213.8	
14a	2.20 (1H, m)	46.8	C-8, 12, 13, 15, 16
14b	2.27 (1H, m)		C-8, 13, 15, 16
15	2.10 (1H, m)	29.9	
16	1.03 (3H, d, 6.4)	22.5	C-8, 14, 15
N-CH_3	2.27 (3H, s)	44.4	C-1, 9

[a] Interchangeable

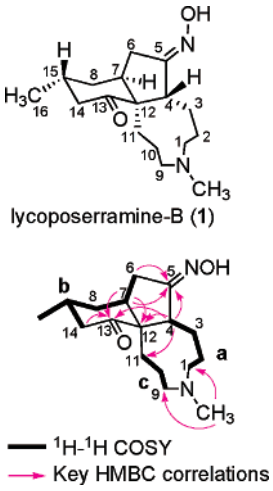

FIGURE 1. Structure and selected 2D NMR data for **1**.

MS gave *m/z* 293.2227 [(M + H)$^+$ (Δ −0.2 mmu)] and established the molecular formula as $C_{17}H_{28}N_2O_2$. The IR spectrum indicated the presence of one ketone (1699 cm^{-1}) and one hydroxyl group (3279 cm^{-1}). ^{1}H and ^{13}C NMR (Table 1) spectra showed the presence of one ketone (δ 213.8), one sp^2 carbon probably ascribable to an imine function (δ 169.6), one quaternary carbon (δ 61.7), one methyl group (δ 2.27, 3H, s) on a nitrogen atom, and one secondary methyl group (δ 1.03, 3H, d, J = 6.4 Hz), besides three methine and nine methylene carbons. The presence of an oxime function was deduced from the intense fragment peak at *m/z* 275 (M$^+$ − OH) and the chemical shift of the isolated sp^2 carbon (δ_c 169.6), and by taking the molecular formula ($C_{17}H_{28}N_2O_2$) into consideration. ^{1}H−^{1}H COSY and HMQC (Figure 1) analyses indicated the presence of three sp^3 carbon chains (**a**: $-CH_2CH_2CH_2CH-$; **b**: $-CH_2CHCH_2CH(CH_3)CH_2-$; **c**: $-CH_2CH_2CH_2-$). The gross structure of **1** was established by HMBC analysis as follows. The HMBC cross-peaks between the *N*-methyl proton (δ 2.27, 3H, s) and the two terminal carbons of fragments **a** (δ 48.5, C-1) and **c** (δ 55.1, C-9) indicated that these two fragments and the methyl group were connected by a nitrogen atom. HMBC correlations between two protons (δ 3.18, H-4 and δ 2.41, H-7) and quaternary carbon (δ 61.7, C-12) and between methine proton (δ 3.18, H-4) and methylene carbon (δ 25.6, C-11) implied these three fragments (**a**, **b**, and **c**) attached to the quaternary carbon (δ 61.7, C-12). HMBC correlations between three protons (δ 3.18, H-4; δ 2.41, H-7; and δ 2.27, H-14) and one carbonyl carbon (δ 213.8, C-13) pointed to the presence of a cyclohexanone ring system. Further HMBC correlations between methylene protons (δ 2.20, 2.54, H-6) as well as two methine protons (δ 2.41, H-7 and δ 3.18, H-4) and the carbon signal at δ 169.6 implied that fragments **a** and **b** were attached to a particular carbon ascribable to the oxime at both terminal carbons (C-4 and C-6). All of these data indicated that lycoposerramine-B (**1**) had a fundamental skeleton of fawcettimine (**2**)[7,8] with the keto-amine form (see Scheme 3).

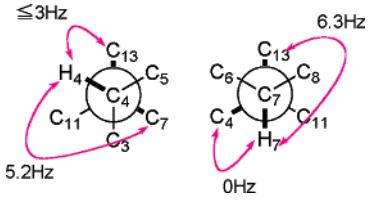

FIGURE 2. *J*-resolved HMBC analysis for **1**.

The stereochemistry at C-7, -12, and -15 was assumed to be the same as those in fawcettimine (**2**) based on the biogenetic speculation described below. The configuration at C-4 was inferred from *J*-resolved HMBC[9] spectral data (Figure 2). The large coupling constants $^3J_{H4-C7}$ (5.2 Hz) and $^3J_{H7-C13}$ (6.3 Hz) as well as the small values $^3J_{H4-C13}$ (≤3 Hz) and $^3J_{H7-C4}$ (0 Hz) are consistent with H-4β configuration.

