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Enantioselective Total Synthesis of Lycoposerramine-Z Using Chiral Phosphoric Acid Catalyzed Intramolecular Michael Addition

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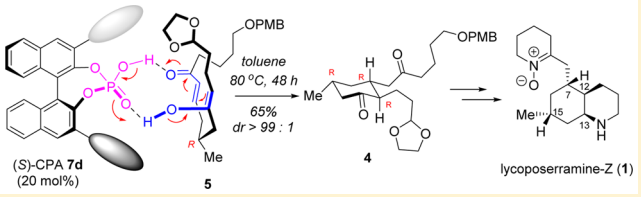
Supporting Information

ABSTRACT: A new enantioselective total synthesis of phlegmarine-type *Lycopodium* alkaloid lycoposerramine-Z (**1**) has been accomplished, using one-pot chemoselective sequential additions of two different Grignard reagents to the bis-Weinreb-amide intermediate and an efficient construction of the fully fuctionalized cyclohexanone intermediate with a chiral phosphoric acid catalyzed enantioselective intramolecular Michael addition.



INTRODUCTION

Typical *Lycopodium* alkloids are quinolizine- or pyridine- and α-pyridone-type alkaloids isolated from club mosses of the genus *Lycopodium* (Lycopodiaceae), featuring unique heterocyclic skeletons of $C_{11}N$, $C_{15}N_2$, $C_{16}N$, $C_{16}N_2$, $C_{22}N_2$, and $C_{27}N_3$.[1,2] Accompanying the discovery of these complex and elegant molecules, it was also revealed that many of them exhibited significant biological activities, especially the capacity to inhibit acetylcholinesterase (AChE). For instance, huperzine A was proven to be a potent natural *Lycopodium* alkaloid AChE inhibitor,[3] and there continues to be common interest in the development of new synthetic strategies for its preparation.[4,5]

As part of our natural-product synthesis program,[6] we recently examined several new approaches to the biologically interesting phlegmarine-type *Lycopodium* alkaloids (Figure 1). The first phlegmarine was discovered by Braekman and co-workers in 1978,[7] and this type of alkaloid commonly contains a variable $C_{16}N_2$ skeleton, in which a piperidine ring and a 5,7-disubstituted decahydroquinoline ring were connected through a methylene unit.[4d,8] They were also proposed as the biogenetic precursor of main classes of *Lycopodium* alkaloids, such as lycopodine, lycodine, and fawcettimine.[4c] Many phlegmarine-type alkaloids exhibit a wide range of biological activities, with particular potential for the treatment of neurogenerative diseases.[9] Lycoposerramine-Z (**1**)[10] is a representative alkaloid with a *cis*-fused decahydroquinoline core in this family, and it was first synthesized by the Takayama group[8f] and then was achieved by Bradshaw and co-workers.[8c] The unusual nitrone moiety[11] of lycoposerramine-Z was postulated to act as a radical trap halting destructive cascades initiated by free radicals and, hence, shows potential application in neurodegenerative diseases.[12] On the basis of our previous work in this family of alkaloids,[13] we wish to report a new enantioselective total synthesis of lycoposerramine-Z (**1**) applying a newly developed chiral phosphoric acid catalyzed intramolecular Michael addition.

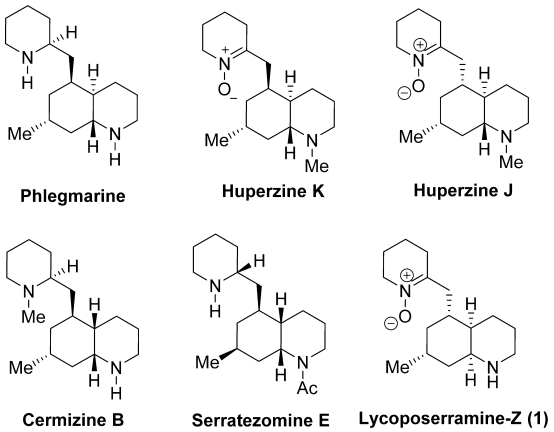


Figure 1. Representative phelgmarine-type *Lycopodium* alkaloids containing a *cis*- or *trans*-decahydroquinoline core.

