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A divergent approach for the total syntheses of cernuane-type and quinolizidine-type *Lycopodium* alkaloids

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ABSTRACT

The divergent total syntheses of cernuane-type and quinolizidine-type *Lycopodium* alkaloids are described. A common intermediate **5** for the two types of alkaloids was assembled practically from (+)-citronellal via organocatalytic α-amination, followed by the construction of oxazolidinone that was used for diastereoselective allylation. Key compound **5** was converted into cermizine C (**3**), and this in turn was converted into senepodine G (**4**) by the regioselective Polonovsky–Potier reaction. The total synthesis of representative cernuane-type alkaloids, (−)-cernuine (**1**) as well as (+)-cermizine D (**2**), was also accomplished from **5** by utilizing asymmetric transfer aminoallylation as a key step.

1. Introduction

The genus *Lycopodium* (Lycopodiaceae) has long been studied because it boasts of a number of alkaloids, the so-called *Lycopodium* alkaloids,[1] which have unique structures and biological activities, such as acetylcholine esterase (AchE) inhibitory activity. It is primarily because of this that *Lycopodium* alkaloids have been an attractive target in synthetic organic chemistry[2] and medicinal chemistry. Cernuine (**1**), which was isolated by Marion and Manske in 1948, is a representative of cernuane-type *Lycopodium* alkaloids.[3a] Its structure featuring a fused tetracyclic ring system containing an aminal moiety was elucidated by Ayer et al. in 1967.[3b–e] Although the total syntheses of various types of *Lycopodium* alkaloids have been achieved, that of cernuane-type alkaloids has not been reported to date. In 2004, Kobayashi et al. reported the isolation of cermizine D (**2**), cermizine C (**3**), and senepodine G (**4**), in which cermizine D and senepodine G exhibited cytotoxicity to murine lymphoma L1210 cells with an IC50 of 7.5 μg/mL and 7.8 μg/mL, respectively (Fig. 1).[4] These compounds are new *Lycopodium* alkaloids possessing a quinolizidine skeleton related to cernuine (**1**). As part of our chemical research on *Lycopodium* alkaloids,[5] we attempted to establish an efficient synthetic route to these cernuane-type and quinolizidine-type alkaloids, and our endeavor has enabled us to confirm their structures and absolute configurations. Recently, we completed the first total synthesis of (−)-cernuine (**1**) and (+)-cermizine D (**2**).[5a] In this article, we present the details of the divergent syntheses of (−)-cernuine (**1**) and related *Lycopodium* alkaloids, (+)-cermizine D (**2**), (+)-cermizine C (**3**), and (−)-senepodine G (**4**).

2. Results and discussion

2.1. Retrosynthesis

Our synthetic plan is outlined in Scheme 1. As the target compounds have the same quinolizidine structure, we envisioned that both cernuane-type and quinolizidine-type *Lycopodium* alkaloids could be provided from a key intermediate such as **5**, which has the common quinolizidine core bearing appropriate functional groups for further transformation into the target compounds. Following the divergent strategy, cermizine C (**3**) and senepodine G (**4**) would be

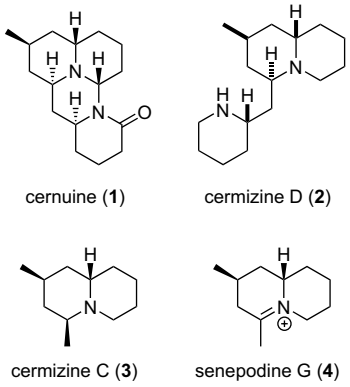

Figure 1. Cernuane-type and quinolizidine-type *Lycopodium* alkaloids isolated from *Lycopodium cernuum*.

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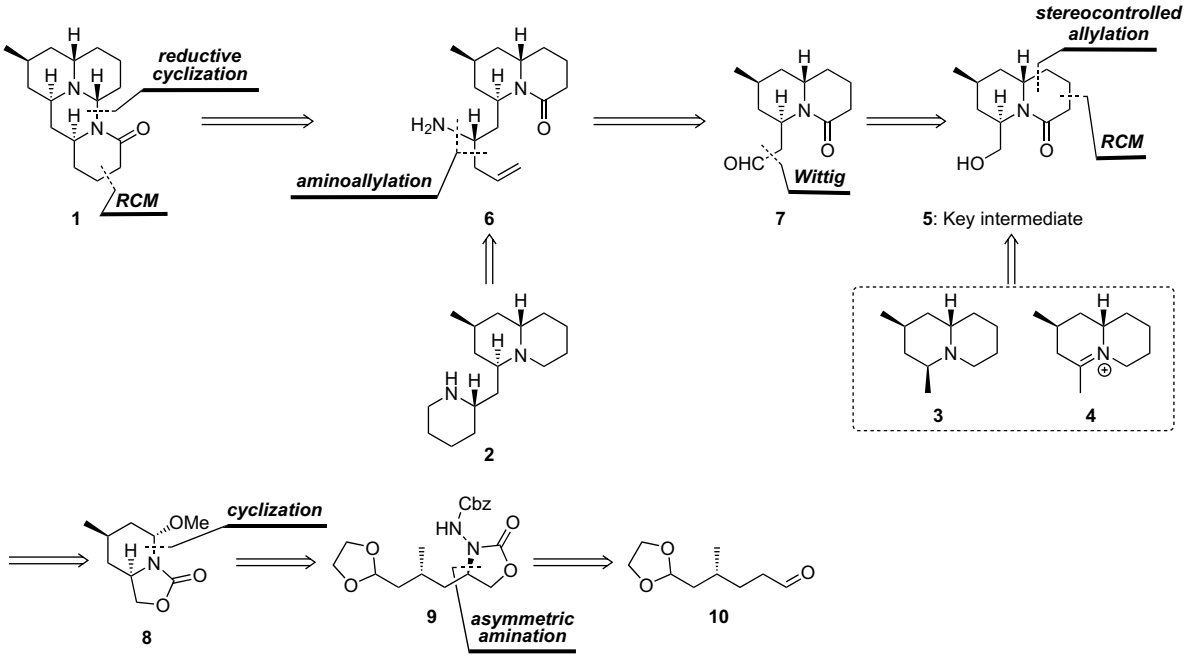
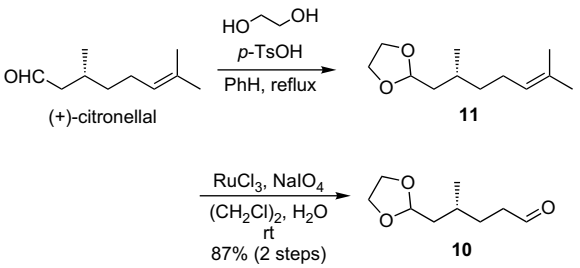


Scheme 1. Divergent strategy for the total syntheses of cernuane-type and quinolizidine-type *Lycopodium* alkaloids.

produced by the reductive removal of oxygen functionalities. On the other hand, the construction of a cyclic system with an aminal moiety in **1** was expected by reductive cyclization of aminolactam **6** that would be used as a common intermediate for the synthesis of cermizine D (**2**). Aminolactam **6** would be derived by stereoselective installation of allyl and amino groups onto aldehyde **7** that could be prepared by Wittig homologation of key intermediate **5**. The quinolizidine core in **5** would be accessible through diastereoselective allylation to aminoacetal **8** utilizing oxazolidinone as the directing group, followed by the RCM reaction. The construction of oxazolidinone in **9**, which would lead to **8** by cyclization, could be performed via organocatalytic α-amination of the known aldehyde **10**.

2.2. Synthesis of key intermediate 5

The preparation of oxazolidinone **9** commenced with the protection of aldehyde in (+)-citronellal with ethylene glycol.[6] The protected citronellal **11** was converted to aldehyde **10** by Ru-catalyzed oxidative cleavage of the olefin function (Scheme 2).[7]



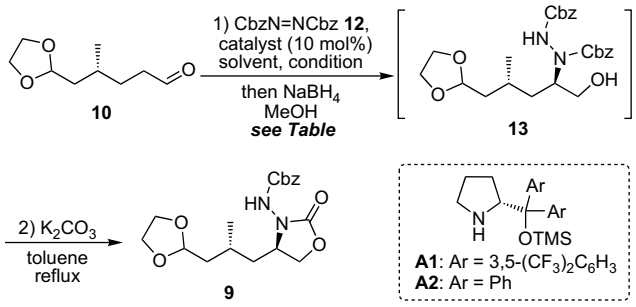
Scheme 2. Synthesis of aldehyde **10**.

At this stage, organocatalytic α-amination was investigated. First, we carried out amination of **10** with dibenzyl azodicarboxylate **12** in the presence of a catalytic amount of (*S*)-proline in CH_2Cl_2 at room temperature followed by in situ reduction to give hydrazinoalcohol **13**.[8] The use of **12** was crucial since subsequent N–N bond cleavage proved troublesome when other azodicarboxylates, such as DEAD and DTAD, were used. Although cyclization of **13** to form **9** was initially conducted by treatment with methanolic NaOH in one pot,[8a] this procedure was not productive (Table 1, entries 1 and 2). It turned out that **13** could be cleanly converted into oxazolidinone **9** under anhydrous conditions using K_2CO_3 in refluxing toluene with good results (94%, 75% de, entry 3). Selectivity could be improved by employing diphenylprolinol silyl ether **A2**[9] as catalyst at room temperature (entry 5), whereas lowering the temperature resulted in a decrease of selectivity (entry 6).