2. Synthesis of 1 from Serratinine. To confirm the structure of **1** that was inferred by spectroscopic analysis, we attempted its synthesis from serratinine (**3**),[10] the

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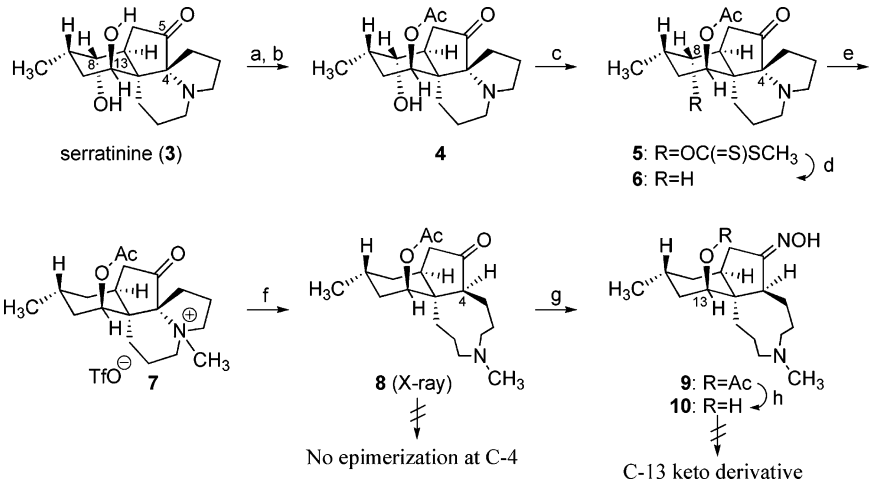
SCHEME 1[a]



[a] Reagents and conditions: (a) Ac_2O, pyridine, 100 °C, 98%. (b) 10% HCl, reflux, 84%. (c) NaH, HMPA, THF, rt then CS_2, MeI, rt, 47% (with 49% recovery of **4**). (d) $^nBu_3SnH$, AIBN, toluene, reflux, 77%. (e) MeOTf, MeCN, rt. (f) Zn, AcOH, rt, 99% (in two steps). (g) $NH_2OH{\cdot}HCl$, AcONa, EtOH, reflux, 80%. (h) NaOH, MeOH, reflux, 52%.

structure and the absolute configuration of which has been proven by X-ray analysis.[10g] To complete the transformation, the removal of a hydroxyl group at C-8, the ring opening at the *N*-C_4 bond, the oxidation of the secondary hydroxyl group at C-13, and the regioselective oximation at C-5 were required. Along this line, two strategies have been assayed as described below.

Initially, according to the procedure reported in the literature,[10c] monoacetate (**4**) was prepared from serratinine (**3**), which has been previously isolated from *Lycopodium serratum* Thunb. var. *Thunbergii* Makino (Japanese name Hosoba-Tohogeshiba).[10a] Then, the free secondary hydroxyl group in **4** was removed by Barton's procedure.[11] Xanthate derivative **5** was exposed to the radical condition by using *n*-Bu_3SnH in the presence of AIBN to afford deoxy derivative **6**. Initial attempts at the reductive bond cleavage between C_4-*N* in **6** by applying known procedures[10c,h] (Zn/Ac_2O or Zn/AcOH) gave the ring-opening product in poor yield. Then, we developed an alternative condition that involved the reductive bond cleavage of an α-ammonium carbonyl function. Quaternary ammonium derivative **7**, which was prepared by using MeOTf in CH_2Cl_2, was treated with Zn powder in AcOH at room temperature to give ring-opening product **8** in high yield. The structure was established by X-ray crystallographic analysis, revealing that the stereochemistry at C-4 was *S*. However, the synthetic route via intermediate **8** met with failure. The epimerization at C-4 in **8** did not occur under basic condition, probably because **8** would be more thermodynamically stable than its C-4 epimer as described by Heathcock in their synthetic study on fawcettimine (**2**).[8] In addition the conversion of the hydroxyl group at C-13 into the ketone failed in **10** that had a labile oxime function under the attempted oxidation conditions.