RESULTS AND DISCUSSION

Our retrosynthesis of lycoposerramine-Z (**1**) is outlined in Figure 2. We envisaged that the characteristic piperidine ring with a nitrone residue in **1** would be constructed by a regio- and stereoselective reaction between hydroxylamine with keto-mesylate **2**,[8f] which could be derived from *cis*-decahydroquinoline **3**. Formation of the *cis*-decahydroquinoline **3** has been accomplished by a reductive amination of the keto-aldehyde **4** with the aid of a commercially available chiral amine. Synthesis of the multifunctionalized hexanone **4** was designed as the key reaction through an intramolecular Michael cyclization of the linear dione **5**. Enone **5** could be functionalized from a bis-Weinreb-amide **6** through two sequential Grignard additions,

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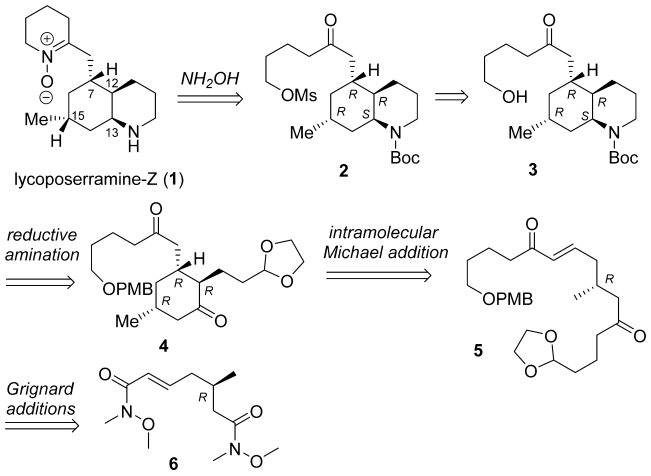
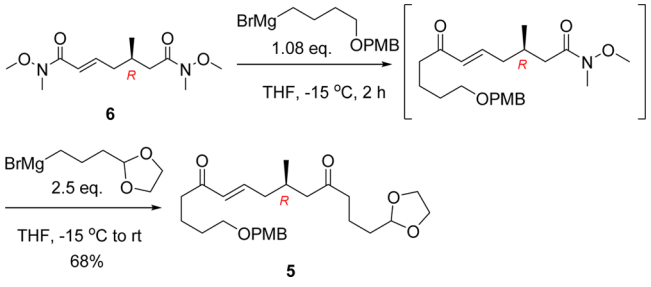


Figure 2. Retrosynthetic analysis of lycoposerramine-Z (**1**).

which were first developed in our previous work[13] and optimized in this study.

In order to achieve the desired enone precursor **5**, our previous work[13] applied a four-step procedure starting from the bis-Weinreb-amide **6**, including regioselective addition of the first Grignard reagent to the α,β-unsaturated amide of the bis-Weinreb-amide **6**, reduction of the enone with $NaBH_4$ and $CeCl_3$, addition of the second Grignard reagent to the remaining aliphatic amide, and final oxidation of the allylic alcohol with MnO_2. To improve step- and redox-economy for the preparation of enone **5**, we here considered a new protocol by successive additions of the two different Grignard reagents to the bis-Weinreb-amide **6** in one reaction vessel (Scheme 1).

Scheme 1. One-Pot Sequential Functionalization of the Bis-amide 6



After a number of experimental trials, we found that such a strategy worked perfectly. The first Grignard reagent was added slowly into the THF solution of bis-Weinreb-amide **6** at −15 °C. After completion of the first addition, excess of the second Grignard reagent was added, and then slowly warmed to room temperature for complete conversion. As a result, the linear enone precursor **5** was provided in a satisfactory isolated yield (68%). Such an improvement avoided the use of reduction/oxidation steps and thus reduced the previous four steps to one single operation. Furthermore, it displayed great flexibility and capability of altering the side chains of the enone precursor **5** by simply changing the two Grignard reagents, if needed.