The next task was reductive N–N bond cleavage in hydrazine **9** (Table 2). We had expected that the reduction of **9** would lead to oxazolidinone **15** directly, but the exposure of **9** to Raney Ni in MeOH could not give **15** in satisfactory yield (entry 1).[8b] After examining the conditions (entry 2),[8,10] we found that removal of the Cbz group in advance is important. In fact, after hydrogenation under mild conditions, the reduction of resultant hydrazine **14** with Raney Ni was carried out successfully to furnish oxazolidinone **15** (entry 3).

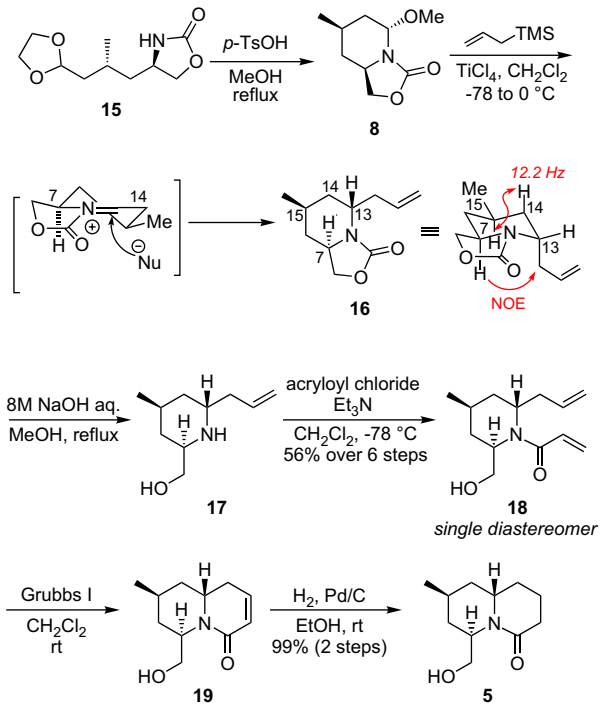
Upon treatment of **15** with a catalytic amount of *p*-TsOH in refluxing MeOH, cyclization involving elimination of ethylene glycol occurred to form aminoacetal **8** as an allylation precursor (Scheme 3).[11] The Hosomi–Sakurai allylation of aminoacetal **8** was conducted by using allyltrimethylsilane with $TiCl_4$ to give the desired **16** exclusively.[12] The stereoselectivity would be interpreted by the axial attack of a nucleophile on the acyliminium intermediate that had a rigid conformation defined by oxazolidinone. The stereochemistry at C-7 and C-13 positions in **16** was unambiguously proved by NOE measurements and the coupling constants of axial proton on C-14 (ddd, *J*=13.4, 12.2, 3.8), 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 the oxazolidinone in **16** afforded amino alcohol **17**, which in turn was directly acylated with acryloyl chloride to give acrylamide **18**. At this stage, the desired diastereomer of **18** was obtained in pure form (56% in six steps) after single chromatographic separation from a concomitant diastereomer derived from the organocatalytic reaction. The

Table 1
Organocatalytic oxazolidinone synthesis



Entry	Catalyst	Solvent	Conditions[a]	% Yield (**9**)[b]	% de[c]
1[d]	(*S*)-Proline	CH_3CN	0 °C, 24 h	53	78
2[d]	(*S*)-Proline	CH_2Cl_2	rt, 1.5 h	74	75
3	(*S*)-Proline	CH_2Cl_2	rt, 1.5 h	94	75
4	**A1**	CH_2Cl_2	rt, 5 min	99	75
5	**A2**	CH_2Cl_2	rt, 0.5 h	94	84
6	**A2**	CH_2Cl_2	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.
[d] Cyclization was performed under aqueous condition in one pot (1 N aqueous NaOH in MeOH at rt).



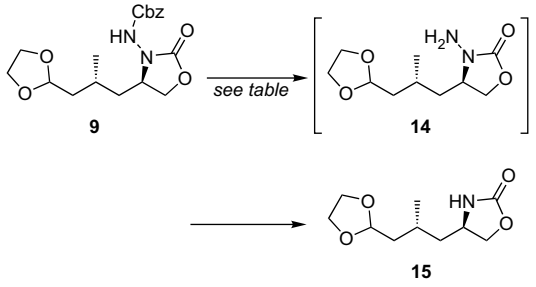
Scheme 3. Practical synthesis of key intermediate **5**.

synthesis of key intermediate **5** was accomplished in 99% yield by RCM with first-generation Grubbs catalyst[13a] followed by hydrogenation of olefin. It is noteworthy that the present procedure for the preparation of **5**, which is a pivotal intermediate in our divergent synthesis, required only two purification steps throughout the eight-step conversion from **9** to **5**.

2.3. Syntheses of (+)-cermizine C and (−)-senepodine G

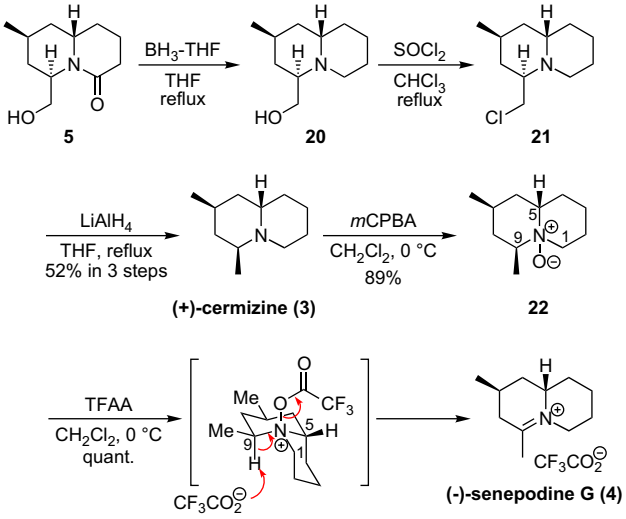
Having developed a practical and large-scale route to key intermediate **5**, we next turned our attention to the further transformation of **5** into quinolizidine-type alkaloids (Scheme 4). After reduction of the amido group with borane, the resulting hydroxyl group of **20** was removed in two steps involving chlorination of **20** with $SOCl_2$ and reductive dehalogenation of chloride **21** with $LiAlH_4$ to yield cermizine C (**3**). As reported in the work of Snider and Grabowski,[2g] the ^1H NMR data of synthetic **3** were not identical to those of the reported data for natural cermizine C. Considering the isolation procedure of the natural product, we elaborated cermizine C as TFA salt while Snider's group leads **3** to its HCl salt. The spectral data of the TFA salt of synthetic **3** were identical with those reported for the natural product including the optical property: synthetic $[\alpha]_D^{17}$ +7.6 (*c* 1.0, MeOH); natural, $[\alpha]_D^{25}$ +4 (*c* 0.8, MeOH), though the $[\alpha]_D$ value is not reliable due to the small value of the optical rotation.[4] Next, we investigated the transformation of cermizine C (**3**) into senepodine G (**4**). We anticipated that cermizine C (**3**) having a *cis*-quinolizidine skeleton would be suitable for the regioselective oxidation to senepodine G (**4**). Because, among the protons on C-1, C-5, and C-9, only the proton (H-9) is situated at *anti*-position to the N–O bond in the *N*-oxide derivative **22** (see the reaction intermediate in Scheme 4). In fact, *N*-oxide **22** obtained by *m*-CPBA oxidation was subjected to the Polonovsky–Potier reaction[14] by treatment with TFAA in CH_2Cl_2 to give regioselectively

Table 2
Investigation of N–N bond cleavage

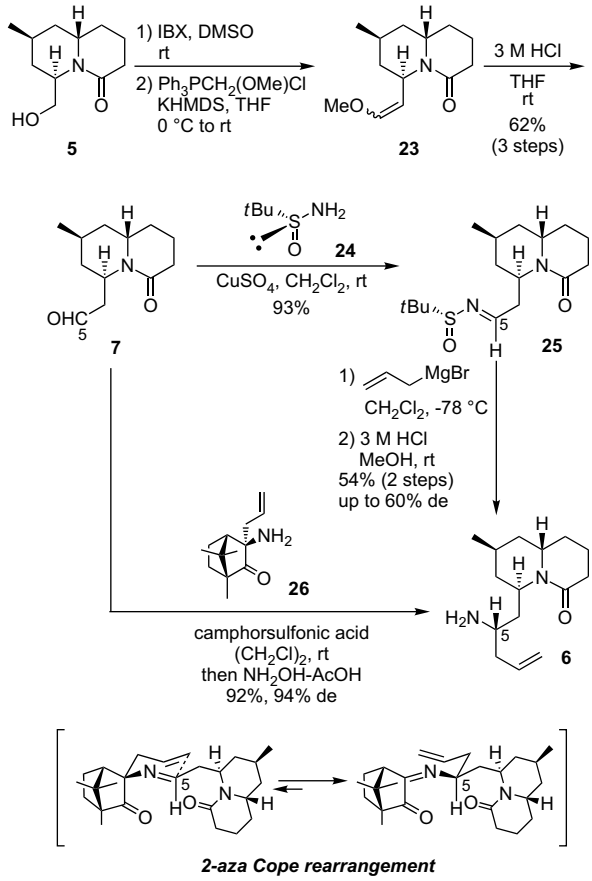


Entry	Conditions	% Yield (**15**)[a]
1	H_2, Raney Ni, MeOH, 60 °C	40
2	H_2, Pd/C, EtOH, rt, then Zn, acetone, AcOH, rt	Decomp.
3	H_2, Pd/C, EtOH, rt, then H_2, Raney Ni, EtOH, rt, 1.5 h	94

[a] Isolated yield.



