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Asymmetric Total Syntheses of Two Phlegmarine-Type Alkaloids, Lycoposerramines-V and -W, Newly Isolated from *Lycopodium serratum*

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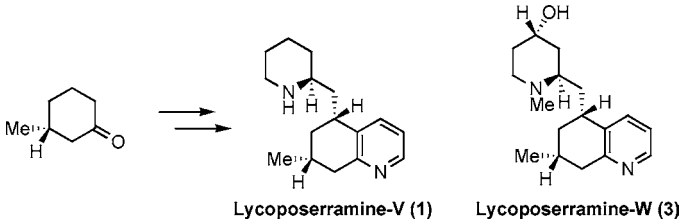
ABSTRACT



Lycoposerramine-V (1) Lycoposerramine-W (3)

Two new Phlegmarine-type alkaloids, lycoposerramines-V and -W, were isolated from *Lycopodium serratum*, and their structures including the absolute configuration were established by asymmetric total synthesis involving such key steps as Johnson–Claisen rearrangement, asymmetric allylation, and ring-closing metathesis (RCM)- or SmI_2-mediated stereoselective piperidine ring construction.

Plants belonging to genus *Lycopodium* are known to contain alkaloids having unique skeletal characteristics and biological activities, such as acetylcholine esterase (AChE) inhibition.[1] This has inspired many groups to investigate the alkaloid constituents in those plants, and a number of novel alkaloids were discovered in recent years.[2] We have reported the isolation and structure elucidation of novel alkaloids having various kinds of skeleton from *L. serratum*.[3] Further investigation of the alkaloidal fraction of this plant has led to the isolation of two new Phlegmarine-type alkaloids:[4] lycoposerramines-V (**1**) and -W (**3**). In this paper, we describe the structure determination based on spectroscopic analyses and asymmetric total syntheses.

Lycoposerramine-V. The crude base fraction obtained by means of a previously reported procedure[3c,4d] was purified

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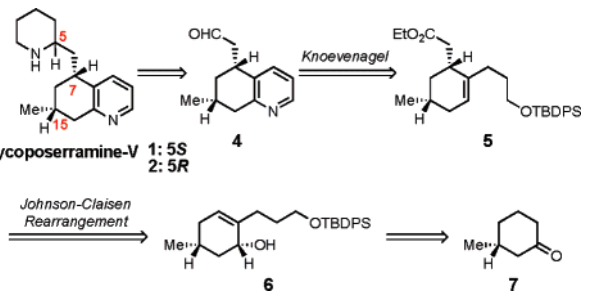
by repeated chromatography over SiO_2 gel to afford new alkaloids **1** and **3** (0.64 and 1.75% yields based on the crude base, respectively). Compound **1**, named lycoposerramine-V, was obtained as a colorless amorphous powder ($[\alpha]^{23}_D$ +17.7 (*c* 0.24, $CHCl_3$)), and its molecular formula was established to be $C_{16}H_{24}N_2$ by HRFAB-MS analysis. In addition to ^1H and ^{13}C NMR data (Table 1), 2D NMR correlations indicated that compound **1** had a Phlegmarine skeleton with the 5,6,7,8-tetrahydroquinoline moiety, which is the first example of Lycopodium alkaloid, and a piperidine ring (see the structure in Scheme 1). The stereochemistry at H7 and H15 was found to be *cis* by NOE analysis. However, it was not possible to elucidate the relative stereochemistry between C7 and C5 by spectroscopic analysis. Then, we attempted the total synthesis of lycoposerramine-V to reveal its relative and absolute configurations.

Table 1. ^1H and ^{13}C NMR Data for Natural Lycoposerramine-V (**1**) and Lycoposerramine-W (**3**) (in $CDCl_3$)

