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First Asymmetric Total Syntheses of Cernuane-Type *Lycopodium* Alkaloids, Cernuine, and Cermizine D

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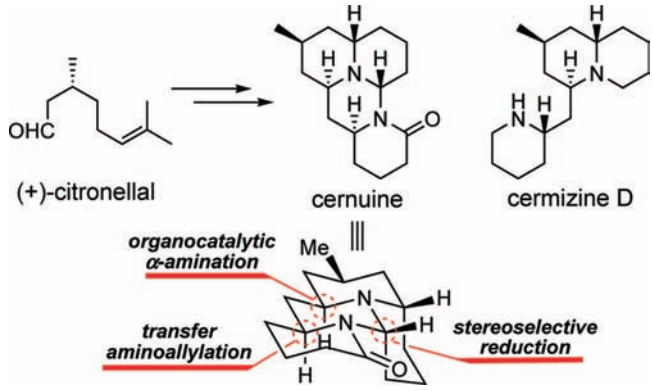
ABSTRACT



The first total syntheses of two cernuane-type *Lycopodium* alkaloids, (−)-cernuine and (+)-cermizine D, were accomplished starting from (+)-citronellal. The syntheses involved organocatalytic α-amination to afford oxazolidinone, which is used for diastereoselective allylation, and asymmetric transfer aminoallylation followed by stereoselective construction of an aminal moiety as key steps.

Plants of the genus *Lycopodium* are known to produce a number of alkaloids that often possess highly diverse, complex structures and a variety of biological activities.[1] Cernuine (**1**) and lycocernuine (**2**) are representatives of cernuane-type *Lycopodium* alkaloids that consist of a fused tetracyclic ring system containing an aminal moiety. Isolated by Marion and Manske in 1948,[2a] their structures were elucidated by Ayer et al. in 1967.[2b−e] However, while the total syntheses of various types of *Lycopodium* alkaloids have been reported,[3] that of cernuane-type alkaloids has yet to be established. In 2004, Kobayashi et al. reported the isolation of cermizine D (**3**), a compound having an *N*-C_9 *seco*-cernuane skeleton and exhibiting cytotoxicity against murine lymphoma L1210 cells with an IC_{50} of 7.5 μg/mL (Figure 1).[4] Although the structure of cermizine D was proposed on the basis of spectroscopic methods, its relative and absolute configuration was not clarified. In relation to our chemical

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(2) (a) Marion, L.; Manske, R. H. F. *Can. J. Res.* **1948**, *26*, 1–2. (b) Ayer, W. A.; Jenkins, J. K.; Valverde-Lopez, S. *Tetrahedron Lett.* **1964**, *32*, 2201–2209. (c) Ayer, W. A.; Jenkins, J. K.; Valverde-Lopez, S.; Burnell, R. H. *Can. J. Chem.* **1967**, *45*, 433–443. (d) Ayer, W. A.; Jenkins, J. K.; Piers, K.; Valverde-Lopez, S. *Can. J. Chem.* **1967**, *45*, 445–450. (e) Ayer, W. A.; Piers, K. *Can. J. Chem.* **1967**, *45*, 451–459.

(3) For recent reports of the synthesis of *Lycopodium* alkaloids, see: (a) Shigeyama, T.; Katakawa, K.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. Lett.* **2007**, *9*, 4069–4073. (b) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7671–7673. (c) Beshore, D. C.; Smith, A. B., III *J. Am. Chem. Soc.* **2007**, *129*, 4148–4149. (d) Snider, B. B.; Grabowski, J. F. *J. Org. Chem.* **2007**, *72*, 1039–1042. (e) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5995–5994.