In the following intramolecular Michael addition, the aliphatic ketone (its enol equivalent) and α,β-unsaturated enone of the precursor **5** would serve as the donor and acceptor, respectively. Initially, we found that treatment of enone **5** with 10 mol % of *t*-BuOK in *t*-BuOH at room temperature provided the expected multisubstituted cyclohexanone **4** as a major product (50% yield) together with another minor diastereomer (~15% yield). However, application of *p*-toluenesulfonic acid or (+)-CSA could not promote the expected intramolecular cyclization of enone **5** (Table 1, entries 2 and 3). Such unsatisfactory diastereoselectivities were also reported in some similar applications using either base- or acid-catalyzed conditions,[14] as well as a few enantioselective approaches.[5f,14a] Very recently, List and co-workers successfully applied chiral phosphoric acid to the Brønsted acid catalyzed intermolecular Michael reaction between ketones and enones.[15] Considering the acid/base dual catalysis nature of chiral phosphoric acids[16−18] and our previous experience of using chiral phosphoric acid in other reactions,[19] we decided to attempt chiral phosphoric acid as the catalyst in the above intramolecular Michael cyclization. To our delight, both the simplest binol-based chiral phosphoric acid (*S*)-**7a** (10 mol %) and the commonly used (*S*)-TRIP (**7b**, 10 mol %)[20] could trigger this reaction under reflux in toluene, affording the desired product **4** in excellent diastereochemical controls but with relatively lower yields (entries 4 and 5). After a number of optimizations, the more acidic catalyst (*S*)-**7d** (20 mol %) was found to smoothly convert the linear precursor **5** (0.01 M) into the desired cyclohexanone **4** with improved yield (65%) and excellent stereoselectivity (dr > 99:1) in toluene at 80 °C (entry 7). However, the corresponding (*R*)-form catalyst, chair phosphoric acid **8d**, did not work at all under the same conditions (entry 11). Higher temperature (80 °C) was believed to favor the enolization of the ketone functionality, and 0.01 M of the substrate in toluene was proven to be a suitable concentration for this intramolecular reaction. *O,O*-Acetal of substrate **5** was unstable when the reaction concentrations were further increased (Table 1, entries 7, 8, and 9). On the basis of the observation, the chiral phosphoric acid is believed to play dual roles in formation of the enol and activation of the enone carbonyl through its acidic P−OH and basic P═O functionalities, respectively, and also helped to form a stereochemically favorable transition state during the reaction (Figure 3). A stronger Brønsted acid catalyst,[21] therefore, improved the efficiency of this intramolecular Michael addition (Table 1, entries 4−7). The significant difference of reaction behaviors with catalytic chiral phosphoric acid (*S*)-**7d** (entry 7, giving 65% yield of product **4**) and the enantiomeric chiral phosphoric acid (*R*)-**8d** (entry 11, no reaction) might be caused by the different steric interactions between their 3,3′-biphenyl substituents and the *O,O*-acetal moiety of substrate **5** when forming the corresponding hydrogen-bond-based transition state.

With gram quantities of chiral multisubstituted cyclohexanone **4** in hand, we continued to furnish the *cis*-decahydroquinoline and complete the total synthesis of lycoposerramine-Z (**1**) (Scheme 2). Removal of the *O,O*-ketal with aq. HCl, followed by reductive amination with commercially available (*S*)-1-(4-methoxyphenyl)-ethylamine, provided the decahydroquinoline **10** as a single diastereomer. Its relative configurations were clearly elucidated with the ^1H, ^{13}C, and 2D NMR experiments of the resulting bicyclic compound. Hydrogenolysis of both *N*-benzyl and *O*-PMB protecting groups was accomplished in the presence of a catalytic amount of 10% Pd/C and Boc_2O in MeOH at 50−60 °C for 6 h, giving the *N*-Boc protected primary alcohol **3**.[22] Mesylation of the primary alcohol **3** (to the corresponding mesylate **2**), followed by treatment with $NH_2OH{\cdot}HCl$ and 0.5

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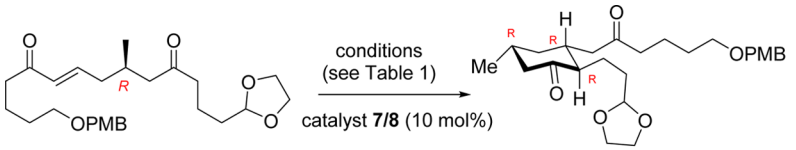
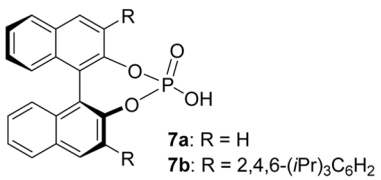
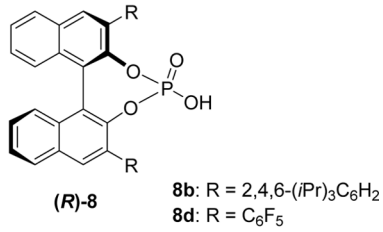
Table 1. Optimization of Intramolecular Michael Addition of Enone 5







entry	catalyst	solvent	c (mol/L)	temp. (°C)	time	yield
1	*t*-BuOK	*t*-BuOH	0.01	30	9 h	50%, dr = 3:1
2	PTSA	toluene	0.01	reflux	3 days	NR
3	(+)-CSA	toluene	0.01	reflux	3 days	NR
4	**7a**	toluene	0.01	reflux	90 h	20%, dr > 99:1
5	**7b**	toluene	0.01	reflux	90 h	32%, dr > 99:1
6[a]	**7c**	toluene	0.01	80	68 h	52%, dr > 99:1
7[a]	**7d**	toluene	0.01	80	48 h	65%, dr > 99:1
8	**7d**	toluene	0.05	80	48 h	40%, dr > 99:1
9	**7d**	toluene	0.1	80	24 h	decomp.
10	**8b**	toluene	0.01	reflux	90 h	NR
11	**8d**	toluene	0.01	reflux	90 h	NR

[a]20 mol % of catalyst was used.