	Lycoposerramine-V (**1**)		Lycoposerramine-W (**3**)	
	δ_H (400 MHz)	δ_C (100 MHz)	δ_H (400 MHz)	δ_C (125 MHz)
1α	2.76 (ddd, 12.6, 12.6, 3.1)	44.8	2.80−2.77 (2H, m)	49.5
1β	3.34 (br d, 13.2)			
2α	1.50−1.43 (m)	22.6[a]	1.71−1.60 (2H, m)	31.0
2β	1.91−1.66 (m)			
3	1.91−1.66 (2H, m)	22.3[a]	4.08 (dddd, 4.9, 4.9, 3.7, 3.7)	65.0
4	1.91−1.66 (2H, m)	30.3	1.71−1.60 (2H, m)	37.7
5	3.15−3.10 (m)	54.8	2.89−2.85 (m)	55.7
6	2.68 (ddd, 13.5, 9.5, 3.3)	41.1	2.30 (ddd, 14.6, 6.4, 4.2)	40.0
	1.53 (ddd, 14.8, 11.1, 3.8)		1.36−1.25 (m)	
7	3.44−3.36 (m)	33.3	2.98−2.93 (m)	35.9
8α	0.90 (ddd, 11.9, 11.9, 11.9)	37.9	1.08 (ddd, 11.9, 11.9, 11.9)	39.0
8β	2.22−2.17 (m)		2.13 (dddd, 12.8, 5.5, 2.6, 2.6)	
9	8.26 (d, 4.0)	146.8	8.34 (d, 4.2)	146.6
10	6.91 (dd, 7.9, 4.8)	121.1	7.07 (dd, 7.9, 4.6)	121.1
11	7.73 (d, 7.7)	135.0	7.61 (d, 7.9)	134.6
12		133.9		135.7
13		157.3		157.6
14α	2.48 (dd, 16.8, 12.1)	41.7	2.53 (dd, 16.8, 11.9)	42.0
14β	2.92 (ddd, 16.8, 4.4, 1.8)		2.96 (ddd, 16.7, 4.4, 2.2)	
15	2.02−1.96 (m)	28.6	1.92−1.88 (m)	29.2
16	1.11 (3H, d, 6.6)	22.2	1.10 (3H, d, 6.6)	22.3
N-CH_3			2.46 (3H, s)	41.1

[a] Interchangeable.

Scheme 1. Retrosynthesis of Lycoposerramine-V (**1** and **2**)



Our synthesis began with the preparation of known cyclohexenone **8**[5] from commercially available (*R*)-3-methylcyclohexanone **7** through sulfenylation, followed by oxidation and dehydrosulfenylation. α-Iodination of cyclohexenone **8** with I_2/pyridine gave iodide **9**.[6] Next, the installation of a 3-hydroxypropane side chain to **9** was accomplished with a tandem sequence involving the regioselective hydroboration of alkene **10**[7] with 9-BBN, followed by coupling of the resulting borane under Pd-catalyzed Suzuki−Miyaura conditions.[8] Reduction of thus obtained enone **11** under Luche conditions gave allyl alcohol **6** as a single isomer, the stereochemistry of which was demonstrated by the coupling constant of the proton bearing a secondary hydroxyl group (δ 4.16, dd, J = 9.3 and 5.4 Hz, β-axial proton). Allylic alcohol **6** was subjected to Johnson−Claisen rearrangement[9] to attach the acetic acid residue to C7 by heating xylene with triethyl orthoacetate in the presence of a small amount of *o*-nitrophenol to give stereoselectively cyclohexene **5** in 92% yield (Scheme 2).

By conventional hydroboration−oxidation procedure, **5** was converted into diastereomeric alcohol **12** as the major product in 75% yield.[10] Removal of the TBDPS group and subsequent Swern oxidation of the resultant diol gave ketoaldehyde **13**, which was subjected to Knoevenagel conditions[11] with slight modification using NH_2OMe to afford the 5,6,7,8-tetrahydroquinoline skeleton. Reduction of the ester in **14** with $LiAlH_4$ and subsequent oxidation under Swern conditions gave aldehyde **4** in good yield (Scheme 3).

Next, we turned our attention to the enantioselective construction of 2-substituted piperidine from aldehyde **4**. For

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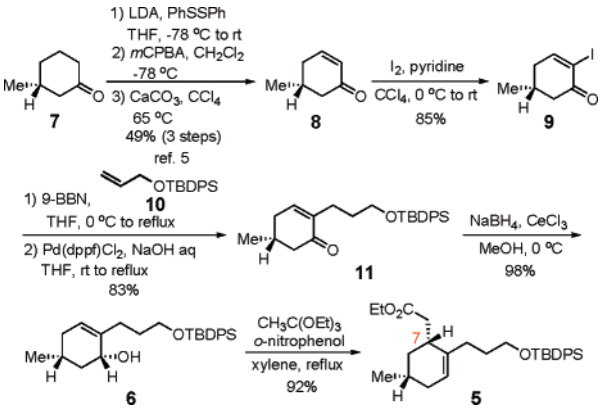
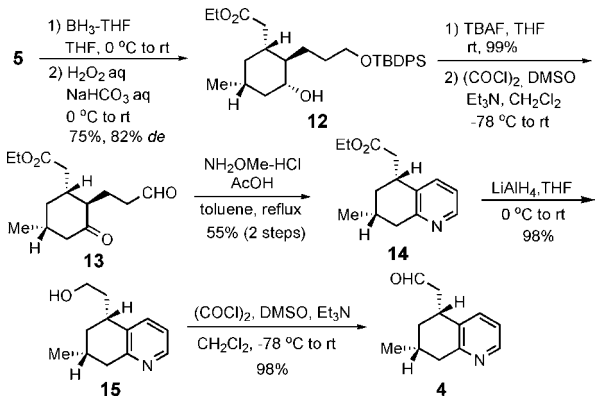
Scheme 2



