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Asymmetric Total Syntheses of Cyclic Nitrone-Containing Phlegmarine-Type *Lycopodium* Alkaloids, Lycoposerramines-X and -Z

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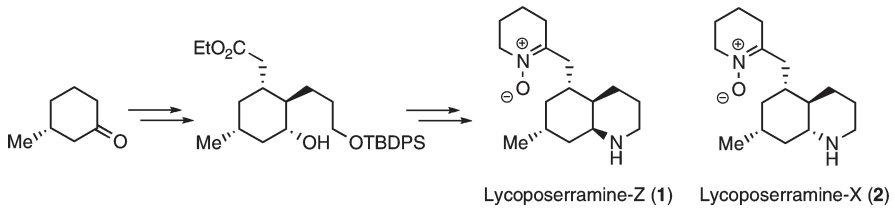

The total syntheses of cyclic nitrone-containing phlegmarine-type *Lycopodium* alkaloids, lycoposerramines-X and -Z, were accomplished starting from (*R*)-3-methylcyclohexanone via Pd-catalyzed Suzuki−Miyaura coupling, Johnson−Claisen rearrangement, stereoselective hydroboration−oxidation reaction, and Mitsunobu reaction, thereby establishing the structures including the absolute configuration.

Introduction

Lycopodium alkaloids have highly diverse, complex structures and a variety of biological activities.[1] This has inspired many groups including ours[2] to investigate the alkaloidal constituents in *Lycopodium* plants and to synthesize structurally unique *Lycopodium* alkaloids.[3,4] We have reported recently the isolation and structure elucidation of new alkaloids, lycoposerramines-Z (**1**) and -X (**2**) (Figure 1), from *Lycopodium serratum*.[2f] From spectroscopic analyses, we found that they were diastereomers of phlegmarine-type alkaloids[5] at the C13 position, but could not establish their absolute configuration. **1** and **2** consist of a piperidine ring with a novel nitrone residue and an decahydroquinoline ring with four chiral centers. Some *Lycopodium* alkaloids having the nitrone residue were also isolated from other *Lycopodium* and *Huperzia* plants in recent years.[6] However, as far as we know, synthetic studies on these types of alkaloids have never been reported. In this paper, we describe the first asymmetric total syntheses of **1** and **2** which assign the absolute stereochemistry as shown and confirm the structure assignment.

The retrosynthesis of lycoposerramine-Z (**1**) is outlined in Scheme 1. The formation of a characteristic piperidine ring with a nitrone residue in **1** was expected by reacting hydroxylamine with keto-mesylate **7**, which would be derived from

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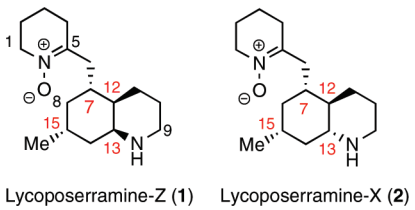
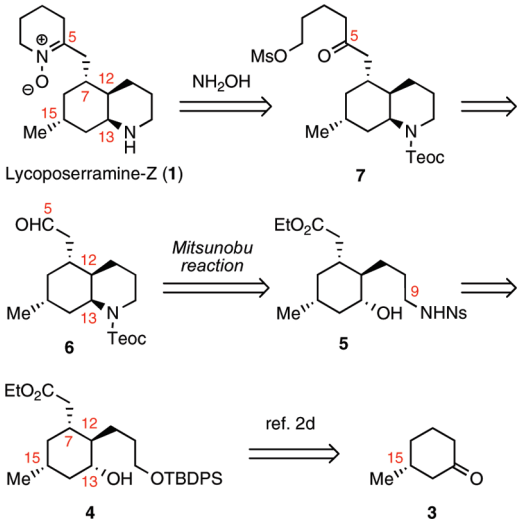


FIGURE 1. Structures of lycoposerramines-Z (**1**) and -X (**2**).

SCHEME 1. Retrosynthesis of lycoposerramine-Z (1)

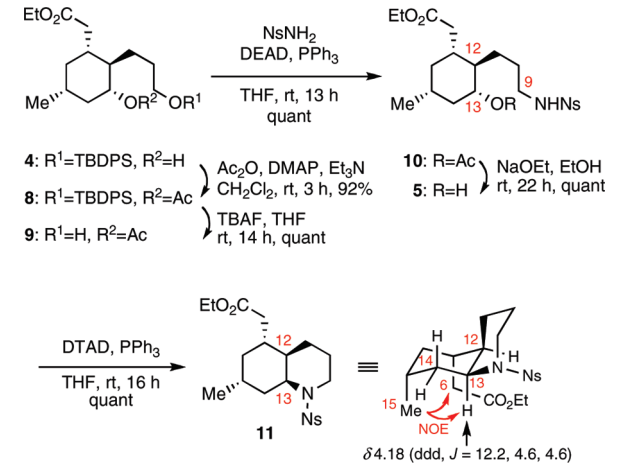


aldehyde **6** via installation of a C4 unit at C5. The stereoselective construction of the *cis*-decahydroquinoline skeleton in **6** would be achieved via the intramolecular Mitsunobu reaction[7] of sulfonamide **5**, which could be formed from cyclohexanol derivative **4**. Compound **4** was also expected to be a common intermediate for the divergent synthesis of lycoposerramine-X (**2**), which has a *trans*-decahydroquinoline skeleton, by manipulating the hydroxy group at C13. Compound **4**[2d] can be constructed from (*R*)-3-methylcyclohexanone (**3**) with the procedure previously developed by us, which included Pd-catalyzed Suzuki−Miyaura coupling,[8] Johnson−Claisen rearrangement,[9] and stereoselective hydroboration−oxidation reaction.[10] The chiral ketone **3** has the same absolute configuration as that at C15 in **1** and **2**, which was deduced to be *R* based on biogenetic consideration of common *Lycopodium* alkaloids.