Therefore, we adopted an alternative strategy that featured regioselective oximation (Scheme 2). Initially, diketone derivative **11**[10h] prepared from **6** was subjected to the reductive ring-opening reaction developed above. Conversion of **11** to a quaternary ammonium intermediate and subsequent treatment with Zn powder in AcOH afforded two C-4 epimeric compounds **12** and **13** in 34% and 30% yields, respectively. **12** showed the desired (*R*) configuration on C-4 (H-4β) by X-ray crystallographic analysis. On the other hand, **13** could be epimerized at C-4 under basic conditions (^{t}BuOK in ^{t}BuOH, **12**:**13** = 1:1), enabling the convergence of **13** into **12**. The oximation of diketone **12** with 1 equiv of hydroxylamine hydrochloride under conventional conditions (AcONa, EtOH, reflux) gave the undesired regioisomer **14**. From the Dreiding-model analysis, we anticipated that when **12** was treated with diethylamine, only the carbonyl function at C-5 would be condensed with the dialkylamine to produce iminium salt **15**. In contrast, the carbonyl group at C-13 in **12** would be intact under these conditions because of the severe steric repulsion between the alkyl group on a quaternary nitrogen atom at C-13 and the alkyl chain at C-12 in spurious iminium intermediate **16**. Therefore, in possible intermediate **15**, hydroxylamine would condense with the more reactive iminium function at C-5 to yield the desired oximation product. On the basis of this idea, **12** was actually treated with excess diethylamine in EtOH, followed by the addition of hydroxylamine hydrochloride to give monooxime compounds (**1** and **17**) in 46% and 19% yields, respectively. The major product was identical with natural lycoposerramine-B (^{1}H, ^{13}C NMR, IR, low- and high-resolution MS, and CD spectra).

The spectroscopic data of minor product **17** were almost superimposable with those of **1** except for the chemical shift of some protons and carbons. The structures inferred by extensive 2D-NMR analyses including NOESY experiments indicated that both compounds were geometrical isomers on the oxime function. The *E*/*Z* geometry of the oxime function in **1** and **17** was estimated by comparing the chemical shifts of the protons[12] and carbons[13] at C-4 and C-6. As shown in Table 2, the proton signal at C-4

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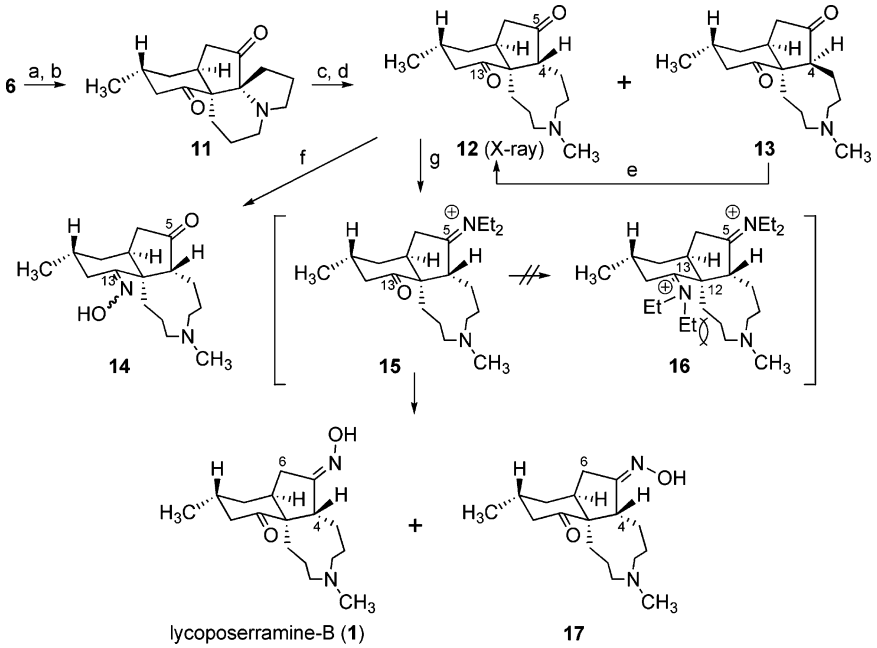
SCHEME 2[a]



[a] Reagents and conditions: (a) KOH, MeOH, reflux, quant. (b) Jones reagent, acetone, rt, 98%. (c) MeOTf, MeCN, rt. (d) Zn, AcOH, rt; **12**, 34%; **13**, 30%. (e) ^{t}BuOK, ^{t}BuOH, rt; **12**, 30%; **13**, 32%. (f) $NH_2OH{\cdot}HCl$, AcONa, EtOH, reflux, 70%. (g) Et_2NH, EtOH then $NH_2OH{\cdot}HCl$; **1**, 46%; **17**, 19%.

SCHEME 3. Hypothetical Biogenetic Route from Fawcettimine (2) to Lycoposerramine-B (1) and Related Alkaloids