Scheme 4. Synthesis of (+)-cermizine C (**3**) and (−)-senepodine G (**4**).



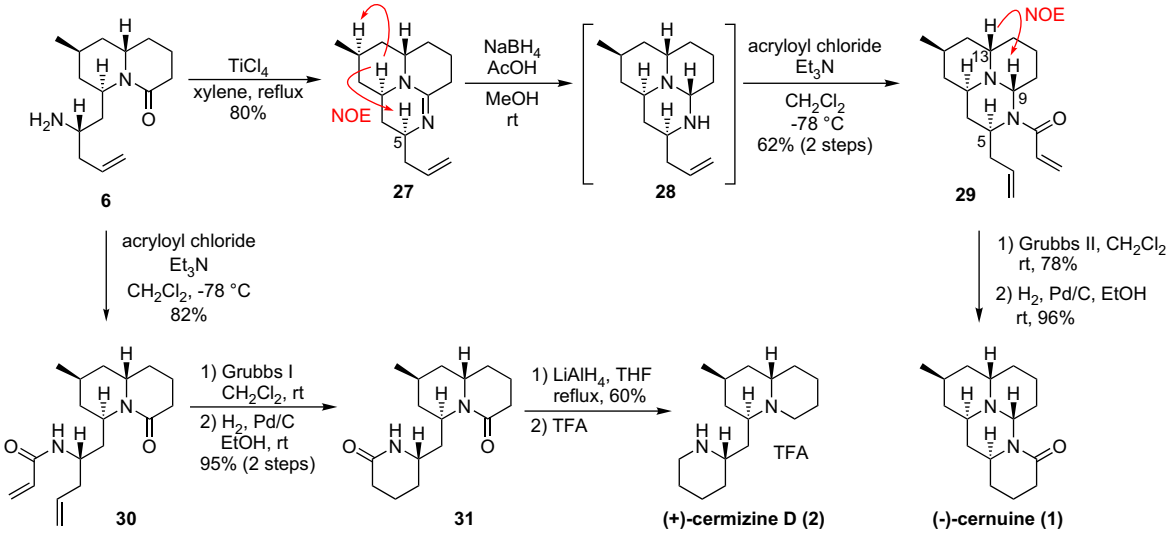
Scheme 5. Stereoselective synthesis of homoallylamine.

senepodine G (**4**), which was identical with the natural senepodine G in all respects.[4]

2.4. Stereoselective synthesis of cernuine (1) and cermizine D (2)

Our next effort on the further transformation of key intermediate **5** into cernuine (**1**) and cermizine D (**2**) is illustrated in Scheme 5. Alcohol **5** was oxidized with IBX in DMSO to give the aldehyde, which in turn was subjected to the Wittig reaction with $Ph_3PCH_2(OMe)Cl$ and KHMDS in THF, followed by mild acid hydrolysis to give carbon-elongated aldehyde **7** in 62% yield over three steps. To install allyl and amino groups onto aldehyde **7**, we initially adopted the Ellman protocol.[15] Condensation of aldehyde **7** and (*R*)-*tert*-butanesulfinamide **24** using $CuSO_4$ afforded sulfinylimine **25**. The addition of allylmagnesium bromide followed by the removal of sulfinyl auxiliary under acidic conditions furnished the desired homoallylamine **6** in good yield (54%, two steps) but with poor stereoselectivity (up to 60% de). After several attempts at the stereoselective synthesis of homoallylamine **6**, we found that transfer aminoallylation developed by Kobayashi et al.[16] gave the best results. Thus, upon treatment of aldehyde **7** with reagent **26** derived from (1*R*)-camphor quinone, condensation, and aza-Cope rearrangement resulted in the simultaneous and highly stereoselective installation of allyl and amine functions onto C-5 in **7** to provide homoallylamine **6** in 92% yield and 94% de. The stereochemistry of the newly generated chiral center was inferred from the reaction mechanism shown in Scheme 5 and later confirmed by using cyclic compound **27** (Scheme 6) (vide infra).

With aminolactam **6** in hand, we focused on the construction of the aminal moiety (Scheme 6). We had envisioned that partial reduction of the amide group in **6** should provide the desired product as seen in the syntheses of pyrrolidinoindolines.[17] However, treatment of aminolactam **6** with any reductant under various conditions gave mostly the over-reduced product. Therefore, to elaborate the aminal ring system, we thought that the cyclization of **6** was necessary prior to reduction. To this end, amine **6** was treated with $TiCl_4$ in refluxing xylene to furnish amidine **27**,[18] whose stereochemistry was confirmed by NOE experiment, as shown in Scheme 5. The conversion into aminal **28** was accomplished by stereoselective reduction with $NaBH_4$ in the presence of AcOH and the obtained aminal **28** was directly acylated with acryloyl chloride and Et_3N to provide acrylamide **29** in 62% yield (two steps). At this stage, the stereochemistry at C-9 was confirmed by NOE experiment in which significant NOE between H-9 and H-13 was observed. This stereoselectivity can be expected by the attack of hydride from the convex face of **27**. Finally, formation of the piperidone ring by RCM with second-generation Grubbs catalyst[13b] and subsequent hydrogenation completed the total synthesis of (−)-cernuine (**1**) in good yield. The spectroscopic data were in agreement with those of the natural product: synthetic, $[\alpha]_D^{25}$ −23.2



Scheme 6. Completion of the total syntheses.

(*c* 0.46, MeOH); natural, $[\alpha]_D$ −20.5 (*c* 1.0, MeOH).[3c] Hence, the structure including the absolute configuration was confirmed. Having succeeded in the synthesis of (−)-cernuine, we next investigated the synthesis of cermizine D (**2**). Synthetic intermediate **6** yielded piperidone **31** via a similar three-step sequence that included acryloylation, RCM, and hydrogenation (78% in three steps). Target compound **2** was obtained by complete reduction of bisamide in **31** with $LiAlH_4$ in THF ($[\alpha]_D^{25}$ +80.3 (*c* 0.06, MeOH)). However, similar to cermizine C, the ^1H NMR data of synthetic **2** were not identical to those reported in the literature,[4] particularly the chemical shifts of protons on the carbon neighboring the nitrogen atom. The ^1H and ^{13}C NMR data of the prepared cermizine D TFA salt were in agreement with the reported data. On the other hand, its optical rotation showed an opposite sign to that of the natural product: synthetic TFA salt, $[\alpha]_D^{20}$ +24.2 (*c* 0.50, MeOH); natural, $[\alpha]_D$ −33 (*c* 0.6, MeOH). We cannot discuss further the absolute configuration of natural cermizine D because the conjugate acid of the natural product is not available in the literature.

3. Conclusion

We have established an efficient synthetic route to cernuane-type and quinolizidine-type *Lycopodium* alkaloids. Key intermediate **5** was successfully prepared from (+)-citronellal over 12 steps involving organocatalytic reaction in a scalable manner. Compound **5** proved to be a valuable intermediate in the total syntheses of four *Lycopodium* alkaloids, (+)-cermizine C (**3**), (−)-senepodine G (**4**), (−)-cernuine (**1**), and (+)-cermizine D (**2**). The fact that the conversion of cermizine C (**3**) into senepodine G (**4**) was enabled by the regioselective Polonovsky–Potier reaction would be helpful in the future synthesis of other related alkaloids under mild conditions.[4,19] The critical stereoselective construction of nitrogen-containing heterocycle could be effected by transfer aminoallylation.

4. Experimental section

4.1. General

IR: recorded on a JASCO FT/IR-230 spectrophotometer. ^1H and ^{13}C NMR spectra: recorded on a JEOL JNM A-400, JNM A-500, JNM ECP-400 or JNM ECP-600 spectrometer, *J* values are given in hertz. EIMS: direct probe insertion at 70 eV recorded on a JEOL JMS GC-mate spectrometer. FABMS: recorded on a JEOL JMS-AX500 or JMS-HX110 mass spectrometer. Optical rotation: measured with a JASCO P-1020 polarimeter. Melting point: measured with a Yanagimoto Micro Melting Point Apparatus 1631A. TLC: precoated Kieselgel 60 F_{254} plates (Merck, 0.25 mm thick). Column chromatography: Kieselgel 60 [Merck, 70–230 mesh (for open chromatography) and 230–400 mesh (for flash chromatography)]. Medium pressure liquid chromatography (MPLC): C.I.G. prepacked column CPS-HS-221-05 (Kusano Kagakukikai, SiO_2). High performance liquid chromatography (HPLC): CAPCELL-PAK C18 MG (SHISEIDO) and Inertsil ODS-2 (GL sciences).