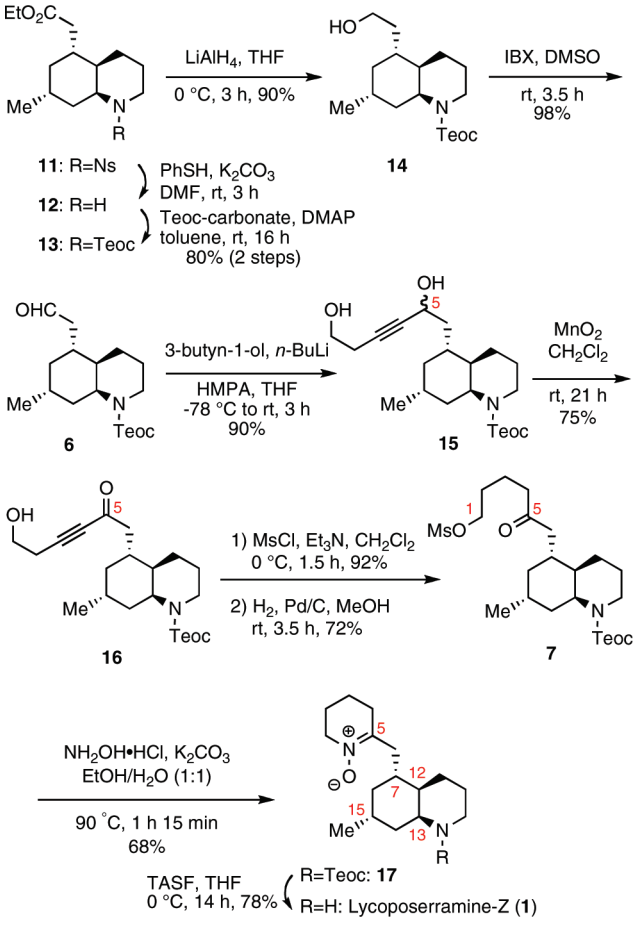
Results and Discussion

Synthesis of Lycoposerramine-Z. *cis*-Decahydroquinoline **11** was obtained from common synthetic intermediate **4** via a five-step sequence. Acetylation of the secondary alcohol and deprotection of the silyl group of the primary alcohol in **4** gave alcohol **9** in good yield. Replacement of the hydroxy group at C9 in **9** with 2-nitrobenzenesulfonamide under Mitsunobu conditions (diethyl azodicarboxylate (DEAD), PPh_3, THF, quant), followed by removal of the acetyl group of the secondary hydroxy group at C13 (NaOEt, EtOH, quant), afforded sulfonamide **5**. Compound **5** was subjected to intramolecular Mitsunobu reaction with di-*tert*-butyl azodicarboxylate (DTAD) and PPh_3 in THF to give *cis*-decahydroquinoline **11** in quantitative yield. The stereochemistry

SCHEME 2



SCHEME 3



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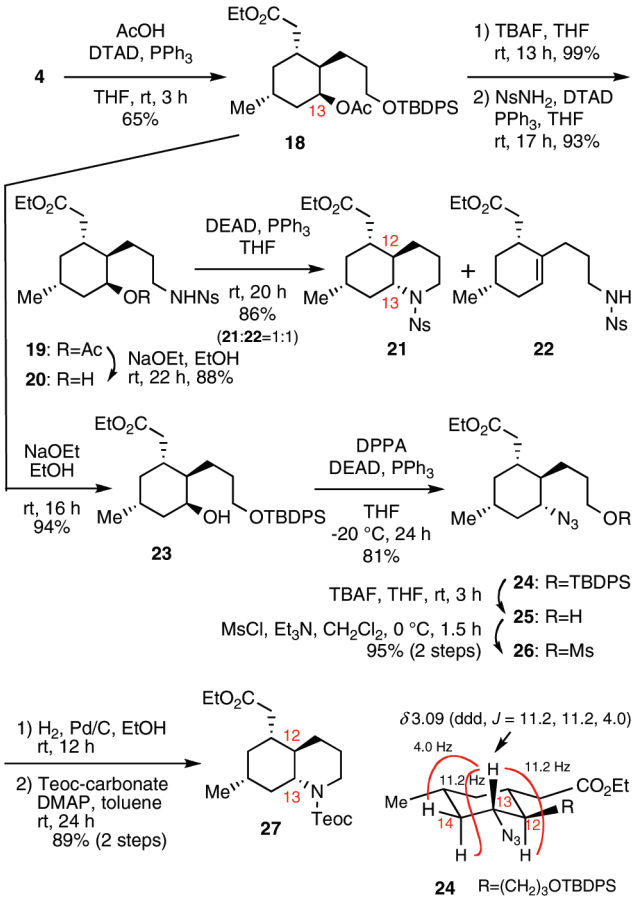
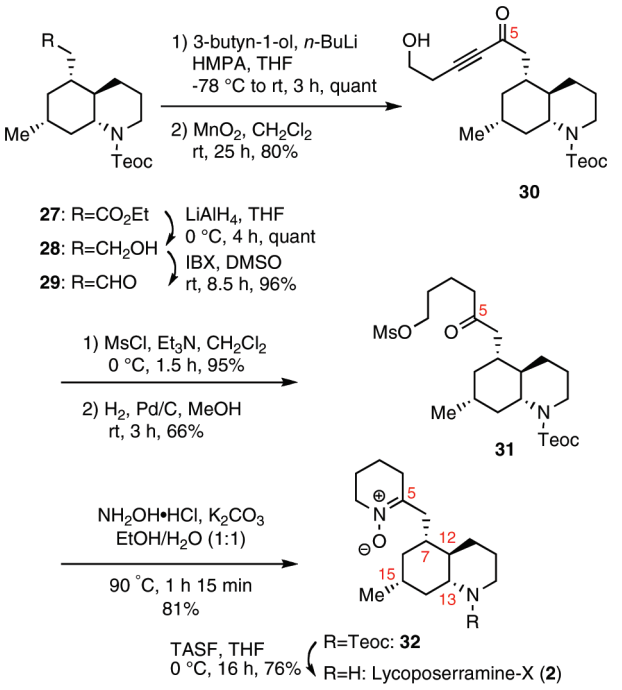
SCHEME 4