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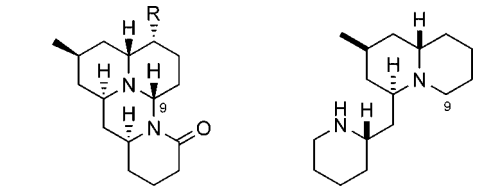
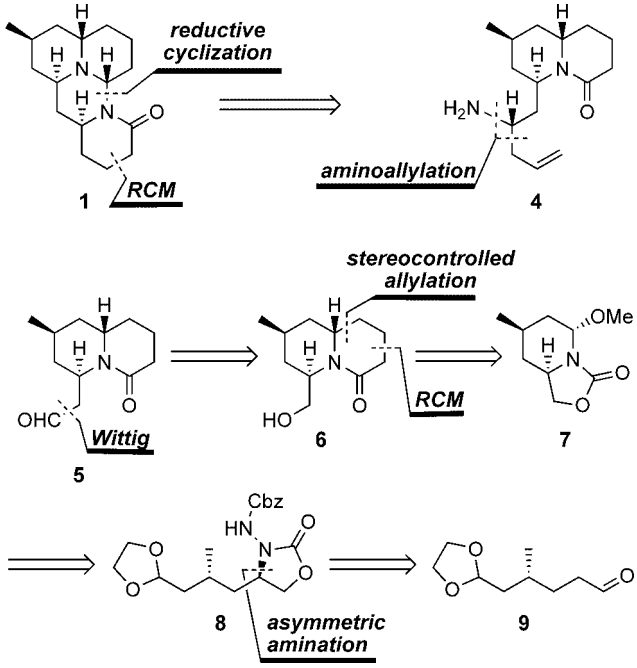


Figure 1. Cernuane-type *Lycopodium* alkaloids isolated from *Lycopodium cernuum*.

studies on *Lycopodium* alkaloids,[5] we planned the synthesis of these cernuane-type alkaloids by which the structure, including the absolute configuration, could be confirmed. In this paper, we describe the first stereocontrolled total syntheses of (−)-cernuine (**1**) and (+)-cermizine D (**3**).

Our retrosynthesis of cernuine (**1**) is outlined in Scheme 1. Construction of a characteristic aminal function in **1**was

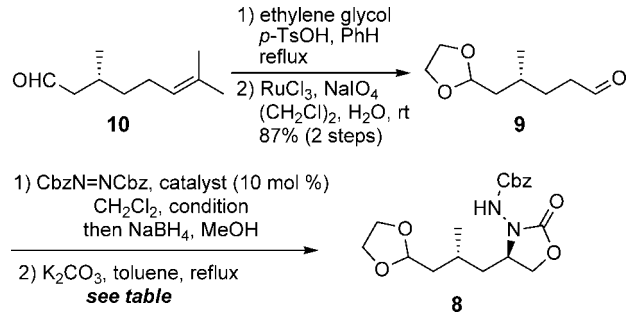
Scheme 1. Retrosynthetic Analysis of Cernuine (**1**)



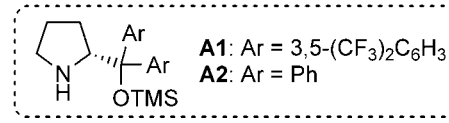
expected by reductive cyclization of aminolactam **4** that would be used as a common intermediate for the synthesis of cermizine D (**3**). Homoallylamine **4** would be derived by stereoselective installation of allyl and amino groups onto aldehyde **5** that could be prepared by Wittig homologation from **6**. The quinolizidine moiety in **6** would be obtained through diastereoselective allylation to aminoacetal **7** followed by RCM reaction. Oxazolidinone **8** could be constructed via organocatalytic α-amination of known aldehyde **9**.

Our synthesis began with the elaboration of oxazolidinone **8** (Table 1). Required aldehyde **9**[6] for organocatalytic

Table 1. Organocatalytic Oxazolidinone Synthesis



entry	catalyst	conditions[a]	% yield[b]	% *de*[c]
1	(*S*)-proline	rt, 1.5 h	94	75
2	**A1**	rt, 5 min	99	75
3	**A2**	rt, 0.5 h	94	84
4	**A2**	0°C, 3 h	82	65



[a] All reactions were carried out with 1.1 equiv of aldehyde and 1 equiv of dibenzyl azodicarboxylate. [b] Isolated yield. [c] The de values were determined by HPLC using CAPCELL PAK C18 MG.