this purpose, we employed Brown's asymmetric allylation with *B*-allyldiisopinocampheylborane,[12] which would enable us to prepare both diastereomeric homoallylic alcohols, followed by RCM. Treatment of aldehyde **4** with *B*-allyldiisopinocampheylborane prepared from (+)-*B*-chlorodiisopinocampheylborane and allylmagnesium bromide yielded

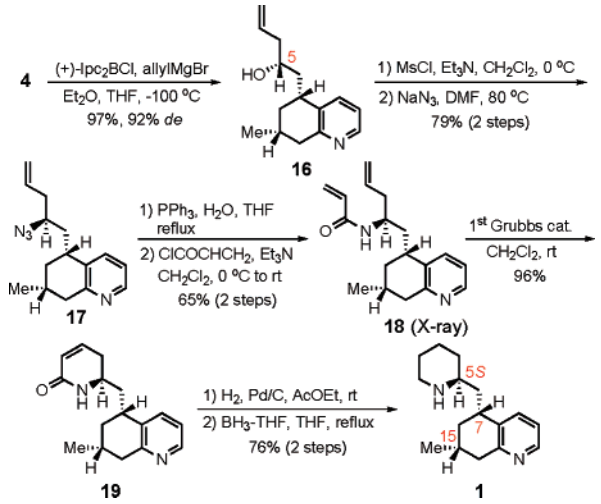
Scheme 3



homoallylic alcohol **16** in 97% yield with good diastereoselectivity (92% de). The absolute configuration of the newly generated chiral center was assigned as *R* based on a well-established reaction mechanism and confirmed later by X-ray crystallographic analysis (see compound **18**). The alcohol thus obtained was converted into azide **17** accompanying the stereoinversion via an O-mesylated derivative. Using Staudinger reaction with PPh_3-H_2O,[13] azide **17** was transformed into primary amine, which was directly acylated with acryloyl chloride in the presence of TEA to give **18** in 65% yield. At this stage, X-ray crystallographic analysis of **18** was conducted, which enabled the unambiguous assignment of all chiral centers. RCM[14] using first-generation Grubbs' ruthenium catalyst proceeded smoothly to generate unsaturated lactam **19**.

Finally, reduction of the double bond with H_2/Pd/C and subsequent reduction of lactam with BH_3-THF afforded desired compound **1** with 5*S*,7*R*,15*R* configuration (Scheme 4). Starting from common intermediate **4**, we achieved the

Scheme 4



asymmetric synthesis of compound **2** possessing 5*R*,7*R*,15*R* configuration via a sequence similar to that described above by employing *B*-allyldiisopinocampheylborane prepared from (−)-*B*-chlorodiisopinocampheylborane in the asymmetric allylation reaction (see the Supporting Information).

Having both target compounds (**1** and **2**) in hand, we compared their physicochemical data with those of the natural product. As a result, compound **1** was completely identical in all respects (chromatographic behavior, mass, IR, UV, ^1H and ^{13}C NMR, $[\alpha]^{23}_D$ +29.2 (*c* 0.35, $CHCl_3$)) with natural lycoposerramine-V. Therefore, the structure including the absolute configuration of the chiral center was established to be **1**.

Lycoposerramine-W. Compound **3**, named lycoposerramine-W, was obtained as a colorless amorphous powder ($[\alpha]^{25}_D$ +22.4 (*c* 0.14, $CHCl_3$)), and its molecular formula was established to be $C_{17}H_{27}N_2O_1$ by HRFAB-MS analysis. ^1H and ^{13}C NMR (Table 1) spectra and 2D NMR correlations indicated the presence of two additional functional groups (i.e., a *N*-methyl group and a secondary hydroxyl group) at C3 of the piperidine ring, compared with the structure of lycoposerramine-V (**1**). Although the stereochemistry at the four chiral centers (C3, C5, C7, and C15) was obscure from the spectroscopic analyses, we deduced that the absolute configuration at C5, C7, and C15 would be the same as that of **1** based on biogenetic consideration, and the remaining chiral center (C3) would be *S*, that is, α-axial orientation,