SCHEME 5



of product **11** was confirmed from the coupling constants of H13 (ddd, $J = 12.2, 4.6, 4.6$ Hz) and by NOE experiments, as depicted in Scheme 2.

Next, aldehyde **6** was prepared from *cis*-decahydroquinoline **11** via a four-step sequence, as follows (Scheme 3). Switching of the protecting group on the amine function from Ns to Teoc [(i) PhSH, K_2CO_3, DMF; (ii) 2-trimethylsilylethyl 4-nitrophenyl carbonate (Teoc-carbonate), 4-(*N*,*N*-dimethylamino)pyridine (DMAP), toluene] provided **13** in 80% overall yield. Then, reduction of the ester group in **13** with $LiAlH_4$ in THF and subsequent oxidation with 2-iodoxybenzoic acid (IBX) in DMSO gave aldehyde **6** in good yield. The installation of a C4 unit at C5 was accomplished by treating **6** with an alkynyl anion that was prepared from 3-butyn-1-ol and *n*-BuLi in the presence of HMPA in THF, to afford diol **15** in 90% yield. Selective oxidation of the hydroxy group on the propargyl position with MnO_2 in CH_2Cl_2 gave α,β-unsaturated ketone **16** in 75% yield. Mesylation of the primary alcohol and subsequent catalytic reduction of the alkyne function yielded keto-mesylate **7**. Next, compound **7** was treated with $NH_2OH \cdot HCl$ in the presence of 0.5 equiv of K_2CO_3 in $EtOH/H_2O$[11] to give the expected cyclic nitrone **17** in 68% yield. Finally, removal of the Teoc group with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) in THF afforded **1** in 78% yield. Synthetic **1** ($[\alpha]^{18}_D$ +9.6 (*c* 0.34, MeOH)) with 7*R*, 12*R*, 13*S*, and 15*R* stereochemistry was completely identical in all respects (^{1}H and ^{13}C NMR, mass, CD) with natural lycoposerramine-Z. Therefore, the structure including the absolute configuration was established to be formula **1**.

Synthesis of Lycoposerramine-X. Next, we turned our attention to the synthesis of lycoposerramine-X (**2**), the key step of which was the introduction of a nitrogen function at C13α to construct the *trans*-decahydroquinoline skeleton. For this purpose, sulfonamide **20** was initially prepared from common intermediate **4** utilizing the Mitsunobu reaction two times, as follows (Scheme 4). The α-hydroxy group at C13 in **4** was converted into a β-acetoxy group by treatment with AcOH, DTAD, and PPh_3 in THF in 65% yield. After removal of the TBDPS group, the resulting primary alcohol was treated with $NsNH_2$ under Mitsunobu conditions (DTAD, PPh_3, THF, 93% yield). This was followed by alkaline hydrolysis of the acetyl group to give the desired sulfonamide **20**. Attempts to perform the intramolecular Mitsunobu reaction of **20** with DEAD (5 equiv) and PPh_3 in THF gave a 1:1 mixture of *trans*-decahydroquinoline **21** and E2 elimination product **22** in 86% yield. Use of DTAD instead of DEAD gave a similar result. Then, the route for the construction of the *trans*-decahydroquinoline skeleton was modified. Secondary alcohol **23**, which was formed by hydrolysis of the acetyl group in **18**, was treated with DPPA, DEAD, and PPh_3 in THF to give 13α-azido compound **24** in 81% yield. The stereochemistry of **24** was confirmed from the coupling constants of H13 (ddd, $J = 11.2, 11.2, 4.0$ Hz), as depicted in Scheme 4. The TBDPS group was changed to an Ms group in 95% yield (two steps). Reduction of the azide group in **26** (H_2, Pd/C, EtOH) led to the spontaneous cyclization, followed by protection of the resulting secondary amine by the Teoc group to give *trans*-decahydroquinoline **27** in 89% yield (two steps).

According to the method for the synthesis of **1** described above, *trans*-decahydroquinoline **27** was converted into **2** in eight steps, including the installation of a C4 unit at C5 and

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the formation of a cyclic nitrone residue (Scheme 5). Synthetic **2** ($[\alpha]^{21}_D$ +50.9 (*c* 0.20, MeOH)) with 7*R*, 12*R*, 13*R*, and 15*R* stereochemistry was completely identical in all respects (^{1}H and ^{13}C NMR, mass, CD) with natural lycoposerramine-X. Therefore, the structure including the absolute configuration was established to be formula **2**. Recently, Morita and co-workers reported the isolation of a nitrone-containing alkaloid named carinatumin C from *L. carinatum*.[6b] Comparison of NMR data and the optical properties of synthetic **2** with those of carinatumin C ($[\alpha]^{25}_D$ +35 (*c* 0.30, MeOH)) demonstrated that the two natural products are identical.