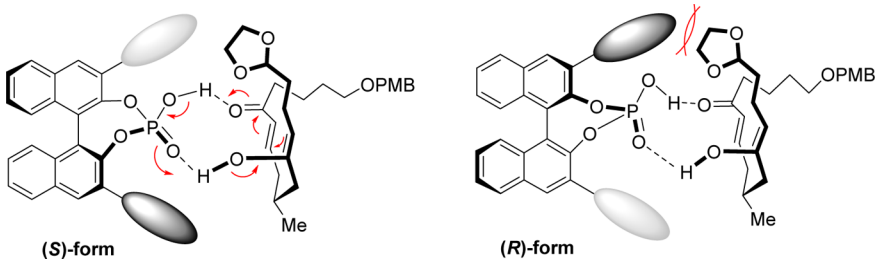


Figure 3. Proposed transition states for the chiral phosphoric acid catalyzed intramolecular Michael addition.

equiv of K_2CO_3 in EtOH/H_2O, provided the expected cyclic nitron **11** in 86% yield.[8f] Finally, the *N*-Boc protecting group of **11** was removed with TFA in DCM, affording the final product, lycoposerramine-Z (**1**). The synthesized lycoposerramine-Z (**1**) showed identical NMR data to those reported for the natural product,[10] as well as the optical rotation{synthetic **1**, $[\alpha]_D^{18}$ +11.4 (*c* 0.5 MeOH); natural **1**,[8f] $[\alpha]_D^{18}$ +9.6 (*c* 0.34, MeOH)}.

CONCLUSION

In summary, we have accomplished a new enantioselective total synthesis of lycoposerramine-Z, featuring the application of a chemoselective one-pot procedure of two sequential Grignard additions to the bis-Weinreb-amide, and an efficient construction of the multifuctionalized cyclohexanone by the chiral phosphoric acid catalyzed enantioselective intramolecular Michael addition. The new synthesis presented much better step- and redox-economy through optimization of the experimental procedure and applying the newly developed catalytic asymmetric reaction. Further application of the new methodology and intermediates to the total synthesis of other *Lycopodium* alkaloids is currently under investigation in our laboratory and will be reported in due course.

EXPERIMENTAL SECTION

Preparation of Enone 5. To a stirred suspension of magnesium turnings (2.9 g, 121 mmol) in anhydrous THF (5 mL) was added a crystal of I_2 as an activator. After 5 min, a solution of 1-bromo-4-(*p*-methoxybenzyloxy)butane (12.3 g, 45 mmol) in anhydrous THF (40 mL) was added dropwise. At the beginning of the addition, the suspension turned yellow and then slowly turned gray. A water bath was used periodically to cool down the reaction temperature (to prevent the temperature from exceeding 35 °C). Upon completion of the addition, the suspension was stirred for 1 h at room temperature. The resulting first Grignard reagent was measured by a titrimetric method as a 0.81 M solution in THF.

The second Grignard reagent (0.55 M in THF solution) was similarly prepared using a solution of 2-(3-bromo-propyl)-1,3-dioxolane (22.4 g, 120 mmol) in dry THF (110 mL), crushed magnesium turnings (7.73 g, 340 mmol), and a crystal of I_2 under a nitrogen atmosphere.

To a solution of bis-Weinreb-amide **6**[13] (5.9 g, 22.8 mmol) in THF (230 mL) was added slowly a solution of the above first Grignard