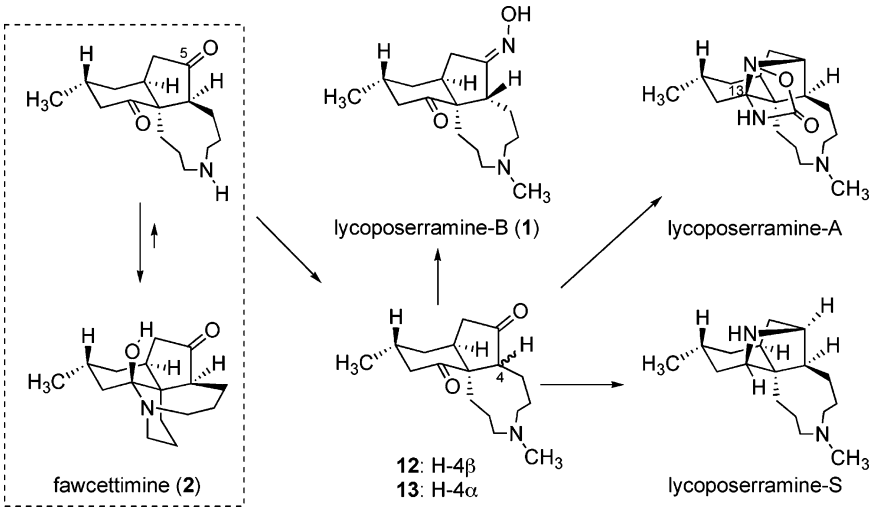


TABLE 2. ^{1}H and ^{13}C Chemical Shift at C-4 and C-6 of 1 and 17 in $CDCl_3$

position	1	17
H-4	3.18 (1H, d-like, 2.8)	3.59 (1H, br s)
H-6a	2.20 (1H, m)	2.12 (1H, m)
H-6b	2.54 (1H, ddd, 1.1, 9.5, 19.0)	2.40 (1H, m)
C-4	42.9	39.6
C-6	28.7	31.3

of **1** (δ 3.18) was observed at a higher field than that of **17** (δ 3.59), whereas the signals at C-6 of **1** (δ 2.20, 2.54) were observed at a lower field than that of **17** (δ 2.12, 2.40) . In addition, the signal due to C-6 of **1** was observed at higher field and, on the contrary, that of C-4 was observed downfield from the corresponding signals of **17**. Consequently, the geometry of the oxime function of **1** was *E* and that of **17** was *Z*. We conclude that the structure of lycoposerramine-B, including the oxime geometry as well as the absolute configuration, corresponds to formula **1**.

3. Hypothetical Biogenetic Route from Fawcettimine. The hypothetical biogenetic route of **1** and other related alkaloids starting from fawcettimine (**2**) was proposed as follows (Scheme 3). Two diketo compounds **12** and **13**, which were obtained in the present synthetic work, would be biogenetic precursors for lycoposerramines-A,[4] -B (**1**), and -S.[5] The carbonyl group at C-5 in **12** would be converted into the oxime function to afford

(13) Levy, G. C.; Nelson, G. L. *J. Am. Chem. Soc.*, **1972**, *94*, 4897–4901.

lycoposerramine-B (**1**). On the other hand, lycoposerramines-A and -S would be produced from **13** via several metabolic processes including amination, reduction, and cyclization.

Experimental Section

Lycoposerramine-B (1). Colorless amorphous powder; CD (0.90 mM, MeOH, 24 °C) ($\Delta\epsilon$) 331 (0), 298 (+3.2), 237 (−0.1), 208 nm (+2.6); IR ($CHCl_3$) ν_{max} 3279 (hydroxyl group), 1699 (ketone) cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; EI-MS (%) *m/z* 292 ($[M]^+$, 21.0), 275 (35.2), 202 (100); HR-FAB-MS (NBA/PEG) *m/z* 293.2227 (M + H, calcd for $C_{17}H_{29}N_2O_2$ 293.2229).

Deoxygenation of 4. To a stirred solution of **4**[10c] (157.0 mg, 0.489 mmol) in dry THF (3.0 mL) were added dry HMPA (170 μL, 0.977 mmol) and NaH (60%, 42.4 mg, 1.06 mmol) at room temperature under argon atmosphere. After the solution was stirred for 30 min, CS_2 (120 μL, 1.99 mmol) was added and the solution was stirred for an additional 4 h at room temperature. Then MeI (97.0 μL, 1.56 mmol) was added and the reaction mixture was stirred for 3.5 h at the same temperature. The reaction mixture was poured into ice-cold water and extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed over SiO_2 gel (15% *n*-hex/$CHCl_3$ then MeOH) to give xanthate **5** (94.5 mg, 47%) as a colorless amorphous powder: $[\alpha]^{22}_D$ −38.1 (*c* 1.37, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1739 (ester, ketone) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (1H, br s), 4.75 (1H, br s), 3.54 (1H, dd, *J* = 10.8, 10.8 Hz), 2.83 (1H, ddd, *J* = 9.3, 9.3, 12.5 Hz), 2.74 (1H, dd, *J* = 10.6, 18.7 Hz), 2.72 (1H, m), 2.60 (3H, s), 2.57 (1H, ddd, *J* = 1.5, 8.4, 12.4 Hz), 2.25−2.17 (2H, m), 2.01−1.44 (10H, m), 1.95 (3H, s), 1.20 (1H, ddd, *J* = 4.2, 13.5, 13.5 Hz), 0.98 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.3, 211.8, 169.5, 83.6, 77.1, 76.0, 52.2, 50.1, 43.5, 36.4, 35.7, 29.3, 26.8, 24.4, 21.11, 21.08, 20.9, 20.4, 19.1, 16.9; EI-MS (%) *m/z* 411 ($[M]^+$, 4.7), 383 (49.4), 368 (40.0), 324 (93.7), 292 (32.3), 276 (100), 256 (53.1), 216 (51.6), 194 (70.5), 152 (82.3); HR-FAB-MS (NBA/PEG) *m/z* 412.1642 (M + H, calcd for $C_{20}H_{30}NO_4S_2$ 412.1616). The MeOH eluate was rechromatographed over SiO_2 gel (2% MeOH/AcOEt) to recover **4** (76.9 mg, 49%).