Conclusion

We have achieved the first asymmetric total syntheses of lycoposerramines-Z (**1**) and -X (**2**) using common intermediate **4**, which enabled us to determine unambiguously the structures including the absolute configurations of the two new phlegmarine-type alkaloids possessing a cyclic nitrone residue.

Experimental Section

Preparation of Sulfonamide 10. To a stirred solution of **9** (593 mg, 1.97 mmol) in dry THF (40.0 mL) were added PPh_3 (1.00 g, 3.95 mmol), $NsNH_2$ (800 mg, 3.95 mmol), and DEAD (1.73 mL, 3.95 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 13 h at room temperature. After removal of the solvent under reduced pressure, the residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1:1 and then MeOH/$CHCl_3$ = 1:50) to afford **10** (1.03 g, quant) as a colorless oil: $[\alpha]^{15}_D$ −10.4 (*c* 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.12−8.10 (1H, m, Ph-*H*), 7.86−7.84 (1H, m, Ph-*H*), 7.76−7.72 (2H, overlapped, Ph-*H*), 5.38 (1H, br t, *J* = 5.7 Hz, NH), 4.65 (1H, ddd, *J* = 10.9, 10.9, 4.4 Hz, H-13), 4.14 (2H, q, *J* = 7.1 Hz, $-OCH_2CH_3$), 3.07−3.03 (2H, m, H_2-9), 2.44 (1H, dd, *J* = 15.0, 3.5 Hz, H-6), 2.09−2.01 (2H, overlapped), 2.06 (3H, s, $-OCOCH_3$), 1.95 (1H, br d, *J* = 12.2 Hz), 1.77−1.67 (2H, overlapped), 1.51−1.24 (3H, overlapped), 1.27 (3H, t, *J* = 7.1 Hz, $-OCH_2CH_3$), 0.98 (1H, q, *J* = 11.8 Hz, H-14), 0.89 (3H, d, *J* = 6.3 Hz, H_3-16), 0.75 (1H, q, *J* = 12.0 Hz, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 172.8 ($-CO_2Et$), 170.9 ($-OCOCH_3$), 148.0 (Ph), 133.54 (Ph), 133.45 (Ph), 132.6 (Ph), 130.9 (Ph), 125.2 (Ph), 73.7 (C-13), 60.4 ($-OCH_2CH_3$), 44.5 (C-7), 44.0 (C-9), 40.4 (C-6), 40.1 (C-14), 38.4 (C-8), 35.1 (C-12), 29.7 (C-15), 24.1 (C-11), 24.0 (C-10), 21.7 (C-16), 21.2 ($-OCOCH_3$), 14.2 ($-OCH_2CH_3$); FAB-MS (NBA) *m*/*z* 485 $[M + H]^+$; HRFAB-MS (NBA/PEG) calcd for $C_{22}H_{32}N_2O_8SNa$ $[M + Na]^+$ 507.1777, found 507.1779; IR ν_{max} (ATR) (cm^{-1}) 3307 (NH), 2950, 2918, 2867, 1722 (C=O), 1540 (NO_2).

Preparation of *cis*-Octahydroquinoline 11. To a stirred solution of **5** (120.5 mg, 0.272 mmol) in dry THF (5.4 mL) were added PPh_3 (357 mg, 1.36 mmol) and DTAD (313 mg, 1.36 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 16 h at room temperature. After removal of the solvent under reduced pressure, the residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1:1 and then MeOH/$CHCl_3$ = 1:50) to afford **11** (120.8 mg, quant) as a colorless oil: $[\alpha]^{16}_D$ +38.2 (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.08−8.05 (1H, m, Ph-*H*), 7.70−7.61 (3H, m, Ph-*H*), 4.18 (1H, ddd, *J* = 12.2, 4.6, 4.6 Hz, H-13), 4.12 (2H, q, *J* = 7.1 Hz, $-OCH_2CH_3$), 3.59 (1H, br d, *J* = 11.0 Hz, H-9), 3.11 (1H, ddd, *J* = 12.7, 12.7, 2.7 Hz, H-9), 2.51 (1H, dd, *J* = 15.6, 7.8 Hz, H-6), 2.37 (1H, dd, *J* = 15.6, 7.1 Hz, H-6), 2.11 (1H, ddd, *J* = 12.9, 12.9, 6.9 Hz, H-14), 1.97−1.90 (2H, overlapped), 1.68−1.57 (5H, overlapped), 1.47−1.43 (1H, m, H-10), 1.25 (3H, t, *J* = 7.1 Hz, $-OCH_2CH_3$), 1.19 (1H, ddd, *J* = 13.2, 4.7, 4.7 Hz, H-14), 1.11 (1H, ddd, *J* = 13.7, 6.9, 6.9 Hz, H-8), 1.01 (3H, d, *J* = 7.1 Hz, H_3-16); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 172.9 ($-CO_2Et$), 147.8 (Ph), 134.1 (Ph), 133.2 (Ph), 131.6 (Ph), 130.7 (Ph), 124.2 (Ph), 60.3 ($-OCH_2CH_3$), 49.7 (C-13), 41.2 (C-9), 40.7 (C-6), 39.1 (C-12), 36.7 (C-7), 32.2 (C-8), 29.4 (C-14), 27.4 (C-15), 25.9 (C-11), 25.1 (C-10), 21.9 (C-16), 14.2 ($-OCH_2CH_3$); EI-MS *m*/*z* (%) 424 (2, M^+), 407 (25), 367 (32), 337 (38), 325 (41), 238 (67), 237 (61), 186 (51), 150 (100); HREI-MS calcd for $C_{20}H_{28}N_2O_6S$ (M^+) 424.1668, found 424.1678; IR ν_{max} (ATR) (cm^{-1}) 2928, 2875, 1726 (C=O), 1542 (NO_2).