α-amination was provided by (+)-citronellal (**10**) through protection of aldehyde as an acetal function, followed by oxidative cleavage of the residual olefin function.[7] First, we conducted amination of **9** with dibenzyl azodicarboxylate in the presence of a catalytic amount of (*S*)-proline in CH_2Cl_2 at room temperature, followed by in situ reduction. The resultant mixture was treated with K_2CO_3 in toluene to furnish oxazolidinone **8** in 94% yield and 75% de (entry 1). Selectivity could be improved by using catalyst **A2**[8,9] at room temperature (entry 3), while lower temperature decreased the selectivity (entry 4).

Next, reductive N−N bond cleavage in **8** was attempted (Scheme 2). Whereas the direct reduction of **8** with Raney Ni leading to **11** was not effective, we found that sequential reduction involving removal of the Cbz group followed by

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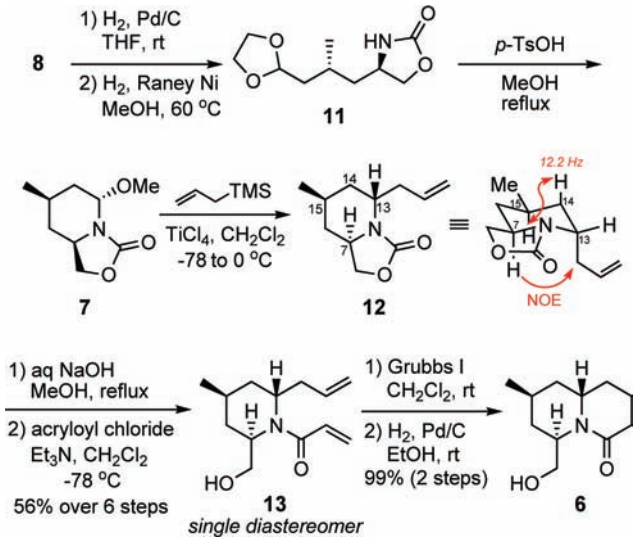
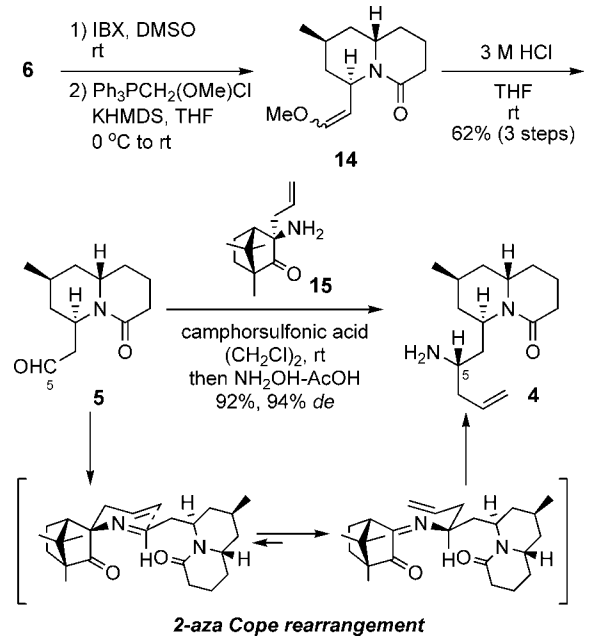
Scheme 2. Practical Synthesis of Key Intermediate **6**