To a solution of the xanthate **5** (249.8 mg, 0.608 mmol) in dry toluene (8.0 mL) were added *n*-Bu_3SnH (330 μL, 1.23 mmol) and AIBN (29.7 mg, 0.181 mmol) at room temperature under argon atmosphere. After being stirred under reflux for 1 h, the reaction mixture was cooled and extracted with 5% HCl aq. The aqueous layer was basified with $NaHCO_3$ and extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified over SiO_2 gel (100% $CHCl_3$) to give **6** (131.7 mg, 77%) as colorless prisms; mp 198−200°C (recrystallized from *n*-hex/$CHCl_3$); $[\alpha]^{24}_D$ −11.0 (*c* 0.94, $CHCl_3$); IR (KBr) ν_{max} 1739 (ketone and ester) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.66 (1H, br s, H-13), 3.07 (1H, ddd, *J* = 5.2, 10.9, 10.9 Hz, H-7), 2.90 (1H, ddd, *J* = 9.4, 9.4, 12.3 Hz, H-1), 2.73 (1H, br d, *J* = 10.4 Hz, H-9), 2.59 (1H, ddd, *J* = 1.5, 8.2, 12.2 Hz, H-1), 2.54 (1H, dd, *J* = 10.4, 18.9 Hz, H-6), 2.35 (1H, dd, *J* = 11.0, 18.9 Hz, H-6), 2.24 (1H, ddd, *J* = 3.1, 12.1, 12.1 Hz, H-9), 1.95 (1H, m, H-2), 1.93 (3H, s, −OAc), 1.90 (2H, m, H-10 and -11), 1.79 (1H, m, H-15), 1.75 (1H, m, H-2), 1.72 (1H, m, H-14), 1.65 (1H, m, H-8), 1.61 (1H, m, H-3), 1.55 (1H, m, H-10), 1.48 (1H, ddd, *J* = 4.9, 10.1, 13.1 Hz, H-3), 1.35 (1H, ddd, *J* = 5.5, 12.5, 14.0 Hz, H-8), 1.30 (1H, ddd, *J* = 2.1, 12.5, 14.6 Hz, H-14), 1.13 (1H, ddd, *J* = 4.7, 14.0, 14.0 Hz, H-11), 0.91 (3H, d, *J* = 6.4 Hz, H-16); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.3 (C-5), 169.7 (OAc), 76.9 (C-4*), 76.8 (C-13*), 52.3 (C-1), 50.1 (C-9), 43.9 (C-12), 38.2 (C-6), 34.1 (C-14), 32.4 (C-7), 31.9 (C-8), 24.8 (C-11), 21.9 (C-16), 21.4 (C-3**), 21.2 (C-2**), 21.1 (OAc**), 20.6 (C-10***), 20.5 (C-15***) [*, **, *** are interchangeable]; EI-MS (%) *m/z* 305 (M^+, 12.3), 291 (42.4), 277 (100), 232 (99.9), 219 (82.9), 218 (95.6), 194 (99.1), 176 (29.3), 152 (94.4), 150 (97.7).

Preparation of Quaternary Salt (7). To an ice-cooled solution of **6** (50.9 mg, 0.167 mmol) in dry MeCN (1.5 mL) was added MeOTf (21.0 μL, 0.186 mmol) under argon atmosphere. After removal from the ice bath, the reaction mixture was stirred at room temperature for 4.5 h. The solvent was removed under reduced pressure and the residue was subjected to the next reaction without purification. ^1H NMR (400 MHz, $CDCl_3$) δ 4.69 (1H, br s), 3.26 (3H, s), 1.94 (3H, s), 0.94 (3H, d, *J* = 6.2 Hz); FAB-MS (NBA) *m/z* 320 $[M]^+$.