Preparation of Diol 15. To a stirred solution of 3-butyn-1-ol (140 μL, 1.85 mmol) and HMPA (0.26 mL, 1.48 mmol) in dry THF (7.5 mL) was added dropwise *n*-BuLi (1.59 mmol/L in *n*-hexane, 2.46 mL, 3.88 mmol) at −78 °C under argon atmosphere. The mixture was stirred for 1 h at −78 °C, and then a solution of **6** (156.7 mg, 0.462 mmol) in dry THF (15.0 mL) was added at −78 °C. After being stirred for 1.5 h at −78 °C and for 1.5 h at room temperature, the reaction mixture was quenched with sat. aq. NH_4Cl and the whole was extracted three times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 3:1) to afford **15** (169.7 mg, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.43−4.34 (4H, overlapped, H-5, H-13), 4.22−4.11 (4H, overlapped), 3.98−3.94 (2H, overlapped, H-9), 3.73−3.70 (4H, overlapped, H_2-1), 2.84−2.78 (6H, overlapped), 2.48−2.45 (4H, overlapped, H_2-2), 2.02−1.51 (18H, overlapped), 1.45−1.41 (2H, overlapped), 1.17−0.92 (14H, overlapped), 0.04 (18H, s, $-CO_2CH_2CH_2Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 155.9, 83.4, 83.2, 82.2, 82.0, 63.3, 61.2, 61.0, 46.54, 46.49, 44.7, 39.2, 39.0, 38.9, 36.6, 33.0, 32.5, 29.02, 28.99, 27.53, 27.46, 26.2, 25.3, 23.0, 22.04, 21.97, 17.7, −1.5; EI-MS *m*/*z* (%) 409 (1, M^+), 308 (8), 101 (17), 73 (100); HREI-MS calcd for $C_{22}H_{39}NO_4Si$ (M^+) 409.2648, found 409.2648; IR ν_{max} (ATR) (cm^{-1}) 3361 (OH), 2952, 2925, 2875, 1663 (C=O).

Preparation of α,β-Unsaturated Ketone 16. To a stirred solution of **15** (165.2 mg, 0.404 mmol) in dry CH_2Cl_2 (25.0 mL) was added MnO_2 (826 mg, 9.50 mmol) at 0 °C under argon atmosphere. After being stirred for 21 h at room temperature, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 2:1) to afford **16** (123.8 mg, 75%) as a colorless oil: $[\alpha]^{19}_D$ +1.3 (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.37 (1H, br ddd, *J* = 11.2, 4.6, 4.6 Hz, H-13), 4.20−4.11 (2H, overlapped), 3.96 (1H, br dd, *J* = 13.4, 2.7 Hz, H-9), 3.81 (2H, q, *J* = 6.1 Hz, H_2-1), 2.82 (1H, ddd, *J* = 10.0, 10.0, 3.2 Hz, H-9), 2.80 (1H, dd, *J* = 16.8, 7.8 Hz, H-6), 2.65 (2H, t, *J* = 6.3 Hz, H_2-2), 2.59 (1H, dd, *J* = 16.3, 6.6 Hz, H-6), 2.16 (1H, t, *J* = 6.1 Hz, −OH), 2.10−2.06 (1H, m), 2.05−1.95 (2H, overlapped), 1.72−1.49 (5H, overlapped), 1.42−1.36 (1H, m), 1.17 (1H, dd, *J* = 9.8, 4.6 Hz, H-12), 1.10 (1H, q, *J* = 6.6 Hz), 1.06 (3H, d, *J* = 6.8 Hz, H_3-16), 1.00 (2H, dd, *J* = 9.0, 7.6 Hz, $-CO_2CH_2CH_2Si(CH_3)_3$), 0.04 (9H, s, $-CO_2CH_2CH_2Si(CH_3)_3$; ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 187.4 (C-5), 155.9 ($-CO_2CH_2CH_2Si(CH_3)_3$), 90.7 (C-3), 82.3 (C-4), 63.3 ($-CO_2CH_2CH_2Si(CH_3)_3$), 60.2 (C-1), 52.0 (C-6), 46.3 (C-13), 39.0 (C-12), 38.9 (C-9), 35.7 (C-7), 32.5 (C-8), 28.8 (C-14), 27.4 (C-15), 26.0 (C-11), 25.2 (C-10), 23.3 (C-2), 21.9 (C-16), 17.7 ($-CO_2CH_2CH_2Si(CH_3)_3$), −1.5 ($-CO_2CH_2CH_2Si(CH_3)_3$); EI-MS *m*/*z* (%) 407 (1, M^+), 224 (6), 101 (15), 73 (100); HREI-MS calcd for $C_{22}H_{37}NO_4Si$ (M^+) 407.2492, found 407.2487; IR ν_{max} (ATR) (cm^{-1}) 3430 (OH), 2949, 2867, 2212 (C≡C), 1664 (C=O).