Scheme 3. Synthesis of Homoallylamine **4**



hydrogenation of the resulting hydrazine with Raney Ni gave oxazolidinone **11** efficiently. Upon treatment of **11** with a catalytic amount of *p*-TsOH in refluxing MeOH, cyclization occurred to give aminoacetal **7**.[10] Treatment of aminoacetal **7** with allyltrimethylsilane in the presence of $TiCl_4$[11] gave **12** as the sole isomer at C-13, which would be formed by stereoselective allylation of (axial attack to) the acyliminium intermediate. At this stage, the stereochemistry of product **12** was determined by NOE experiments and the coupling constants of the β-proton on C-14 (ddd, $J = 13.4$, 12.2, 5.9 Hz), which indicated an all-*syn* relationship among the two protons on C-7 and C-15 and the allyl group on C-13. Hydrolysis of oxazolidinone in **12** and subsequent acryloylation of the resultant amine gave acrylamide **13** in 56% yield over six steps as a single diastereomer. The synthesis of quinolizidinone **6** was accomplished in 99% yield by RCM[12] with first-generation Grubbs catalyst, followed by hydrogenation of olefin. It is important to note that only two purification steps were required throughout the conversion of **8** into **6**, which would serve as a key intermediate leading to various quinolizidine alkaloids.

Having developed a practical and multigram scale route to the key intermediate, we focused on the further transformation of **6** into cernuine (**1**) (Scheme 3). After oxidation of the hydroxyl group in **6** with IBX in DMSO, the resulting aldehyde was homologated to **14** by the Wittig reaction with $Ph_3PCH_2(OMe)Cl$ and KHMDS in THF, followed by mild acid hydrolysis to give aldehyde **5** in 62% yield over three steps. Next, the simultaneous installation of an alkyl chain and an amine function onto C-5 in **5** was examined. To our delight, this transformation was stereoselectively accomplished by transfer aminoallylation developed by Kobayashi et al.[13] Thus, using **15** derived from (1*R*)-camphor quinone, homoallylamine **4** was obtained in high yield and good selectivity (92%, 94% de). The stereochemistry of the newly generated chiral center was inferred from the reaction mechanism shown in Scheme 3 and later confirmed by using cyclic compound **18** (vide infra).

With cyclization precursor **4** in hand, we next investigated the construction of an aminal moiety. We had envisioned that reductive cyclization should lead to desired transformation, but exposure of amine **4** to several reductants ($LiAlH_4$, Red-Al, DIBAH, etc.) under various conditions mostly gave over-reduction product **16**. Accordingly, elaboration of **17** via amidine **18** was attempted as follows. Treatment of amine **4** with $TiCl_4$ in refluxing xylene furnished amidine **18**,[14] the stereochemistry of which, particularly of the chiral center at C-5, was assigned by NOE experiment, as shown in Scheme 4. Stereoselective reduction was conducted with $NaBH_4$ in the presence of AcOH to give aminal **17**, which was directly acylated with acryloyl chloride and Et_3N to provide acrylamide **19** in 62% yield (two steps). The stereochemistry at C-9 was confirmed by NOE experiment. This stereoselectivity can be explained by the attack of hydride from the convex face on **18**. Construction of the piperidone ring by RCM with second-generation Grubbs catalyst and subsequent