Reductive Ring Opening Reaction of 7. The crude quaternary salt prepared above was dissolved in AcOH (2.0 mL) at room temperature. Then zinc powder (744.5 mg) was added and the reaction mixture was stirred vigorously. After the solution was stirred for 14.5 h, the zinc powder was filtered off, and the filtrate was basified with $NaHCO_3$ and extracted with $CHCl_3$. The combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified over SiO_2 gel (100% AcOEt) to afford **8** (53.2 mg, 99%) as colorless prisms; mp 123−124 °C (recrystallized from AcOEt); $[\alpha]^{24}_D$ +92.4 (*c* 0.42, $CHCl_3$); IR (KBr) ν_{max} 1738 (ester and ketone) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.96 (1H, br s, H-13), 2.81 (1H, br s, H-4), 2.51 (1H, m, H-9), 2.31 (3H, m, H-1, 1, 9), 2.25 (3H, s, *N*-CH_3), 2.25 (2H, m, H-6, 6), 2.15 (1H, m, H-7), 1.88 (3H, s, −OAc), 1.85 (1H, m, H-3), 1.77 (1H, m, H-15), 1.71 (3H, m, H-11, -11, -14), 1.63 (1H, m, H-8), 1.60 (1H, m, H-2), 1.58 (1H, m, H-10), 1.40 (2H, m, H-8, -10), 1.32 (1H, m, H-2), 1.31 (2H, m, H-3, 14), 0.91 (3H, d, *J* = 6.4 Hz, H-16); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.5 (C-5), 169.8 (OAc), 74.9 (C-13), 58.9 (C-1), 57.0 (C-4), 55.9 (C-9), 46.8 (C-12), 45.7 (*N*-CH_3), 39.7 (C-6), 37.5 (C-7), 34.2 (C-14), 32.6 (C-11), 32.1 (C-8), 26.7 (C-2), 22.4 (C-10), 21.9 (C-3 and -16), 21.0 (−OAc), 20.7 (C-15); EI-MS (%) *m/z* 321 ($[M]^+$, 61.9), 292 (25.6), 278 (18.4), 262 (33.4), 249 (14.0), 232 (8.6), 219 (10.1), 206 (100), 189 (22.9), 178 (8.3); HR-FAB-MS (NBA/PEG) *m/z* 322.2358 (M + H, calcd for $C_{19}H_{32}NO_3$ 322.2382).

Oxime Formation of 8. To a stirred solution of **8** (21.2 mg, 0.0660 mmol) in dry EtOH (1.0 mL) were added NH_2OH·HCl (18.4 mg, 0.265 mmol), AcONa (35.1 mg, 0.428 mmol), and H_2O (55 μL) at room temperature under argon atmosphere. After refluxing for 11.5 h, the mixture was cooled, poured into chilled $NaHCO_3$ solution, and extracted with 5% MeOH/$CHCl_3$. The combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed over silica gel (0−8% MeOH/$CHCl_3$) to afford **9** (17.7 mg, 80%) as a colorless amorphous powder; $[\alpha]^{22}_D$ +0.8 (*c* 0.96, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3292 (hydroxyl group), 1727 (ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.99 (1H, br s), 3.19 (1H, br s), 2.47−2.65 (3H, m), 2.27−2.45 (3H, m), 2.27 (3H, s), 1.91 (3H, s), 1.20−2.00 (15H, m), 0.89 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.1, 74.7, 58.9, 55.6, 48.1, 47.3, 45.8, 39.0, 34.6, 32.2, 32.1, 30.7, 26.2, 24.3, 22.1, 22.0, 21.2, 20.7; EI-MS (%) *m/z* 336 ($[M]^+$, 10.5), 320 (97.6), 319 (100), 277 (14.6), 259 (26.3), 242 (16.6), 221 (20.6), 216 (18.3), 204 (21.7), 186 (27.4); HR-FAB-MS (NBA/PEG) *m/z* 337.2460 (M + H, calcd for $C_{19}H_{33}N_2O_3$ 337.2491).