Preparation of Cyclic Nitrone 17. To a stirred solution of **7** (29.8 mg, 0.073 mmol) in EtOH/H_2O (1:1, 1.2 mL) were added

K_2CO_3 (4.0 mg, 0.037 mmol) and $NH_2OH \cdot HCl$ (6.4 mg, 0.110 mmol) at room temperature under argon atmosphere. After being stirred for 1 h and 15 min at 90 °C, the reaction mixture was quenched with sat. aq. $NaHCO_3/H_2O$ (1:1) and the whole was extracted three times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by silica gel flash column chromatography (MeOH/$CHCl_3$ = 1:10) to afford **17** (16.5 mg, 68%) as a colorless oil: $[\alpha]^{19}_D$ −17.2 (*c* 0.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.34 (1H, br ddd, *J* = 11.7, 4.9, 4.9 Hz, H-13), 4.22−4.11 (2H, overlapped), 3.97 (1H, br d, *J* = 13.4 Hz, H-9), 3.80 (2H, br t, *J* = 5.9 Hz, H_2-1), 2.81 (1H, ddd, *J* = 12.4, 12.4, 2.7 Hz, H-9), 2.67 (1H, dd, *J* = 13.2, 6.3 Hz, H-6), 2.46−2.41 (3H, overlapped), 2.09−1.83 (5H, overlapped), 1.78−1.71 (2H, overlapped), 1.68−1.59 (2H, overlapped), 1.55−1.39 (4H, overlapped), 1.14−1.06 (2H, overlapped), 1.03 (3H, d, *J* = 7.1 Hz, H_3-16), 1.00 (2H, t, *J* = 8.5 Hz, $-CO_2CH_2CH_2Si(CH_3)_3$), 0.04 (9H, s, $-CO_2CH_2CH_2Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 155.9 ($-CO_2CH_2CH_2Si(CH_3)_3$), 148.0 (C-5), 63.2 ($-CO_2CH_2CH_2Si(CH_3)_3$), 58.3 (C-1), 47.3 (C-13), 39.5, 39.1, 38.3, 36.2, 34.0 (C-7), 30.8 (C-8), 29.5 (C-14), 27.2, 26.4 (C-11), 24.8, 23.1, 22.5 (C-16), 18.9 (C-2), 17.7 ($-CO_2CH_2CH_2Si(CH_3)_3$), −1.5 ($-CO_2CH_2CH_2Si(CH_3)_3$); EI-MS *m*/*z* (%) 408 (2, M^+), 268 (28), 97 (54), 84 (85), 73 (100); HRFAB-MS calcd for $C_{22}H_{41}N_2O_3Si$ $[M + H]^+$ 409.2886, found 409.2871; IR ν_{max} (ATR) (cm^{-1}) 3362, 2948, 1684 (C=O), 1611 (N=C).

Preparation of Lycoposerramine-Z (1). To a stirred solution of **17** (17.1 mg, 0.042 mmol) in dry THF (0.4 mL) was added dropwise TASF (2.0 M in DMF, 0.21 mL, 0.420 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 14 h at 0 °C and then quenched with MeOH. After removal of the solvent under reduced pressure, the residue was purified by silica gel flash column chromatography (MeOH/$CHCl_3$/concd NH_4OH = 1:2:0.1) and amino-silica gel open column chromatography (CH_3CN/H_2O = 15:1) to afford synthetic **1** (8.4 mg, 78%) as a colorless amorphous solid: $[\alpha]^{18}_D$ +9.6 (*c* 0.34, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 3.82 (2H, br t, *J* = 5.8 Hz, H_2-1), 3.12 (1H, br d, *J* = 11.9 Hz, H-9), 2.91 (1H, br s, H-13), 2.72−2.67 (2H, overlapped, H-6, H-9), 2.53−2.39 (3H, overlapped, H_2-4, H-7), 2.34 (1H, dd, *J* = 13.1, 10.7 Hz, H-6), 2.03 (1H, br d, *J* = 13.4 Hz, H-11), 1.97−1.92 (2H, overlapped, H_2-2), 1.79−1.71 (3H, overlapped, H_2-3, H-15), 1.68−1.60 (2H, overlapped, H-10, H-14), 1.55 (1H, br d, *J* = 12.8 Hz, H-8), 1.44 (1H, dddd, *J* = 13.7, 13.7, 4.3, 4.3 Hz, H-11), 1.36−1.25 (2H, overlapped, H-10, H-12), 1.19 (1H, ddd, *J* = 13.4, 13.4, 3.7 Hz, H-14), 0.83 (3H, d, *J* = 6.7 Hz, H_3-16), 0.79 (1H, q, *J* = 12.2 Hz, H-8); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 148.7 (C-5), 58.3 (C-1), 56.6 (C-13), 47.9 (C-9), 41.6 (C-14), 41.4 (C-8), 40.9 (C-12), 35.8 (C-6), 29.84 (C-4), 29.81 (C-7), 26.9 (C-11), 26.7 (C-15), 23.3 (C-3), 22.7 (C-16), 21.2 (C-10), 18.9 (C-3); FAB-MS (NBA) *m*/*z* 265 $[M + H]^+$; HRFAB-MS (NBA/PEG) calcd for $C_{16}H_{29}N_2O$ $[M + H]^+$ 265.2280, found 265.2295; IR ν_{max} (ATR) (cm^{-1}) 3275 (NH), 2940, 2914, 1604 (N=C); CD (MeOH, 24 °C, *c* 0.496 mmol/L), λ (nm) ($\Delta\varepsilon$) 277 (0), 255 (−1.2), 245 (0), 229 (+2.7), 208 (0).