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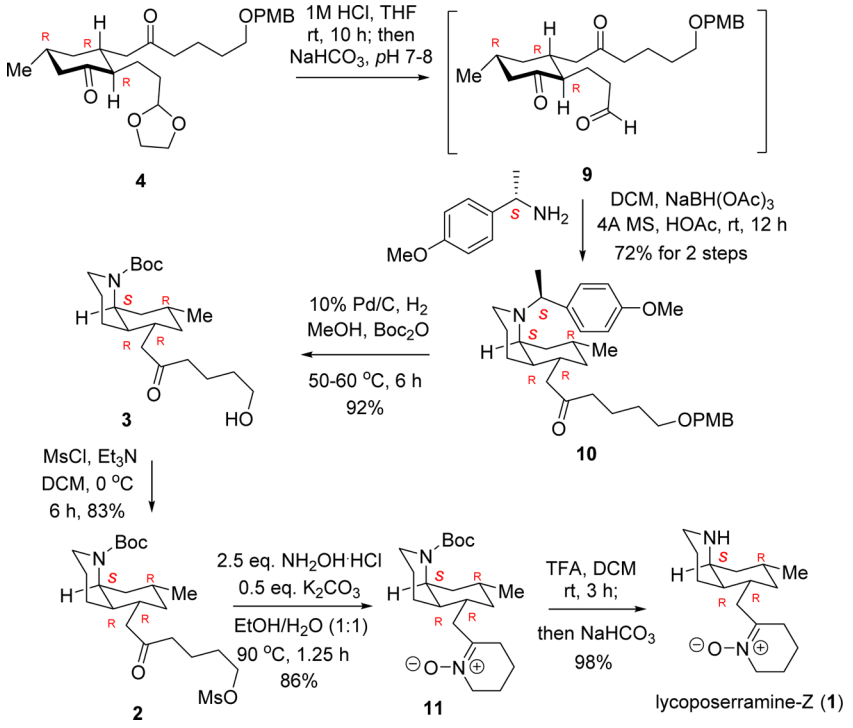
Scheme 2. Completion of the Total Synthesis of Lycoposerramine-Z (1)



reagent (0.81 M, 30.4 mL, 24.6 mmol, 1.08 equiv) at −15 °C. After completion of the addition, the reaction was stirred for 2 h until TLC showed that the starting material was consumed. The second Grignard reagent (0.55 M, 103.6 mL, 57.0 mmol, 2.5 equiv) was then added slowly into the reaction mixture. The reaction mixture was warmed to room temperature and stirred overnight. Saturated aqueous NH_4Cl (100 mL) was added, and the whole mixture was extracted with ethyl acetate for four times. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1/4 to 1/1) to afford enone **5** (6.9 g, 68%) as a pale yellow oil. $[\alpha]_D^{25}$ +1.80 (*c* 1.0 $CHCl_3$). IR (KBr, film): 2954, 2875, 1711, 1672, 1613, 1513, 1459, 1410, 1366, 1248, 1140, 1099, 1034, 983 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91 (d, J = 6.2 Hz, 3H), 1.73−1.59 (m, 8H), 2.11−2.05 (m, 1H), 2.29−2.16 (m, 3H), 2.40−2.34 (m, 1H), 2.43 (t, J = 7.1 Hz, 2H), 2.54 (t, J = 7.2 Hz, 2H), 3.45 (t, J = 6.2 Hz, 2H), 3.80 (s, 3H), 3.87−3.81 (m, 2H), 3.96−3.90 (m, 2H), 4.42 (s, 2H), 4.83 (t, J = 4.3 Hz, 1H), 6.06 (d, J = 15.8 Hz, 1H), 6.77−6.70 (m, 1H), 6.88−6.85 (m, 2H), 7.25 (d, J = 9.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 18.2, 20.0, 21.1, 28.6, 29.4, 33.1, 39.7, 39.9, 43.1, 49.3, 55.4, 65.0, 69.9, 72.7, 104.4, 113.9, 129.4, 130.8, 132.0, 145.0, 159.2, 200.4, 209.9. MS (ESI, m/z): 469 $(M + 23)^+$. ESI-HRMS calcd for $C_{26}H_{38}NaO_6$ $[M + Na]^+$: 469.2561, found: 469.2560.