4.2. (*R*)-5-(1,3-Dioxolan-2-yl)-4-methylpentanal (10)

To a stirred solution of 2-((*R*)-2,6-dimethylhept-5-enyl)-1,3-dioxolane (4.00 g, 20.2 mmol, prepared by following literature procedure[20]) and $RuCl_3 \cdot nH_2O$ (146 mg, 0.71 mmol) in $(CH_2Cl)_2$ (100 mL) and H_2O (100 mL) was added in portions $NaIO_4$ (8.60 g, 40.4 mmol) over a period of 5 min at room temperature. After stirring vigorously for 2 h at the same temperature, the reaction was quenched by adding saturated aqueous $NaHCO_3$ and 1 M aqueous $Na_2S_2O_3$ and the two layers were separated. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel chromatography (EtOAc/*n*-hexane=30:70) to give 3.04 g (87% over two steps) of **10** as a colorless oil. $[\alpha]_D^{25}$+3.55 (*c* 1.14, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2953, 2879, 2723, 1720, 1411, 1133, 1032, 945; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 9.78 (1H, t, *J*=1.7 Hz), 4.90 (1H, dd, *J*=5.3, 4.8 Hz), 3.97 (2H, m), 3.84 (2H, m), 2.46 (2H, m), 1.63–1.79 (3H, m), 1.49–1.58 (2H, m), 0.97 (3H, d, *J*=6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 202.6, 103.4, 64.71, 64.65, 41.5, 40.5, 30.0, 28.9, 19.7; FABMS (Gly) *m*/*z*: 173 $[M+H]^+$; HR-FABMS (Gly/PEG): calcd for $C_9H_{17}O_3$ $[M+H]^+$: 173.1178, found: 173.1180.

4.3. Synthesis of hydradine 9 using catalyst A2 (Table 1, entry 5)

To a stirred solution of dibenzyl azodicarboxylate (31.0 mg, 97.7 μmol, 94% purity) and aldehyde **10** (19.8 mg, 115 μmol) in CH_2Cl_2 (0.4 mL) was added (*R*)-2-(diphenyltrimethylsilyloxymethyl)pyrrolidine (**A2**) (20 μL, 10.4 μmol, 0.5 M solution in CH_2Cl_2), and the reaction mixture was stirred at room temperature for 30 min. Then, the mixture was treated with MeOH (0.4 mL) and $NaBH_4$ (4.7 mg, 124 μmol) at 0 °C and stirred at room temperature for 30 min. The reaction was quenched by adding water and the whole mixture was extracted two times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford a crude product that was used for the next reaction without purification. The mixture of the above crude product and K_2CO_3 (43 mg, 0.31 mmol) in toluene was refluxed for 1 h. The reaction mixture was cooled to room temperature and diluted with EtOAc. The mixture was washed with water and then with brine, dried over $MgSO_4$, and evaporated. The crude product was purified by silica gel chromatography (EtOAc/*n*-hexane=1:1) to give 33.4 mg (94% over two steps, 84% de) of **9** as a colorless oil. The de value was determined by HPLC analysis using CAPCELL-PAK C18 MG [55% H_2O, 45% MeOH, flow=0.4 mL/min, *t*R (major)=88.5 min, *t*R (minor)=93.0 min]. $[\alpha]_D^{25}$ −16.1 (*c* 0.95, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 3277, 2957, 1755, 1731, 1455, 1118, 1026, 753, 697; ^1H NMR ($CDCl_3$, 400 MHz, VT50) δ ppm: 7.29–7.38 (5H, m), 6.67 (1H, br s), 5.21 (1H, d, *J*=12.2 Hz), 5.17 (1H, d, *J*=12.4 Hz), 4.85 (1H, t, *J*=5.0 Hz), 4.50 (1H, t, *J*=8.2 Hz), 4.08 (1H, br s), 3.86–3.99 (3H, m), 3.72–3.84 (2H, m), 1.92 (1H, ddd, *J*=13.7, 6.6, 5.0 Hz), 1.80 (1H, sep, *J*=6.5 Hz), 1.50–1.70 (2H, m), 1.39 (1H, dt, *J*=14.3, 7.1 Hz), 0.96 (3H, d, *J*=6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, VT50) δ ppm: 163.1, 143.4, 136.5, 136.3, 136.1, 111.0, 76.2, 76.0, 72.7, 72.6, 63.2, 48.5, 48.0, 34.0, 28.9; FABMS (NBA) *m*/*z*: 365 $[M+H]^+$; HR-FABMS (NBA+KI/PEG): calcd for $C_{18}H_{24}N_2O_6K$ $[M+K]^+$: 403.1271, found: 403.1260.

4.4. (*R*)-4-((*R*)-3-(1,3-Dioxolan-2-yl)-2-methylpropyl)oxazolidin-2-one (15)

A mixture of **9** (5.25 g, 14.4 mmol, 75% de prepared from entry 3 in Table 1) and 10% Pd/C (766 mg) in THF (48 mL) was stirred at room temperature for 3 h under hydrogen atmosphere. The reaction mixture was filtered with Celite and the filtrate was evaporated to give the crude product as a pale yellow oil, which was subjected for the next reaction without purification. To a solution of the above product in MeOH (53 mL) was added Raney Ni W1 (6.1 g, wet weight). The reaction mixture was heated to 60 °C for 7 h under hydrogen atmosphere. The reaction mixture was filtered with Celite and the filtrate was evaporated to give a crude product (3.03 g) of **15** as a pale yellow oil, which was used for the next reaction without purification. For analytical data, the crude product of **15** was purified by silica gel chromatography (EtOAc) to afford **15** as colorless oil (single diastereomer). $[\alpha]_D^{16}$ +21.1 (*c* 0.37, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 3246, 2917, 1742, 1409, 1241, 1112, 1021, 942, 772; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 5.93 (1H, br s), 4.87 (1H, t,

J=4.9 Hz), 4.50 (1H, m), 3.92–4.01 (4H, m), 3.80–3.89 (2H, m), 1.70–1.82 (2H, m), 1.57–1.69 (2H, m), 1.40 (1H, m), 1.00 (3H, d, J=6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 159.6, 103.1, 70.7, 64.8, 64.7, 50.8, 42.8, 40.8, 26.4, 20.3; FABMS (NBA) m/z: 216 $[M+H]^+$; HR-FABMS (NBA/PEG): calcd for $C_{10}H_{18}NO_4$ $[M+H]^+$: 216.1236, found: 216.1237.

4.5. (5*S*,7*R*,8a*R*)-Tetrahydro-5-methoxy-7-methyl-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (8)

To a stirred solution of the above crude product of **15** (3.03 g, ca. 14.1 mmol) in MeOH (53 mL) was added *p*-toluenesulfonic acid monohydrate (254 mg, 1.34 mmol) at room temperature. The mixture was heated to reflux for 2 h under argon atmosphere. The reaction was quenched by adding saturated aqueous $NaHCO_3$ at room temperature. The whole mixture was evaporated to half volume and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to afford a crude product (2.44g) of **8** as a pale yellow oil, which was used for the next reaction without purification. For analytical data, the crude product of **8** was purified by silica gel chromatography (EtOAc/*n*-hexane=30:70) to afford **8** as a colorless oil. $[\alpha]_D^{23}$ −26.0 (c 0.49, $CHCl_3$); IR (neat) ν_{max} cm^{-1}: 2954, 2873, 2831, 1751, 1410, 1271, 1080, 825, 762; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 5.04 (1H, dd, J=3.7, 1.7 Hz), 4.48 (1H, m), 3.90–3.98 (1H, m), 3.90 (1H, t, J=7.6 Hz), 3.33 (3H, s), 1.99 (1H, m), 1.90 (1H, ddt, J=13.6, 3.6, 1.8 Hz), 1.85 (1H, m), 1.24 (1H, ddd, J=13.7, 12.3, 3.8 Hz), 1.02 (1H, q, J=12.0 Hz), 0.96 (3H, d, J=6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 156.9, 80.8, 68.6, 55.3, 50.1, 38.7, 38.0, 24.3, 21.6; EIMS m/z (%): 185 (8, M^+), 154 (bp); HR-EIMS m/z: calcd for $C_9H_{15}NO_3$ $[M]^+$: 185.1052, found: 185.1045.