Deacetylation of 9. Oxime derivative **9** (7.5 mg, 0.0223 mmol) was dissolved in 5% NaOH/MeOH solution (2.0 mL) and refluxed for 7 h under argon atmosphere. After cooling, the solution was poured into ice and extracted with 5% MeOH/$CHCl_3$. The combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed over amino silica gel (0−5% MeOH/$CHCl_3$) to give **10** (3.4 mg, 52%) as a colorless amorphous powder; $[\alpha]^{23}_D$ +24.0 (*c* 0.42, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3315 (hydroxyl group) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.92 (1H, br s), 3.27 (1H, br s), 2.65 (1H, ddd, *J* = 1.5, 12.1, 18.1 Hz), 2.59 (1H, m), 2.49 (1H, dd, *J* = 9.5, 18.1 Hz), 2.29 (3H, s), 2.20−2.45 (3H, m), 1.80−2.10 (4H, m), 1.20−1.75 (12H, m), 0.91 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 73.2, 58.9, 55.9, 47.9, 47.8, 46.1, 38.8, 38.0, 32.5, 32.3, 31.1, 26.3, 24.6, 22.6, 22.2, 20.0; EI-MS (%) *m/z* 294 ($[M]^+$, 16.0), 278 (100), 277 (99.3), 260 (66.7), 234 (27.8), 220 (58.8), 204 (54.3); HR-FAB-MS (NBA/PEG) *m/z* 295.2364 (M + H, calcd for $C_{17}H_{31}N_2O_2$ 295.2386).

Preparation of 12 and 13. 12 and **13** were obtained from **11** (25.1 mg, 0.0954 mmol) as a mixture, using the same procedure as that described above. The mixture was purified over SiO_2 gel (0−4% MeOH/$CHCl_3$) to afford **12** (9.1 mg, 34%) as colorless prisms and **13** (7.9 mg, 30%) as a colorless amorphous powder.

Spectroscopic data for **12**: mp 112−113°C (crystallized from *n*-hexane); $[\alpha]^{23}_D$ +191 (*c* 0.49, $CHCl_3$); IR (KBr) ν_{max} 1739, 1700 (ketone) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.89 (1H, d-like, J = 5.2 Hz), 1.20−2.60 (20H, overlap), 2.26 (3H, s, *N*-CH_3), 1.07 (3H, d, J = 6.4 Hz, H_3-16); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.2, 214.2, 60.6, 54.7, 50.2, 48.7, 46.6, 44.2, 42.5, 39.4, 31.1, 30.2, 28.0, 25.3, 22.5, 22.3, 21.6; FAB-MS (NBA) *m/z* 278 (M + H); HR-FAB-MS (NBA/PEG) *m/z* 278.2100 (M + H, calcd for $C_{17}H_{28}NO_2$ 278.2120).

Spectroscopic data for **13**: $[\alpha]^{22}_D$ +123 (*c* 0.43, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1736, 1699 (ketone) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25−2.55 (21H, overlap), 2.25 (3H, s, *N*-CH_3), 1.06 (3H, d, J = 6.0 Hz, H_3-16); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.2, 214.8, 60.5, 58.1, 57.1, 55.0, 46.9, 45.7, 42.1, 38.5, 31.5, 31.2, 30.6, 27.1, 23.3, 22.21, 22.17; FAB-MS (NBA) *m/z* 278 (M + H); HR-FAB-MS (NBA/PEG) *m/z* 278.2100 (M + H, calcd for $C_{17}H_{28}NO_2$ 278.2120).

Epimerization of 13 for Conversion into 12. To a stirred solution of **13** (11.4 mg, 0.0412 mmol) in dry ^{t}BuOH (0.8 mL) was added ^{t}BuOK (2.6 mg, 0.0231 mmol) at room temperature under argon atmosphere. After being stirred for 3 h at room temperature, the reaction mixture was poured into water and extracted with 5% MeOH/$CHCl_3$. The combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on SiO_2 gel (0−5% MeOH/$CHCl_3$) to afford **12** (3.4 mg, 30%) and recovered **13** (3.6 mg, 32%).