Preparation of 13β-Acetate 18. To a stirred solution of **4** (140 mg, 0.282 mmol) and PPh_3 (222 mg, 0.846 mmol) in dry THF (1.9 mL) were added DTAD (195 mg, 0.846 mmol) and dry AcOH (48 μL, 0.846 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 3 h at room temperature. After removal of the solvent under reduced pressure, the residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1:9) to afford **18** (98.1 mg, 65%) as a pale yellow oil along with the starting material **4** (37.2 mg, 27%). **18**: $[\alpha]^{23}_D$ +42.0 (*c* 1.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.66−7.63 (4H, overlapped, Ph-H), 7.42−7.36 (6H, overlapped, Ph-*H*), 5.10 (1H, br-q, *J* = 2.7 Hz, H-13), 4.12 (2H, q-like, *J* = 7.1 Hz, $-OCH_2CH_3$), 3.61 (2H, t, *J* = 6.1 Hz, H_2-9), 2.52 (1H, dd, *J* = 13.7, 2.7 Hz, H-6), 2.05 (3H, s, $-OCOCH_3$), 2.03−1.91 (3H, overlapped), 1.75−1.49 (4H, overlapped), 1.44−1.33 (1H, m), 1.26 (3H, t, *J* = 7.1 Hz, $-OCH_2CH_3$), 1.22−1.15 (2H, overlapped), 1.03 (9H, s, -^{t}Bu), 1.05−0.97 (1H, m), 0.85 (3H, d, *J* = 6.3 Hz, H_3-16), 0.75 (1H, q, *J* = 12.9 Hz, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 173.3 ($-CO_2Et$), 170.6 ($-OCOCH_3$), 135.6 (Ph), 134.0 (Ph), 129.5 (Ph), 127.6 (Ph), 70.9 (C-13), 63.9 (C-9), 60.2 ($-OCH_2CH_3$), 43.7 (C-7), 41.0 (C-6), 39.0 (C-14), 38.6 (C-8), 34.4 (C-12), 29.8 (C-11), 26.9 ($-C(CH_3)$), 26.2 (C-15), 24.9 (C-10), 22.0 (C-16), 21.2 ($-OCOCH_3$), 19.2 (-$C(CH_3)$), 14.3 ($-OCH_2CH_3$); FAB-MS (NBA) *m*/*z*: 539 $[M+H]^+$; HRFAB-MS (NBA/PEG): calcd for $C_{32}H_{47}O_5Si$ $[M + H]^+$: 539.3193, found: 539.3201; IR ν_{max} (ATR) cm^{-1}: 2930, 2858, 1732 (C=O).

Preparation of 13α-Azido Compound 24. To a stirred solution of **23** (138.2 mg, 0.279 mmol) in dry THF (1.9 mL) were added PPh_3 (351 mg, 1.40 mmol), DPPA (0.29 mL, 1.40 mmol), and DEAD (40 wt % in toluene, 0.58 mL, 1.40 mmol) at −20 °C under argon atmosphere. The reaction mixture was stirred for 24 h at −20 °C. After removal of the solvent under reduced pressure, the residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1:15) to afford **24** (117.3 mg, 81%) as a colorless oil: $[\alpha]^{24}_D$ −19.5 (*c* 1.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.68−7.66 (4H, overlapped, Ph-*H*), 7.44−7.36 (6H, overlapped, Ph-*H*), 4.12 (2H, q, *J* = 7.1, $-OCH_2CH_3$), 3.69−3.60 (2H, overlapped, H_2-9), 3.09 (1H, ddd, *J* = 11.2, 11.2, 4.0 Hz, H-13), 2.57 (1H, dd, *J* = 15.2, 3.3 Hz, H-6), 2.08−1.98 (2H, overlapped), 1.80−1.67 (3H, overlapped), 1.61−1.43 (4H, overlapped), 1.25 (3H, t, *J* = 7.1 Hz, $-OCH_2CH_3$), 1.14−1.05 (2H, overlapped), 1.05 (9H, s, −^{t}Bu), 0.94 (3H, d, *J* = 6.4 Hz, H_3-16), 0.75 (1H, q, *J* = 12.1 Hz, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 172.8 ($-CO_2Et$), 135.5 (Ph), 133.9 (Ph), 129.5 (Ph), 127.6 (Ph), 64.0 (C-9), 62.7 (C-13), 60.2 ($-OCH_2CH_3$), 45.0 (C-7), 40.3 (C-6), 39.9 (C-14), 38.3 (C-8), 35.8 (C-12), 30.4 (C-15), 27.4 (C-11), 26.8 ($-C(CH_3)_3$), 24.1 (C-10), 21.9 (C-16), 19.1 ($-C(CH_3)$), 14.2 ($-OCH_2CH_3$); FAB-MS (NBA) *m*/*z* 522 $[M + H]^+$; HRFAB-MS (NBA/PEG) calcd for $C_{30}H_{44}N_3O_3Si$ $[M + H]^+$ 522.3152, found 522.3137; IR ν_{max} (ATR) (cm^{-1}) 2926, 2855, 2091 (N_3), 1732 (C=O).