4.6. (5*S*,7*S*,8a*R*)-5-Allyl-tetrahydro-7-methyl-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (16)

To a stirred solution of the above crude product of **8** (2.44 g, ca. 13.2 mmol) and allyltrimethylsilane (4.2 mL, 26.4 mmol) in CH_2Cl_2 (53 mL) was added $TiCl_4$ (26.3 mL, 26.3 mmol, 1 M solution in CH_2Cl_2) at −78 °C under argon atmosphere. After stirring at the same temperature for 1 h, the mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was cooled in ice bath and then quenched by adding 8 M aqueous NaOH and the basified mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford a crude product (2.48 g) of **16** as a pale yellow oil, which was used for the next reaction without purification. For analytical data, the crude product of **16** was purified by silica gel chromatography (EtOAc/*n*-hexane=1:1) to afford **16** as a colorless oil. $[\alpha]_D^{23}$ +16.9 (c 0.54, $CHCl_3$); IR (neat) ν_{max} cm^{-1}: 3076, 2951, 1743, 1641, 1414, 1273, 1055, 916, 762; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 5.78 (1H, ddt, J=17.0, 10.8, 6.8 Hz, H-11), 5.09 (1H, m, H-17), 5.06 (1H, t, J=1.3 Hz, H-17), 4.38 (1H, t, J=8.2 Hz, H-6), 4.06 (1H, q, J=7.0 Hz, H-13), 3.87 (1H, dd, J=8.3, 5.9 Hz, H-6), 3.79 (1H, m, H-7), 2.40 (1H, m, H-12), 2.26 (1H, m, H-12), 1.73–1.86 (2H, m, H-15 and H-8a), 1.66 (1H, ddt, J=13.6, 3.3, 1.7 Hz, H-14a), 1.26 (1H, ddd, J=13.4, 12.2, 5.9 Hz, H-14b), 0.99 (1H, q, J=12.3 Hz, H-8b), 0.96 (3H, d, J=6.4 Hz, H-16); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 157.0, 134.6, 117.4, 68.1, 50.7, 49.1, 39.1, 35.4, 24.6, 22.0; FABMS (NBA) m/z: 196 $[M+H]^+$; HR-FABMS (NBA/PEG): calcd for $C_{11}H_{18}NO_2$ $[M+H]^+$: 196.1338, found: 196.1338.

4.7. 1-((2*S*,4*S*,6*R*)-2-Allyl-6-(hydroxymethyl)-4-methylpiperidin-1-yl)prop-2-en-1-one (18)

To a stirred solution of the above crude product of **16** (2.48 g, ca. 12.7 mmol) in MeOH (64 mL) was added 8 M aqueous NaOH (32 mL) at room temperature. The mixture was heated to 100 °C for 36 h under argon atmosphere. The reaction mixture was cooled to room temperature and then H_2O (32 mL) was added. The whole mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to afford crude product (2.10 g) as a yellow oil, which was used for the next reaction without purification. To a solution of the above product and Et_3N (1.9 mL, 13.7 mmol) in CH_2Cl_2 (40 mL) was added acryloyl chloride (1.0 mL, 12.3 mmol) at −78 °C under argon atmosphere. After stirring at the same temperature for 3 h, the reaction mixture was quenched by adding MeOH (2.0 mL) and warmed to room temperature. The mixture was treated with H_2O and the whole mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel chromatography (EtOAc/*n*-hexane=1:1) to afford 1.816 g (56% in six steps, single diastereomer) of **18** as a colorless oil. $[\alpha]_D^{23}$ +91 (c 2.6, $CHCl_3$); IR (neat) ν_{max} cm^{-1}: 3386, 3076, 2952, 2870, 1643, 1601, 1454, 1255, 1055, 991; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 6.53 (1H, dd, J=16.8, 10.6 Hz), 6.17 (1H, dd, J=16.8, 1.6 Hz), 5.71 (1H, ddt, J=15.7, 10.0, 7.1 Hz), 5.64 (1H, dd, J=10.6, 1.7 Hz), 5.09 (1H, m), 5.04 (1H, br s), 4.13 (1H, q, J=6.5 Hz), 3.88 (1H, ddd, J=12.6, 5.7, 2.2 Hz), 3.80 (1H, ddd, J=12.5, 8.7, 6.0 Hz), 3.41 (1H, m), 2.55 (1H, dt, J=14.5, 7.4 Hz), 2.33 (1H, dt, J=14.4, 7.2 Hz), 1.93 (1H, m), 1.71 (2H, m), 1.35 (1H, q, J=12.3 Hz), 1.24 (1H, ddd, J=13.7, 12.4, 5.4 Hz), 0.94 (3H, d, J=6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 168.0, 133.9, 130.8, 126.7, 118.0, 64.3, 56.9, 55.7, 37.1, 36.4, 35.3, 25.8, 22.0; EIMS m/z (%): 223 (4, M^+), 192 (30), 182 (bp); HR-EIMS m/z: calcd for $C_{13}H_{21}NO_2$ $[M]^+$: 223.1572, found: 223.1584.

4.8. (6*R*,8*S*,9a*S*)-Hexahydro-6-(hydroxymethyl)-8-methyl-1*H*-quinolizin-4(6*H*)-one (5)

To acrylamide **18** (52 mg, 0.23 mmol) and first-generation Grubbs catalyst (1.9 mg, 2.3 μmol) was added degassed CH_2Cl_2 (3.1 mL) at room temperature under N_2 atmosphere. After stirring for 30 h at the same temperature, the mixture was concentrated under reduced pressure. The residue and 10% Pd/C (12 mg) were suspended in EtOH (1.2 mL) and the mixture was stirred at room temperature for 6 h under H_2 atmosphere. The reaction mixture was filtered with Celite and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 and triphenylphosphine oxide (32 mg, 0.11 mmol)[21] was added, which was stirred at room temperature for 20 h and then evaporated. The obtained residue was purified by silica gel chromatography (MeOH/EtOAc=5:95) to afford 46 mg (99% in two steps) of **5** as a colorless oil. $[\alpha]_D^{22}$ +197 (c 2.10, $CHCl_3$); IR (neat) ν_{max} cm^{-1}: 3356, 2947, 2868, 1614, 1471, 1335, 1186, 1066; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 4.62 (1H, dq, J=11.6, 5.9 Hz), 4.09 (1H, t, J=4.4 Hz), 3.67 (1H, m), 3.64 (2H, dd, J=5.9, 4.6 Hz), 2.43 (1H, dddd, J=18.0, 5.5, 3.8, 1.7 Hz), 2.34 (1H, ddd, J=17.8, 9.8, 6.4 Hz), 1.82–1.93 (2H, m), 1.58–1.81 (4H, m), 1.11–1.23 (3H, m), 1.00 (3H, d, J=6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 173.1, 66.4, 55.0, 47.4, 38.2, 32.3, 31.2, 27.5, 25.8, 21.6, 16.4; EIMS m/z (%): 197 (19, M^+), 167 (78), 166 (bp), 98 (72); HR-EIMS m/z: calcd for $C_{11}H_{19}NO_2$ $[M]^+$: 197.1416, found: 197.1418.

4.9. (2*S*,4*R*,9a*S*)-4-(Chloromethyl)-octahydro-2-methyl-1*H*-quinolizine (21)

To a stirred solution of alcohol **5** (46 mg, 0.23 mmol) in dry THF was added dropwise a BH_3 solution (0.71 mL, 1.0 M in THF, 0.71 mmol) at 0 °C under argon atmosphere. The mixture was heated at 70 °C for 6 h. Aqueous 1 M NaOH solution (1.2 mL) and MeOH (0.38 mL) were added to the mixture at 0 °C, which was then heated at 100 °C for 2 h. The reaction mixture was treated with water and the whole mixture was extracted three times with

CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude product (44 mg) that was used for the next reaction without purification. To a solution of the above crude product (44 mg) in $CHCl_3$ was added thionyl chloride (44 μL, 0.61 mmol) at room temperature and the reaction mixture was warmed to 70 °C for 1 h under argon atmosphere. The reaction mixture was cooled to room temperature and then quenched by adding saturated aqueous Na_2CO_3 and the whole mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to afford crude product (45 mg) as a yellow oil, which was unstable under silica gel chromatography and so used for the next reaction without purification. For analytical data, the crude product of **21** was purified by silica gel chromatography (EtOAc/*n*-hexane=35:65) to afford **21** as a yellow oil. $[\alpha]_D^{22}$ (as TFA salt) +8.80 (*c* 1.01, MeOH); IR (neat) ν_{max} cm^{-1}: 2929, 2870, 1456, 1093, 754; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 3.59–3.67 (2H, m), 3.30 (1H, m), 3.25 (1H, m), 3.12 (1H, dddd, *J*=12.2, 3.2, 3.2, 3.2 Hz), 2.79 (1H, ddd, *J*=15.0, 12.2, 2.8 Hz), 1.70–1.90 (4H, m), 1.40–1.65 (4H, m), 1.12–1.31 (3H, m), 0.92 (3H, d, *J*=6.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 57.6, 52.2, 49.4, 47.2, 39.4, 38.7, 25.59, 25.55, 24.4, 22.2, 18; FABMS (NBA) *m*/*z*: 202 $[M+H]^+$; HR-FABMS (NBA/PEG): calcd for $C_{11}H_{21}NCl$ $[M+H]^+$: 202.1363, found: 202.1375.