Preparation of 14. To a solution of **12** (1.5 mg, 0.00542 mmol) in dry EtOH (0.2 mL) were added an aqueous solution containing hydroxylamine hydrochloride (0.42 mg, 0.00607 mmol) and AcONa (0.82 mg, 0.00996 mmol) at room temperature under argon atmosphere. The reaction mixture was refluxed for 6 h and then cooled to room temperature. The reaction mixture was basified with chilled sat. $NaHCO_3$ solution and extracted with 5% MeOH/$CHCl_3$. The combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed over SiO_2 gel (0−20% MeOH/$CHCl_3$) to afford **14** (1.1 mg, 70%) as a colorless amorphous powder; CD (0.48 mM, MeOH, 25 °C) ($\Delta\epsilon$) 328 (0), 295 (+6.1), 243 (0), 210 nm (+10.0); IR ($CHCl_3$) ν_{max} 3339 (hydroxyl group), 1730 (ketone) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.29 (1H, ddd, J = 13.4, 4.1, 1.4 Hz, H-14), 2.84 (1H, br s, H-4), 2.64 (1H, dd, J = 13.0, 13.0 Hz, H-1), 2.40 (1H, m, H-7), 2.35 (2H, m, H_2-9), 2.28 (3H, s, *N*-CH_3), 2.20 (1H, dd, J = 8.9, 19.2 Hz, H-6), 2.05 (3H, m, H-1, -11, -11), 2.04 (1H, m, H-6), 1.98 (1H, m, H-3), 1.79 (1H, m, H-15), 1.75 (1H, m, H-2), 1.58 (1H, m, H-8), 1.42 (3H, m, H-2, -10, -14), 1.28 (2H, m, H-3, -10), 1.02 (3H, d, J = 6.4 Hz, H_3-16); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.5 (C-5), 161.2 (C-13), 55.1 (C-9), 52.7 (C-12), 51.6 (C-4), 48.3 (C-1), 44.3 (*N*-CH_3), 40.8 (C-7), 38.5 (C-6), 31.3 (C-8), 28.5 (C-14), 28.0 (C-2), 27.2 (C-15), 24.4 (C-11), 22.4 (C-3), 22.3 (C-16), 21.4 (C-10); FAB-MS (NBA) *m/z* 293 (M + H); HR-FAB-MS (NBA/PEG) *m/z* 293.2203 (M + H, calcd for $C_{17}H_{29}N_2O_2$ 293.2229).

Preparation of Lycoposerramine-B (1) from 12. To a solution of **12** (7.6 mg, 0.0274 mmol) in dry EtOH (0.5 mL) was added diethylamine (13.0 μL, 0.126 mmol) at room temperature under argon atmosphere. After the mixture was stirred for 3 h at room temperature, a solution of hydroxylamine hydrochloride (2.1 mg, 0.0302 mmol) in EtOH (84 μL) was added to the reaction mixture, and then it was stirred for 15 h at room temperature. The reaction mixture was basified with chilled sat. $NaHCO_3$ solution and extracted with 5% MeOH/$CHCl_3$. The combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed over SiO_2 gel (0−20% MeOH/$CHCl_3$) to afford crude **1** and pure **17** (1.5 mg, 19%). Crude **1** (12−18% MeOH/$CHCl_3$ eluate) was rechromatographed over amino silica gel (0−50% AcOEt/*n*-hex) to afford **1** (3.7 mg, 46%) as a colorless amorphous powder. The spectroscopic data (IR, CD, NMR, and MS) for **1** were completely identical with those of natural lycoposerramine-B.

Spectroscopic data for **17**: colorless solid; CD (0.27 mM, MeOH, 25 °C) ($\Delta\epsilon$) 336 (0), 298 (+16.2), 243 (+0.9), 206 nm (+18.9); IR ($CHCl_3$) ν_{max} 3292 (hydroxyl group), 1699 (ketone) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.59 (1H, br s, H-4), 2.71 (1H, br, H-1), 2.40 (1H, m, H-6), 2.39 (1H, m, H-7), 2.30 (2H, m, H_2-9), 2.28 (1H, m, H-14), 2.28 (3H, br s, *N*-CH_3), 2.24 (1H, m, H-11), 2.22 (1H, m, H-14), 2.12 (1H, m, H-6), 2.10 (1H, m, H-15), 2.00 (2H, m, H-1, -11), 1.92 (1H, m, H-3), 1.74 (2H, m, H_2-8), 1.67 (1H, br, H-2), 1.62 (1H, br, H-2), 1.37 (1H, br, H-10), 1.25 (1H, m, H-3), 1.17 (1H, m, H-10), 1.04 (3H, d, J = 6.3 Hz, H-16); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.0 (C-13), 169.0 (C-5), 61.8 (C-12), 55.0 (C-9), 48.3 (C-1), 46.6 (C-14), 44.2 (*N*-CH_3), 43.2 (C-7), 39.6 (C-4), 31.3 (C-6), 31.2 (C-8), 30.0 (C-15), 27.9 (C-2), 24.8 (C-11), 24.0 (C-3), 22.4 (C-16), 21.2 (C-10); FAB-MS (NBA) *m/z* 293 (M + H); HR-FAB-MS (NBA/PEG) *m/z* 315.2039 (M + Na, calcd for $C_{17}H_{28}N_2O_2Na$ 315.2048).

Supporting Information Available: General experimental procedure, NMR spectra (^1H NMR, ^{13}C NMR, $^1H-^1H$ COSY, HMQC, HMBC and *J*-resolved HMBC) of **1**, NMR spectra (^1H and ^{13}C) of **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, **13**, **14**, and **17**, X-ray crystallographic data of **8** and **12**, and comparison of NMR spectra of natural and synthetic **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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