Multisubstituted Cyclohexanone 4. To a solution of enone **5** (32.1 mg, 0.07 mmol) in dry toluene (7 mL) under argon was added the (*S*)-chiral phosphoric acid **7d** (9.8 mg, 0.014 mmol). The reaction mixture was stirred at 80 °C for 48 h. The solution was cooled down to room temperature and basified to pH 7−8 with saturated aq. $NaHCO_3$, and then extracted with ethyl acetate for four times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1/4 to 1/2) to afford **4** (20.8 mg, 65%) as a colorless oil. $[\alpha]_D^{25}$ +10.06 (*c* 1.0 $CHCl_3$). IR (KBr, film): 2951, 2870, 1710, 1613, 1586, 1513, 1456, 1410, 1366, 1247, 1174, 1099, 1035, 945, 821 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.94 (d, J = 6.3 Hz, 3H), 1.11 (q, J = 12.3 Hz, 1H), 1.71−1.48 (m, 8H), 1.84−1.75 (m, 2H), 2.06−1.93 (m, 2H), 2.12 (dd, J_1 = 11.8 Hz, J_2 = 7.7 Hz, 1H), 2.44−2.28 (m, 4H), 2.62 (dd, J_1 = 16.8 Hz, J_2 = 3.2 Hz), 3.41 (t, J = 6.1 Hz, 2H), 3.77 (s, 3H), 3.83−3.78 (m, 2H), 3.92−3.85 (m, 2H), 4.39 (s, 2H), 4.79 (t, J = 4.8 Hz, 1H), 6.86−6.82 (m, 2H), 7.22 (d, J = 8.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 20.1, 20.6, 22.3, 29.2, 31.1, 33.4, 38.1, 40.7, 43.3, 47.1, 50.3, 53.2, 55.3, 64.8, 64.9, 69.7, 72.6, 104.5, 113.8, 129.3, 130.6, 159.2, 209.7, 210.8. MS (ESI, m/z): 469 $(M + 23)^+$. ESI-HRMS calcd for $C_{26}H_{38}NaO_6$ $[M + Na]^+$: 469.2561, found: 469.2562.

***cis*-Decahydroquinoline 10.** To a stirred solution of **4** (133.3 mg, 0.3 mmol) in THF (10.0 mL) was added 1 N aq. hydrochloride acid (2.5 mL). After being stirred at room temperature for 10 h, the reaction was basified to pH 7−8 with saturated aq. $NaHCO_3$ and then extracted with CH_2Cl_2 for six times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude keto-aldehyde **9** was unstable and used directly for the next step without further purification.

A mixture of the above crude **9** (0.28 mmol), 4 Å molecular sieves (220.6 mg, 2.0 eq. w/w), and (*S*)-1-(4-methoxyphenyl)ethylamine (41.5 μL, 0.28 mmol, 1.0 equiv) in anhydrous DCM (30 mL) was stirred under N_2 at room temperature for 1 h, and $NaBH(OAc)_3$ (145.2 mg, 0.7 mmol, 2.5 equiv) and HOAc (1.6 μL, 0.03 mmol, 0.1 equiv) were then added. After being stirred at room temperature for 12 h, the reaction mixture was basified with saturated aq. $NaHCO_3$ and then filtered through a pad of Celite. The filtrate was extracted with CH_2Cl_2 for six times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (MeOH/DCM = 1/60) to afford **10** (112.1 mg, 72%, for 2 steps) as a yellow oil. $[\alpha]_D^{25}$ −3.38 (*c* 1.0 $CHCl_3$). IR (KBr, film): 2923, 2854, 2793, 1711, 1612, 1510, 1458, 1362, 1245, 1173, 1149, 1094, 1035, 805 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.70 (q, J = 11.6 Hz, 1H), 0.83 (d, J = 6.6 Hz, 3H), 1.05−0.97 (m, 1H), 1.19−1.15 (m, 1H), 1.19 (d, J = 6.8 Hz, 3H), 1.32 (dd, J_1 = 11.8 Hz, J_2 = 2.6 Hz, 2H), 1.53−1.43 (m, 1H), 1.78−1.58 (m, 6H), 1.93−1.84 (m, 1H), 2.09−1.97 (m, 3H), 2.49−2.38 (m, 3H), 2.54 (dd, J_1 = 15.4 Hz, J_2 = 4.0 Hz, 1H), 2.68 (d, J = 2.0 Hz, 1H), 2.84−2.75 (m, 1H), 3.46 (t, J = 6.1 Hz, 2H), 3.80 (2 × s, 2 × 3H), 4.15 (q, J = 6.8 Hz, 1H), 4.43 (s, 2H), 6.89−6.85 (m, 4H), 7.27−7.24 (m, 2H), 7.38 (d, J = 8.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 8.0, 20.7, 21.6, 22.8, 26.6, 28.0, 29.4, 30.5, 38.5, 42.4, 42.8, 43.3, 46.2, 47.7, 52.1, 55.36, 55.39, 58.9, 69.9, 72.7, 113.4, 113.9, 128.6, 129.4, 130.8, 137.2, 158.1, 159.3, 211.7. MS (ESI, m/z): 522 $(M + 1)^+$. ESI-HRMS calcd for $C_{33}H_{48}NO_4$ $[M + H]^+$: 522.3578, found: 522.3577.