4.10. Cermizine C TFA salt (3)

To a solution of the above crude product (45 mg) in dry THF (2.1 mL) was added $LiAlH_4$ (91 mg, 2.4 mmol) at 0 °C under argon atmosphere. The mixture was heated to reflux for 3 h. After dilution with Et_2O and careful addition of water at 0 °C, 1 M aqueous NaOH was added to the mixture. The mixture was stirred overnight at room temperature and then filtered with Celite. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography ($CHCl_3$/MeOH/NH_4OH=90:9:1) to afford cermizine C (**3**) as a pale yellow oil. To a solution of the cermizine C (**3**) in MeOH (0.5 mL) was added TFA (five drops, excess). The mixture was concentrated under reduced pressure to afford 33 mg (52% in three steps) of TFA salt of **3** as a yellow oil. The spectral data were identical with those reported for the natural product: $[\alpha]_D^{17}$ +7.64 (*c* 1.00, MeOH); IR (ATR) ν_{max} cm^{-1}: 2957, 1668, 1457, 1133, 796; ^1H NMR (CD_3OD, 600 MHz) δ ppm: 3.82 (1H, m), 3.65 (1H, dddd, *J*=13.6, 3.8, 1.9, 1.9 Hz), 3.59 (1H, br d, *J*=12.9 Hz), 3.08 (1H, ddd, *J*=13.6, 13.6, 3.2 Hz), 2.17 (1H, m), 1.91–2.02 (3H, m), 1.76–1.84 (2H, m), 1.69 (1H, m), 1.60–1.68 (2H, m), 1.55 (1H, ddd, *J*=14.4, 12.4, 5.3 Hz), 1.31 (3H, d, *J*=6.3 Hz), 1.19 (1H, ddd, *J*=14.7, 12.5, 12.5 Hz), 0.95 (3H, d, *J*=6.3 Hz); ^{13}C NMR (CD_3OD, 150 MHz) δ ppm: 61.5, 51.2, 50.0, 41.9, 38.5, 25.4, 24.6, 23.8, 21.6, 18.4, 17.7; EIMS *m*/*z* (%): 167 ($[M]^+$, 12), 166 (8), 152 (bp); HR-EIMS *m*/*z*: calcd for $C_{11}H_{19}NO_2$ $[M]^+$: 167.1674, found: 167.1673.

4.11. Cermizine C *N*-oxide (22)

To a stirred solution of cermizine C (**3**) TFA salt (20 mg, 71 μmol) in CH_2Cl_2 (0.5 mL) were added K_2CO_3 (29 mg, 0.21 mmol) and *m*-CPBA (24 mg, 0.11 mmol, 77% in H_2O) at 0 °C. After stirring for 1.5 h at the same temperature, the mixture was filtered through a short pad of silica gel. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (MeOH/$CHCl_3$=5:95 to MeOH/$CHCl_3$/NH_4OH=9/90/1) to afford 9.3 mg (71%) of **22** as a yellow oil. $[\alpha]_D^{25}$ −1.97 (*c* 0.375, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 3379, 2949, 2918, 2870, 1451, 1373, 979, 923; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 3.74 (1H, br d, *J*=13.2 Hz), 3.63 (1H, m), 3.36 (1H, br d, *J*=13.2 Hz), 3.07 (1H, ddd, *J*=13.6, 13.6, 3.2 Hz), 2.49 (1H, ddd, *J*=13.2, 13.2, 5.1 Hz), 2.05 (1H, m), 1.96 (1H, q, *J*=12.6 Hz), 1.87 (1H, m), 1.64–1.83 (3H, m), 1.62 (1H, m), 1.57 (1H, ddd, *J*=12.6, 4.4, 4.4 Hz), 1.41 (1H, br d, *J*=13.4 Hz), 1.31 (1H, br d, *J*=13.7 Hz), 1.24 (3H, d, *J*=6.4 Hz), 0.94 (3H, d, *J*=6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 73.8, 65.5, 57.7, 36.8, 33.6, 27.5, 24.7, 23.2, 22.8, 21.3, 13.9; FABMS (NBA) *m*/*z*: 184 $[M+H]^+$; HR-FABMS (NBA/PEG): calcd for $C_{11}H_{22}NO$ $[M+H]^+$: 184.1701, found: 184.1713.

4.12. Senepodine G (4)

To a stirred solution of cermizine C *N*-oxide (**22**) (9.3 mg, 51 μmol) in CH_2Cl_2 (0.85 mL) was added TFAA (35 μL, 0.25 mmol) at 0 °C. After stirring for 4 h at the same temperature, the solvent was evaporated. The obtained residue was dissolved in CH_2Cl_2 (0.85 mL) and TFAA was added at 0 °C again. After stirring for 4 h at the same temperature, the reaction mixture was concentrated under reduced pressure to afford 18 mg (quant.) of **4** as a yellow oil. $[\alpha]_D^{19}$ −23.0 (*c* 0.66, MeOH); IR (ATR) ν_{max} cm^{-1}: 3840, 2938, 2877, 1668, 1448, 1174, 1130, 799; ^1H NMR (CD_3OD, 600 MHz) δ ppm: 4.51 (1H, br d, *J*=12.9 Hz), 3.96 (1H, br s), 3.53 (1H, br t, *J*=13.1 Hz), 3.00 (1H, dd, *J*=4.7, 1.9 Hz), 2.46 (1H, m), 2.45 (3H, s), 1.98–2.08 (2H, m), 1.84–1.98 (4H, m), 1.83 (1H, m), 1.79 (1H, m), 1.76 (1H, m), 1.05 (3H, d, *J*=6.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ ppm: 187.1, 64.8, 56.0, 43.7, 35.5, 34.7, 27.5, 24.6, 23.6, 21.9, 20.3; FABMS (NBA) *m*/*z*: 166 $[M]^+$; HR-FABMS (NBA/PEG): calcd for $C_{11}H_{20}N$ $[M]^+$: 166.1596, found: 166.1590.

4.13. 2-((2*S*,4*R*,9a*S*)-Octahydro-2-methyl-6-oxo-1*H*-quinolizin-4-yl)acetaldehyde (7)

To a stirred solution of alcohol **5** (2.00 g, 10.1 mmol) in DMSO (30 mL) was added *o*-iodoxybenzoic acid (IBX) at room temperature. After stirring at the same temperature for 1 h under argon atmosphere, H_2O (30 mL) was carefully added to precipitate a white solid, which was removed by filtration. The filtrate was extracted three times with EtOAc. The combined organic layers were washed two times with a mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure to afford a crude product (1.89 g) as a yellow oil, which was used in the next reaction without purification. To a suspension of methoxymethyltriphenylphosphonium chloride (6.95 g, 20.3 mmol) in THF (25 mL) was added KHMDS (27 mL, 20.3 mmol, 15% solution in toluene) at 0 °C under argon atmosphere. After stirring at the same temperature for 0.5 h, the solution of the above crude product (1.89 g) in THF (9 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 1 h. It was quenched by adding propionaldehyde (1.5 mL, 20.3 mmol). After stirring for 0.5 h at room temperature, saturated aqueous NH_4Cl was added. The whole mixture was extracted three times with EtOAc and the combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel chromatography (EtOAc) to obtain a mixture of *E*/*Z* isomers of **23** and triphenylphosphine oxide, which was difficult to separate. To a solution of the mixture in THF (65 mL) was added 3 M aqueous HCl (13 mL) at 0 °C under argon atmosphere. After stirring at room temperature for 2 h, the reaction mixture was neutralized with saturated aqueous Na_2CO_3. The whole mixture was extracted three times with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel chromatography (EtOAc/$CHCl_3$=1:1) to afford 1.32 g (62% in three steps) of **7** as a pale yellow oil: $[\alpha]_D^{17}$ +162 (*c* 0.90, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2948, 2870, 1717, 1624, 1460, 1416, 749; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 9.72 (1H, dd, *J*=3.3, 2.0 Hz), 4.83 (1H, dq, *J*=9.8, 6.8 Hz), 3.61 (1H, m), 2.63 (1H, ddd, *J*=15.3, 7.1, 3.2 Hz), 2.53 (1H, ddd, *J*=15.2, 6.2, 2.1 Hz), 2.33 (1H, dddd, *J*=17.5, 5.1, 5.1, 1.5 Hz), 2.24 (1H, ddd, *J*=17.5, 9.5, 5.9 Hz) 1.65–1.95 (6H, m), 1.59 (1H, m), 1.20–1.32 (2H, m), 0.98 (3H, d, *J*=6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 200.5, 170.1, 48.5, 47.3, 46.9, 38.6, 35.0, 32.6, 28.1, 26.0, 21.4, 17.0; EIMS *m*/*z* (%): 209 ($[M]^+$, 14), 180 (16), 166

(bp); HR-EIMS *m*/*z*: calcd for $C_{11}H_{19}NO_2$ $[M]^+$: 209.1416, found: 209.1414.