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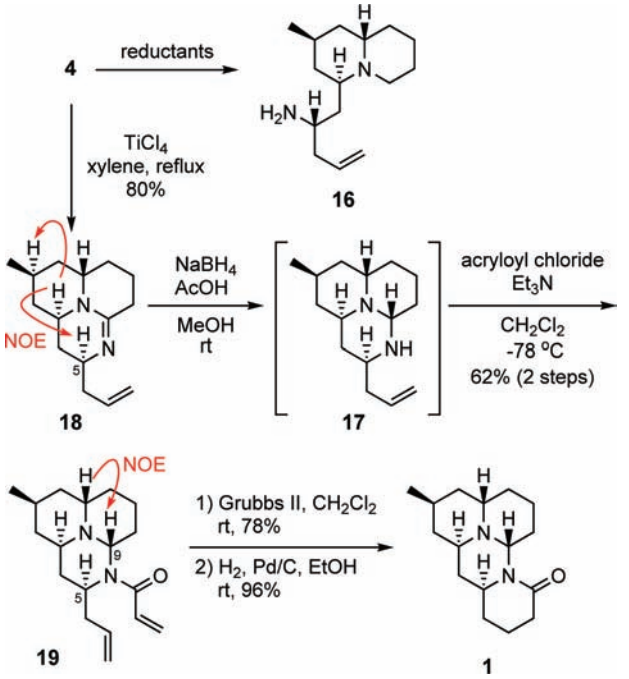
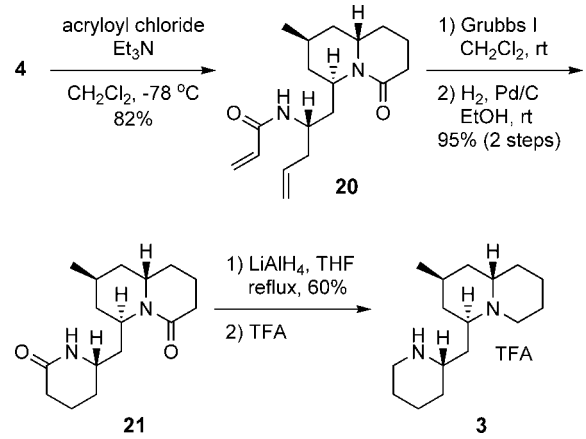
Scheme 4. Completion of Synthesis of Cernuine (**1**)



Scheme 5. Completion of Synthesis of Cermizine D (**3**)



hydrogenation completed the total synthesis of cernuine (**1**) in good yield. Synthetic **1** was identical to the natural product in all respects including optical property: synthetic, $[\alpha]^{25}_D$ −23.2 (*c* 0.46, MeOH); natural, $[\alpha]_D$ −20.5 (*c* 1.0, MeOH).[2c,4] Therefore, the structure including the absolute configuration was confirmed.

Next, we turned our attention toward the synthesis of cermizine D (**3**) from homoallylamine **4**, as shown in Scheme 5. Synthetic intermediate **4** was converted into piperidone **21** by a three-step sequence that included acryloylation, RCM, and hydrogenation (78% in three steps). Reduction of bisamide in **21** with $LiAlH_4$ in THF gave target compound **3** in 60% yield. However, the ^1H NMR data of synthetic **3** were not identical to that of reported data for natural cermizine D,[4] particularly the chemical shifts of protons on the carbons neighboring the nitrogen atom. On the basis of those data and its isolation procedure in literature, we considered that the natural product might be isolated in its protonated form. Indeed, ^1H and ^{13}C NMR data of the TFA salt of synthetic **3** were in agreement with reported data. On the other hand, its optical rotation showed an opposite sign to that of the natural product: synthetic free base, $[\alpha]^{25}_D$ +80.3 (*c* 0.06, MeOH), synthetic TFA salt, $[\alpha]^{20}_D$ +24.2 (*c* 0.50, MeOH); natural, $[\alpha]^{25}_D$ −33 (*c* 0.6, MeOH). The absolute configuration of natural cermizine D remains a question because the counteranion of the natural product has not been reported so far.

In conclusion, we have achieved the first asymmetric total syntheses of (−)-cernuine (**1**) (19 steps, 11.0% overall yield) and (+)-cermizine D (**3**) (18 steps, 13.9% overall yield), starting from known aldehyde **9**. The highlights of the syntheses are (1) organocatalytic α-amination to construct oxazolidinone, which in turn is utilized for diastereoselective allylation; (2) synthesis of homoallylamine by asymmetric transfer aminoallylation; and (3) stereoselective construction of the aminal ring system. The syntheses of other quinolizidine-type alkaloids will be reported in due course.

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Supporting Information Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectral data for **4**−**13**, **18**−**21**, synthetic cernuine (**1**), and (+)-cermizine D (**3**) and its TFA salt. This material is available free of charge via the Internet at http://pubs.acs.org.

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