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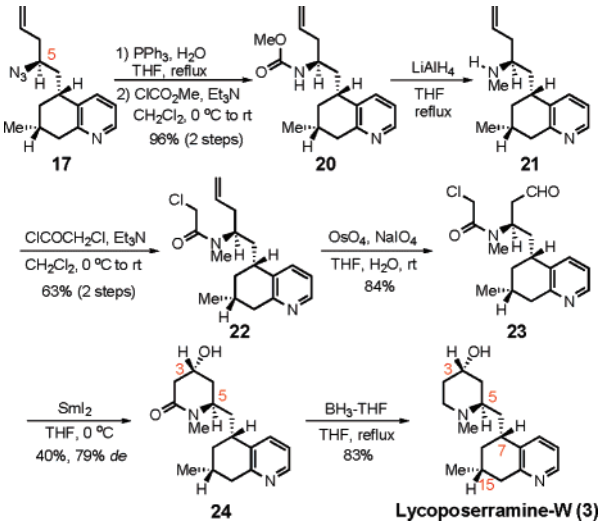
from the coupling constant of the proton on C3 (dddd, J = 4.9, 4.9, 3.7, 3.7 Hz). Then, we focused on the asymmetric synthesis of the compound having 3*S*,5*R*,7*R*,15*R* configuration to elucidate the structure of lycoposerramine-W. In the key step of the synthesis of lycoposerramine-W, we employed the intramolecular Reformatsky reaction promoted by samarium(II) iodide, which led to 1,3-asymmetric induction in a C−C bond-forming process. However, as far as we know, this reaction has been applied only to β-haloacetoxy carbonyl substrates, forming a lactone ring. None of the studies that employed this reaction used substrates that contained nitrogen atom (i.e., β-haloacetamide−carbonyl compound) to produce a 4-hydroxy-2-substituted piperidine ring.[15] Then, we prepared key substrate **23** and investigated the reaction conditions for this new type of substrate.

The primary amine prepared from azide **17**, which was an intermediate for the synthesis of lycoposerramine-V, was directly converted into methyl carbamate derivative **20** (Scheme 5). Reduction of the carbamate with $LiAlH_4$ gave

Scheme 5



N-methyl derivative **21**, which was then acylated with chloroacetylchloride to yield amide **22** in 63% overall yield from **20**. Oxidative cleavage of the terminal double bond in **22** with the Johnson−Lemieux[16] protocol using a catalytic amount of OsO_4 and 4 equiv of $NaIO_4$ produced β-chloroacetamine−aldehyde **23** in 84% yield. After several attempts at the investigation of the reaction conditions of samarium(II)-promoted stereoselective intramolecular Reformatsky reaction,[17] we found that the use of samarium(II) iodide[18] freshly prepared from samarium metal and diiodomethane in THF gave the best result, producing lactam **24** in 40% yield with good diastereoselectivity (79% de). The relative stereochemistry between C3 and C5 was demonstrated by careful NMR analysis (δ 2.81, 1H, dd, J = 17.4, 5.5 Hz, H-2; δ 2.39, 1H, dd, J = 17.4, 7.0 Hz, H-2; δ 4.24, 1H, dddd, J = 7.0, 7.0, 5.8, 5.5, H-3) and NOE experiments. The stereochemical control of the reaction could be due to a chair-like transition structure as described by Molander.[17a,b] Finally, reduction of lactam **24** with BH_3−THF afforded target compound **3**, which was completely identical in all respects (chromatographic behavior, mass, IR, UV, ^{1}H and ^{13}C NMR, $[\alpha]^{25}_D$ +21.5 (*c* 0.07, $CHCl_3$)) with natural lycoposerramine-W. Therefore, the structure including the absolute configuration of the four chiral centers was established for **3**.

In conclusion, we have achieved the asymmetric total syntheses of lycoposerramine-V (**1**) (22 steps, 4.3% overall yield) and lycoposerramine-W (**3**) (23 steps, 1.4% overall yield) starting from (*R*)-3-methylcyclohexanone, which enabled us to determine unambiguously the structures including the absolute configurations of two novel Phlegmarine-type alkaloids newly isolated from *Lycopodium serratum*.

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Supporting Information Available: Experimental procedures for isolation of lycoposerramine-V and -W, and preparation of compounds **1**−**6**, **9**−**24**, and **S1**−**S6**, and copies of ^{1}H and ^{13}C NMR spectral data for natural lycoposerramine-V, -W, and compounds **1**−**3**, **5**, **14**, **16**, **17**, **22**, **24**, and **S3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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