4.14. Sulfinyl aldimine (25)

To a stirred solution of aldehyde (**7**) (55 mg, 0.26 mmol) in dry CH_2Cl_2 (0.9 mL) were added (*R*)-*tert*-butylsulfinamide (35 mg, 0.29 mmol) and anhydrous $CuSO_4$ (84 mg, 0.53 mmol) successively at room temperature. After stirring for 24 h at the same temperature, the reaction mixture was filtered through a pad of Celite and the filter cake was washed with CH_2Cl_2. The filtrate was evaporated and the obtained residue was purified by silica gel chromatography (EtOAc/$CHCl_3$=1:1) to afford 76 mg (93%) of **25** as a pale yellow oil. $[\alpha]_D^{24}$ −53 (*c* 0.28, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 3450, 2950, 2870, 1615, 1459, 1416, 1080, 681; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 8.05 (1H, t, *J*=5.1 Hz), 4.78 (1H, m), 3.61 (1H, m), 2.83 (1H, dt, *J*=14.9, 5.2 Hz), 2.76 (1H, ddd, *J*=14.8, 7.7, 5.3 Hz), 2.37 (1H, dtd, *J*=17.5, 5.2, 1.3 Hz), 2.29 (1H, ddd, *J*=17.5, 9.4, 5.9 Hz), 1.54–1.95 (8H, m), 1.20–1.32 (1H, m), 1.20 (9H, s), 1.00 (3H, d, *J*=6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 170.0, 166.9, 56.7, 48.8, 47.7, 40.3, 38.6, 34.6, 32.7, 28.2, 26.0, 22.4, 21.5, 17.1; FABMS (NBA) *m*/*z*: 313 $[M+H]^+$; HR-FABMS (NBA/PEG): calcd for $C_{16}H_{29}N_2O_2S$ $[M+H]^+$: 313.1950, found: 313.1953.

4.15. (6*R*,8*S*,9a*S*)-6-((*S*)-2-Aminopent-4-enyl)-hexahydro-8-methyl-1*H*-quinolizin-4(6*H*)-one (6)

To a stirred solution of aldehyde **7** (325 mg, 1.55 mmol) and (1*R*,3*R*,4*S*)-3-allyl-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**26**) (354 mg, 1.71 mmol, prepared according to literature procedure[13]) in $(CH_2Cl)_2$ (3.9 mL) was added camphorsulfonic acid (36 mg, 0.155 mmol) at room temperature. After stirring at the same temperature for 24 h under argon atmosphere, a 0.5 M solution of NH_2OH/AcOH (6.2 mL, 3.1 mmol) in MeOH was added and the reaction mixture was warmed at 50 °C for 2.5 h. The mixture was acidified with 1 M aqueous HCl (pH ca. 1) and then washed two times with CH_2Cl_2. The combined organic layers were extracted two times with 1 M aqueous HCl. The combined aqueous layers were basified with 8 M aqueous NaOH (pH ca. 10) and then extracted four times with CH_2Cl_2. The latter CH_2Cl_2 layers were dried over Na_2SO_4 and evaporated. The crude product was purified by silica gel chromatography ($CHCl_3$/MeOH/NH_4OH=90:9:1) to afford 357 mg (92%, 94% de) of **6** as a yellow oil. The de value as a benzoylated product was determined by HPLC analysis using Inertsil ODS-2 [40% H_2O/60% MeOH, flow=0.5 mL/min, *t*R (major)=39.0 min, t_R (minor)=31.0 min]. $[\alpha]_D^{23}$ +128 (*c* 1.41, $CHCl_3$); IR (neat) ν_{max} cm^{-1}: 3234, 3076, 3008, 2841, 1618, 752; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 5.78 (1H, m), 5.08 (2H, d, *J*=13.5 Hz), 4.66 (1H, quin, *J*=7.5 Hz), 3.61 (1H, m), 2.82 (1H, tt, *J*=8.5, 4.3 Hz), 2.36 (1H, dt, *J*=17.6, 4.9 Hz), 2.22–2.32 (2H, m), 2.03 (1H, dt, *J*=14.6, 7.3 Hz), 1.56–1.93 (8H, m), 1.50 (1H, ddd, *J*=13.2, 7.9, 4.9 Hz), 1.10–1.24 (2H, m), 0.99 (3H, d, *J*=7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 169.5, 135.7, 117.4, 48.5, 48.4, 46.9, 43.5, 41.6, 38.9, 35.1, 32.7, 28.1, 26.0, 21.3, 17.1; FABMS (NBA) *m*/*z*: 251 $[M+H]^+$; HR-FABMS (NBA/PEG): calcd for $C_{15}H_{27}N_2O$ $[M+H]^+$: 251.2123, found: 251.2125.

4.16. (2*S*,3a*R*,5*S*,6a*S*)-2-Allyl-2,3,3a,4,5,6,6a,7,8,9-decahydro-5-methylpyrimido[6,1,2-*de*]quinolizine (27)

To a stirred solution of homoallylamine **6** (250 mg, 1.00 mmol) in xylene (16 mL) was added $TiCl_4$ (2.0 mL, 2.0 mmol, 1.0 M solution in toluene) at room temperature. The reaction mixture was heated at 150 °C for 1 h under argon atmosphere. It was then cooled to 0 °C and quenched by adding a methanolic solution (14 mL) of NaOH (400 mg). Filtration, washing of the residue with $CHCl_3$, and purification by silica gel chromatography ($CHCl_3$/MeOH/NH_4OH=70:27:3) gave 186 mg (80%) of **27** as a brown oil. $[\alpha]_D^{18}$ +20.3 (*c* 1.11, $CHCl_3$); IR (neat) ν_{max} cm^{-1}: 3070, 2925, 2856, 1600, 1411, 1310, 1086, 906, 746; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 5.85 (1H, ddt, *J*=17.2, 10.1, 7.1 Hz, H-3), 5.07 (1H, d, *J*=17.3 Hz, H-17), 5.02 (1H, d, *J*=10.1 Hz, H-17), 3.47 (1H, m, H-7), 3.41 (1H, tt, *J*=11.7, 2.7 Hz, H-13), 3.31 (1H, m, H-5), 2.59 (2H, m), 2.48 (1H, m, H-4), 2.13 (1H, dt, *J*=13.9, 8.2 Hz), 1.98 (1H, m, H-15), 1.82–1.90 (2H, m), 1.70–1.82 (3H, m), 1.64 (1H, m), 1.30–1.40 (2H, m), 1.24 (1H, br q, *J*=12.5 Hz, H-14b), 1.13 (1H, q, *J*=11.8 Hz, H-8b), 0.98 (3H, d, *J*=6.8 Hz, H-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 156.6, 135.5, 116.9, 51.6, 51.5, 49.3, 41.2, 37.5, 36.9, 34.1, 30.9, 30.5, 24.3, 22.4, 19.5; EIMS *m*/*z* (%): 232 (39, M^+), 191 (bp), 91 (42); HR-EIMS *m*/*z*: calcd for $C_{15}H_{24}N_2$ $[M]^+$: 232.1939, found: 232.1932.

4.17. 1-((2*S*,3a*R*,5*S*,6a*S*,9a*S*)-2-Allyl-decahydro-5-methylpyrimido[6,1,2-*de*]quinolizin-1(2*H*)-yl)prop-2-en-1-one (29)

To a stirred solution of amidine **27** (12 mg, 52 μmol) in EtOH (0.8 mL) was added AcOH (3.0 μL, 52 μmol) at room temperature under argon atmosphere. After cooling in an ice bath, $NaBH_4$ (3.9 mg, 104 μmol) was added and the reaction mixture was stirred at room temperature for 1 h. H_2O was added to the reaction mixture and the whole mixture was diluted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated. To a solution of the residue and Et_3N (14 μL, 104 μmol) in CH_2Cl_2 (0.8 mL) was added acryloyl chloride (103 μL, 52 μmol, 0.5 M solution in CH_2Cl_2) at −78 °C under argon atmosphere. After stirring at the same temperature for 3 h, the reaction mixture was quenched by adding MeOH (0.4 mL) and warmed to room temperature. The mixture was treated with H_2O and the whole mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (MeOH/$CHCl_3$=5:95) to afford 9.2 mg (62% in two steps) of **29** as a colorless oil. $[\alpha]_D^{23}$ −100 (*c* 0.86, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 3075, 2924, 2866, 1643, 1606, 1421, 1142, 975, 912, 795; ^1H NMR ($CDCl_3$, 400 MHz, VT50) δ ppm: 6.51 (1H, dd, *J*=16.7, 10.4 Hz), 6.29 (1H, dd, *J*=16.8, 2.2 Hz), 5.76 (1H, m), 5.61 (1H, dd, *J*=10.4, 2.1 Hz), 5.02–5.10 (2H, m), 4.77 (1H, br s, H-9), 3.88 (1H, dq, *J*=9.1, 4.6 Hz), 3.19 (1H, m), 3.09 (1H, m, H-13), 2.78 (1H, dt, *J*=14.0, 8.7 Hz, H-4), 2.57–2.62 (1H, m, H-4), 1.82–1.99 (3H, m), 1.56–1.74 (6H, m), 1.48 (1H, dt, *J*=4.2, 2.1 Hz), 1.41 (1H, td, *J*=12.6, 5.3 Hz), 1.11 (1H, q, *J*=11.9 Hz), 1.01 (1H, br d, *J*=12.4 Hz), 0.88 (3H, d, *J*=6.3 Hz, H-16); ^{13}C NMR ($CDCl_3$, 100 MHz, VT50) δ ppm: 165.6, 135.8, 129.0, 126.9, 117.1, 72.9, 58.1, 51.2, 44.4, 44.2, 41.1, 39.1, 30.9, 26.9, 24.3, 23.2, 22.2, 21.2; EIMS *m*/*z* (%): 288 (50, M^+), 273 (16), 259 (78), 245 (bp); HR-EIMS *m*/*z*: calcd for $C_{18}H_{28}N_2O$ $[M]^+$: 288.2201, found: 288.2201.