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Primary Alcohol 3. A suspension of **10** (84.1 mg, 0.16 mmol), 10% Pd/C (8.4 mg, 10% w/w), and Boc_2O (70.4 mg, 0.32 mmol, 2.0 equiv) in MeOH (4.5 mL) was stirred under hydrogen (1 atm) at 50−60 °C for 6 h. After being cooled down to rt, the solid was removed by filtration through a pad of Celite. The filter cake was washed with DCM. The combined filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1/2) to afford **3** (54.5 mg, 92%) as a colorless oil. $[\alpha]_D^{25}$ +1.56 (*c* 0.64 $CHCl_3$). IR (KBr, film): 3438, 2925, 2859, 1688, 1413, 1365, 1270, 1159, 1058, 889, 843 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.01−0.96 (m, 1H), 1.02 (d, J = 7.0 Hz, 3H), 1.13−1.08 (m, 1H), 1.46−1.29 (m, 2H), 1.42 (s, 9H), 1.58−1.48 (m, 5H), 1.68−1.59 (m, 3H), 2.03−1.89 (m, 3H), 2.20 (brs, 1H), 2.47−2.34 (m, 3H), 2.63 (dd, J_1 = 17.0 Hz, J_2 = 7.6 Hz, 1H), 2.72 (td, J_1 = 13.1 Hz, J_2 = 3.0 Hz, 1H), 3.58 (t, J = 6.3 Hz, 2H), 3.86 (dd, J_1 = 13.2 Hz, J_2 = 2.8 Hz, 1H), 4.28−4.23 (m, 1H). ^{13}C NMR (101 MHz,$CDCl_3$) δ: 20.0, 22.1, 25.4, 26.1, 27.5, 28.6, 28.8, 32.2, 32.6, 35.3, 39.1, 39.2, 43.1, 46.1, 49.4, 62.3, 79.3, 155.2, 210.8. MS (ESI, m/z): 390 $(M + 23)^+$. ESI-HRMS calcd for $C_{21}H_{37}NNaO_4$ $[M + Na]^+$: 390.2615, found: 390.2617.

Mesylate 2. To a stirred solution of **3** (27.3 mg, 0.074 mmol) in dry CH_2Cl_2 (2.5 mL) was added MsCl (11.5 μL, 0.15 mmol, 2.0 equiv) and Et_3N (21.0 μL, 0.15 mmol, 2.0 equiv) at 0 °C under an argon atmosphere. After stirring for 2 h at 0 °C, the reaction was quenched with H_2O and extracted with CH_2Cl_2 for four times. The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated. The residue was purified by silica gel flash column chromatography (AcOEt/*n*-hexane = 1:3) to give **2** (32.4 mg, 98%) as a colorless oil. $[\alpha]_D^{25}$ +2.90 (*c* 0.62 $CHCl_3$). IR (KBr, film): 2925, 2858, 1683, 1415, 1361, 1268, 1174, 1098, 935, 802 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.02−0.97 (m, 1H), 1.02 (d, J = 7.0 Hz, 3H), 1.14−1.09 (m, 1H), 1.40−1.33 (m, 2H), 1.43 (s, 9H), 1.55−1.48 (m, 2H), 1.63−1.59 (m, 2H), 1.78−1.65 (m, 4H), 2.01−1.94 (m, 3H), 2.46−2.40 (m, 3H), 2.59 (dd, J_1 = 17.2 Hz, J_2 = 7.6 Hz, 1H), 2.73 (td, J_1 = 13.2 Hz, J_2 = 3.2 Hz, 1H), 2.99 (s, 3H), 3.88 (dd, J_1 = 13.6 Hz, J_2 = 2.8 Hz, 1H), 4.21 (t, J = 6.1 Hz, 2H), 4.26 (dd, J_1 = 11.6 Hz, J_2 = 5.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 19.6, 22.1, 25.4, 26.2, 27.5, 28.6, 28.7, 28.8, 32.7, 35.4, 37.5, 39.1, 39.3, 42.4, 46.2, 49.6, 69.7, 79.3, 155.2, 209.7. MS (ESI, m/z): 468 $(M + 23)^+$. ESI-HRMS calcd for $C_{22}H_{39}NNaO_6S$ $[M + Na]^+$: 468.2390, found: 468.2390.