Preparation of *trans*-Octahydroquinoine 27. To a stirred solution of **26** (280.5 mg, 0.777 mmol) in dry EtOH (10.0 mL) was added Pd/C (10%, 56.7 mg) at room temperature under H_2 atmosphere. After being stirred for 12 h at room temperature, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. To a stirred solution of the crude product (190.6 mg) in dry toluene (5.0 mL) were added DMAP (455 mg, 1.60 mmol) and Teoc-carbonate (197 mg, 1.60 mmol) at 0 °C under argon atmosphere. After being stirred for 24 h at room temperature, the reaction mixture was poured into H_2O and the whole was extracted three times with AcOEt. The combined organic layers were washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1:7) to afford **27** (264.2 mg, 89%) as a colorless oil: $[\alpha]^{18}_D$ −37.2 (*c* 1.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.15−4.07 (4H, overlapped, $-OCH_2CH_3$, $-CO_2CH_2CH_2Si(CH_3)_3$), 3.56 (1H, ddd, *J* = 13.9, 6.6, 3.9 Hz, H-9), 3.22−3.12 (2H, overlapped, H-9, H-13), 2.46 (1H, dd, *J* = 14.9, 4.6 Hz, H-6), 2.05−2.00 (1H, overlapped), 2.01 (1H, dd, *J* = 14.9, 8.3 Hz, H-6), 1.86−1.73 (2H, overlapped), 1.71−1.47 (4H, overlapped), 1.27−1.14 (2H, overlapped), 1.04−0.94 (3H, overlapped), 1.23 (3H, t, *J* = 7.1 Hz, $-OCH_2CH_3$), 0.88 (3H, d, *J* = 6.6 H, H_3-16), 0.77 (1H, q, *J* = 12.2 Hz, H-8), 0.01 (9H, s, $-CO_2CH_2CH_2Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 173.1 ($-CO_2Et$), 156.1 ($-CO_2CH_2CH_2Si(CH_3)_3$), 63.0 ($-CO_2CH_2CH_2Si(CH_3)_3$), 61.0 (C-13), 60.3 ($-OCH_2CH_3$), 42.1 (C-12), 41.2 (C-9), 39.5 (C-6), 39.3 (C-8), 38.7 (C-7), 38.6

(C-14), 31.0 (C-15), 23.9 (C-11), 23.1 (C-10), 22.1 (C-16), 17.8 ($-CO_2CH_2CH_2Si(CH_3)_3$), 14.2 ($-OCH_2CH_3$), −1.5 ($-CO_2CH_2CH_2Si(CH_3)_3$); EI-MS *m*/*z* (%) 383 (11, M^+), 355 (11), 340 (25), 282 (33), 268 (35), 252 (93), 224 (52), 101 (51), 73 (100); HREI-MS calcd for $C_{20}H_{37}NO_4Si$ (M^+) 383.2492, found 383.2497; IR ν_{max} (ATR) (cm^{-1}) 2950, 2900, 1733 (C=O), 1689 (C=O).

Preparation of Lycoposerramine-X (2). To a stirred solution of **32** (14.0 mg, 0.034 mmol) in dry THF (0.3 mL) was added dropwise TASF (2.0 M in DMF, 0.17 mL, 0.340 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 16 h at 0 °C and then quenched with MeOH. After removal of the solvent under reduced pressure, the residue was purified by silica gel flash column chromatography ($MeOH/CHCl_3$/concd NH_4OH = 1:2:0.1) and amino-silica gel open column chromatography (CH_3CN/H_2O = 15:1) to afford synthetic **2** (6.9 mg, 76%) as a colorless amorphous solid: $[\alpha]^{21}_D$ +50.9 (*c* 0.20, MeOH); ^1H NMR (CD_3OD, 600 MHz) δ (ppm) 3.75 (2H, br t, *J* = 5.8 Hz, H_2-1), 3.02 (1H, br d, *J* = 11.8 Hz, H-9), 2.80 (1H, br dd, *J* = 12.9, 4.1 Hz, H-6), 2.62 (1H, br t, *J* = 12.6 Hz, H-9), 2.57−2.49 (2H, overlapped, H_2-4), 2.31−2.25 (1H, m, H-13), 2.25 (1H, dd, *J* = 13.2, 10.4 Hz, H-6), 2.04 (1H, br d, *J* = 12.9 Hz, H-11), 1.98−1.94 (2H, overlapped, H_2-3), 1.80−1.74 (5H, overlapped, H_2-3, H-7, H-10, H-14), 1.59−1.49 (3H, overlapped, H-8, H-10, H-15), 1.06 (1H, dddd, *J* = 12.4, 12.4, 12.4, 3.8 Hz, H-11), 0.96−0.88 (1H, m, H-12), 0.93 (1H, q, *J* = 12.4 Hz, H-14), 0.93 (3H, d, *J* = 6.6 Hz, H_3-16), 0.84 (1H, q, *J* = 12.4 Hz, H-8); ^{13}C NMR (CD_3OD, 150 MHz) δ (ppm) 157.0 (C-5), 61.6 (C-13), 58.9 (C-1), 47.9 (C-12), 47.2 (C-9), 42.4 (C-8), 41.9 (C-14), 39.2 (C-7), 36.5 (C-6), 32.0 (C-15), 31.4 (C-4), 29.3 (C-11), 27.1 (C-10), 23.9 (C-2), 22.7 (C-16), 19.3 (C-3); FAB-MS (NBA) *m*/*z* 265 $[M + H]^+$; HRESI-MS calcd for $C_{16}H_{29}N_2O$ $[M + H]^+$ 265.2274, found 265.2270; IR ν_{max} (ATR) (cm^{-1}) 3281 (−NH), 3231, 2924, 2849, 2789, 1619 (N=C); CD (MeOH, 24 °C, *c* 0.617 mmol/L), λ (nm) ($\Delta\varepsilon$) 283 (0), 254 (−1.17), 241 (0), 228 (+1.59).

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Supporting Information Available: Additional procedures and spectral data for all new compounds **5**−**9**, **12**−**14**, **23**, **25**, **26**, **28**−**32**, and **S1**−**S3**, and copies of NMR spectra of compounds **5**−**18**, **23**−**32**, **S1**−**S3**, and synthetic lycoposerramines-Z (**1**) and -X (**2**). This material is available free of charge via the Internet at http://pubs.acs.org.