***N*-Boc Cyclic Nitron 11.** To a stirred solution of **2** (20.0 mg, 0.045 mmol) in EtOH/H_2O (1:1, 6 mL) was added K_2CO_3 (3.1 mg, 0.022 mmol, 0.5 equiv) and $NH_2OH{\cdot}HCl$ (7.8 mg, 0.11 mmol, 2.5 equiv) at room temperature under an argon atmosphere. After stirring for 1 h and 15 min at 90 °C, the reaction mixture was basified to pH 7−8 with sat. aq. $NaHCO_3$, and extracted with $CHCl_3$ for six times. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel flash column chromatography (MeOH/$CHCl_3$ = 1:20) to afford **11** (14.8 mg, 84%) as a colorless oil. $[\alpha]_D^{25}$ −4.14 (*c* 0.29 $CHCl_3$). IR (KBr, film): 2927, 2866, 1686, 1602, 1449, 1414, 1365, 1271, 1253, 1158, 867, 754 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.03 (d, J = 6.9 Hz, 3H), 1.15−1.04 (m, 2H), 1.41−1.37 (m, 1H), 1.45 (s, 9H), 1.52−1.46 (m, 2H), 1.62 (d, J = 8.0 Hz, 2H), 1.75−1.71 (m, 2H), 2.04−1.85 (m, 6H), 2.43 (t, J = 6.0 Hz, 2H), 2.46 (dd, J_1 = 13.2 Hz, J_2 = 8.4 Hz, 1H), 2.65 (dd, J_1 = 13.1 Hz, J_2 = 6.3 Hz, 1H), 2.73 (td, J_1 = 13.1 Hz, J_2 = 2.7 Hz, 1H), 3.79 (t, J = 6.0 Hz, 2H), 3.92 (dd, J_1 = 13.2 Hz, J_2 = 3.6 Hz, 1H), 4.28 (dt, J_1 = 11.1 Hz, J_2 = 4.1 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 19.0, 22.7, 23.3, 25.1, 26.6, 27.3, 28.7, 29.3, 30.8, 34.0, 36.6, 38.9, 39.2, 39.6, 47.0, 58.4, 79.3, 148.3, 155.3. MS (ESI, m/z): 365 $(M + 1)^+$. ESI-HRMS calcd for $C_{21}H_{37}N_2O_3$ $[M + H]^+$: 365.2799, found: 365.2800.

Lycoposerramine-Z (1). To a stirred solution of **11** (11.7 mg, 0.032 mmol) in dry CH_2Cl_2 (5.0 mL) was added TFA (1.0 mL). The reaction mixture was stirred at rt for 3 h and then concentrated under reduced pressure. The resulting crude product was dissolved with water (0.1 mL), MeOH (0.3 mL) and CH_2Cl_2 (12 mL) and treated with solid $NaHCO_3$ (450 mg). The resulting mixture was stirred for 5 min and Na_2SO_4 (~1.5 g) was added. After being stirred for 5 min, the whole mixture was filtered. The filter cake was washed with CH_2Cl_2 (with 5% MeOH), and the filtrate was concentrated under reduced pressure. The resulting crude material was purified by silica column chromatography (MeOH/$CHCl_3$ = 7:10) to give lycoposerramine-Z (**1**, 8.3 mg, 98%) as a colorless oil. $[\alpha]_D^{18}$ +11.4 (*c* 0.5 MeOH). IR (KBr, film): 3275, 2940, 2914, 1604, 1453, 1260, 1141, 1020 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 0.78 (q, J = 12.2 Hz, 1H), 0.84 (d, J = 6.3 Hz, 3H), 1.21−1.17 (m, 1H), 1.43−1.36 (m, 2H), 1.47 (dt, J_1 = 13.8 Hz, J_2 = 4.0 Hz, 1H), 1.56 (br dd, J_1 = 13.2 Hz, J_2 = 1.8 Hz, 1H), 1.75 (m, 5H), 1.94 (p, J = 6.1 Hz, 2H), 2.04 (m, 1H), 2.22 (dd, J_1 = 12.9 Hz, J_2 = 10.8 Hz, 1H), 2.48−2.40 (m, 2H), 2.58−2.49 (m, 1H), 2.77−2.72 (m, 2H), 3.05−3.02 (m, 1H), 3.20 (br d, J = 11.4 Hz, 1H), 3.84−3.77 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 18.8, 20.1, 22.6, 23.2, 26.3, 26.6, 29.6, 30.3, 36.1, 40.3, 40.5, 41.1, 47.2, 56.6, 58.3, 149.6. MS (ESI, m/z): 265 $(M + 1)^+$. ESI-HRMS calcd for $C_{16}H_{29}N_2O$ $[M + H]^+$: 265.2274, found: 265.2278.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02723.

General methods, ^1H and ^{13}C NMR copies of new compounds, 2D NMR copies of compound **10**, and ^1H and ^{13}C NMR data comparison of the final product (PDF)

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Notes

The authors declare no competing financial interest.

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