4.18. Dehydrocernuine (S1)

To aminal **29** (20 mg, 69 μmol) and second-generation Grubbs catalyst (2.9 mg, 3.4 μmol) was added degassed CH_2Cl_2 (3.1 mL) at room temperature under N_2 atmosphere. After 12 h and 18 h, the mixture was treated twice with an additional amount of second-generation Grubbs catalyst (2.9 mg, 3.4 μmol). After 24 h, triphenylphosphine oxide (142 mg, 0.51 mmol)[21] was added and the reaction mixture was stirred at room temperature for 12 h and then evaporated. The obtained residue was purified by MPLC (MeOH/$CHCl_3$=5:95) twice to yield 14 mg (78%) of **S1** as transparent needles still contaminated with a minuscule amount of the ruthenium catalyst. $[\alpha]_D^{16}$ −45 (*c* 0.59, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2920, 2859, 1664, 1612, 1419, 1097, 824, 790; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 6.46 (1H, ddd, *J*=9.8, 6.0, 2.6 Hz), 5.88 (1H, dd, *J*=9.8, 2.9 Hz), 5.29 (1H, dd, *J*=11.5, 2.7 Hz), 3.70 (1H, tdd, *J*=12.0, 5.7, 3.7 Hz), 3.16 (1H, m), 3.11 (1H, tt, *J*=11.1, 2.6 Hz), 2.40 (1H, dt, *J*=17.9, 5.9 Hz), 2.22 (1H, ddt, *J*=17.9, 12.4, 2.8 Hz), 1.69–1.92 (6H,

m), 1.66 (1H, m), 1.55 (1H, dt, J=4.0, 2.0 Hz), 1.48 (1H, dd, J=12.6, 5.0 Hz), 1.31–1.42 (2H, m), 1.07 (1H, br d, J=11.7 Hz), 0.89 (3H, d, J=6.3 Hz), 0.88 (1H, q, J=12.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 163.8, 137.8, 125.1, 68.6, 57.6, 48.4, 45.4, 42.1, 41.0, 39.3, 31.2, 25.2, 24.4, 22.5, 22.3, 18.9; EIMS m/z (%): 260 (88, M^+), 231 (94, M^+), 218 (bp); mp: 145–146 °C; HR-EIMS m/z: calcd for $C_{16}H_{24}N_2O$ $[M]^+$: 260.1889, found: 260.1889.

4.19. Cernuine (1)

A mixture of **S1** (11 mg, 42 μmol) and 10% Pd/C (6.0 mg) in EtOH was stirred at room temperature for 2 h under H_2 atmosphere. The reaction mixture was filtered with Celite and the filtrate was evaporated. The residue was purified by silica gel chromatography (MeOH/EtOAc=5:95) to afford 11 mg (96%) of **1** as a white solid. $[\alpha]_D^{20}$ −23 (c 0.46, MeOH); IR (ATR) ν_{max} cm^{-1}: 2918, 2861, 1635, 1435, 1416, 1227, 854; ^{1}H NMR (CD_3OD, 600 MHz) δ ppm: 5.44 (1H, dd, J=12.2, 3.2 Hz), 3.64 (1H, m), 3.24 (1H, tt, J=11.2, 2.9 Hz), 3.08 (1H, ddt, J=12.4, 5.1, 2.6 Hz), 2.31–2.39 (2H, m), 2.12 (1H, qd, J=12.7, 4.1 Hz), 2.02 (1H, m), 1.95 (1H, m), 1.89 (1H, qd, J=13.1, 4.0 Hz), 1.75–1.86 (2H, m), 1.73 (1H, dt, J=13.0, 3.0 Hz), 1.61–1.70 (3H, m), 1.58 (1H, ddt, J=13.3, 3.8, 1.9 Hz), 1.49 (1H, tdd, J=12.8, 9.6, 3.0 Hz), 1.40 (1H, td, J=12.9, 5.2 Hz), 1.20 (1H, q, J=12.1 Hz), 1.12 (1H, br d, J=13.5 Hz), 0.89 (3H, d, J=6.6 Hz), 0.81 (1H, q, J=12.1 Hz); ^{13}C NMR (CD_3OD, 150 MHz) δ ppm: 171.1, 68.7, 59.2, 52.1, 47.6, 42.5, 41.7, 40.0, 33.7, 31.2, 26.3, 25.6, 23.5, 22.5, 21.5, 19.9; EIMS m/z (%): 262 (57, M^+), 233 (93, M^+), 220 (bp); mp: 104–106 °C; HR-EIMS m/z: calcd for $C_{16}H_{26}N_2O$ $[M]^+$: 260.2045, found: 260.2052. The spectral data were identical to those of the natural product.[3c,4]

4.20. *N*-((*S*)-1-((2*S*,4*R*,9a*S*)-Octahydro-2-methyl-6-oxo-1*H*-quinolizin-4-yl)pent-4-en-2-yl)acrylamide (30)

To a solution of amine **6** (50 mg, 0.20 mmol) and Et_3N (55 μL, 0.40 mmol) in CH_2Cl_2 (2.0 mL) was added acryloyl chloride (20 μL, 0.25 mmol) at −78 °C under argon atmosphere. After stirring at the same temperature for 2 h, the reaction mixture was quenched by adding MeOH (0.4 mL) and warmed to room temperature. The mixture was treated with H_2O and the whole mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (MeOH/EtOAc=5:95) to afford 50 mg (82%) of **30** as pale yellow oil. $[\alpha]_D^{23}$ +77.9 (c 2.50, $CHCl_3$); IR (neat) ν_{max} cm^{-1}: 3275, 3076, 2954, 1666, 1614, 754; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.01 (1H, br d, J=8.2 Hz), 6.29 (1H, dd, J=17.0, 1.8 Hz), 6.19 (1H, dd, J=17.1, 10.0 Hz, H-2), 5.76 (1H, m, H-3), 5.61 (1H, dd, J=10.1, 1.8 Hz, H-17), 5.01–5.06 (2H, m, H-18), 4.25 (1H, m), 4.02 (1H, m), 3.63 (1H, m), 2.17–2.42 (4H, m, H-10 and H-4), 1.56–1.94 (9H, m), 1.13–1.27 (2H, m), 0.98 (3H, d, J=6.8 Hz, H-16); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 170.2, 165.7, 134.6, 131.5, 125.6, 117.5, 49.1, 47.5, 46.8, 39.7, 38.7, 38.0, 34.9, 32.8, 28.1, 25.9, 21.5, 17.0 (C-16); FABMS (NBA) m/z: 305 $[M+H]^+$; HR-FABMS (NBA/PEG): calcd for $C_{18}H_{29}N_2O_2$ $[M+H]^+$: 305.2229, found: 305.2224.

4.21. (6*R*,8*S*,9a*S*)-Hexahydro-8-methyl-6-(((*S*)-6-oxopiperidin-2-yl)methyl)-1*H*-quinolizin-4(6*H*)-one (31)

To acrylamide **30** (45 mg, 0.15 mmol) and first-generation Grubbs catalyst (3.6 mg, 4.4 μmol) was added degassed CH_2Cl_2 (3.0 mL) at room temperature under N_2 atmosphere. After stirring for 7 h at the same temperature, an additional amount of first-generation Grubbs catalyst (3.6 mg, 4.4 μmol) was added to the mixture. After further stirring for 9 h, the reaction mixture was concentrated under reduced pressure. The residue and 10% Pd/C (22 mg) were suspended in EtOH (1.5 mL) and the mixture was stirred at room temperature for 3 h under H_2 atmosphere. The reaction mixture was filtered with Celite and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 and triphenylphosphine oxide (122 mg, 0.22 mmol)[21] was added, which was stirred at room temperature for 15 h and then evaporated. The obtained residue was purified by silica gel chromatography (MeOH/$CHCl_3$=10:90) to afford 39 mg (95% in two steps) of **31** as a colorless oil. $[\alpha]_D^{23}$ +53.3 (c 1.96, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2947, 2871, 1655, 1614, 1462, 1416, 1330, 1173, 745; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 6.36 (1H, br s, –N*H*–), 4.59 (1H, qd, J=7.9, 4.9 Hz), 3.60 (1H, dddd, J=10.6, 5.7, 5.7, 3.7 Hz), 3.39 (1H, m), 2.25–2.42 (3H, m), 2.25 (1H, ddd, J=17.6, 10.7, 6.6 Hz), 2.09 (1H, m), 1.75–1.95 (5H, m), 1.58–1.75 (5H, m), 1.56 (1H, ddd, J=14.0, 6.1, 5.0 Hz), 1.35 (1H, m), 1.12–1.26 (2H, m), 1.00 (3H, d, J=6.8 Hz, H-16); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 172.0, 170.2, 51.4, 47.9, 46.8, 42.8, 38.6, 36.1, 32.5, 31.2, 28.9, 28.0, 25.9, 21.2, 16.9 (C-16); EIMS m/z (%): 278 ($[M]^+$, 25), 180 (36), 167 (bp), 152 (89); HR-EIMS m/z: calcd for $C_{16}H_{26}N_2O_2$ $[M]^+$: 278.1994, found: 278.1985.

4.22. (+)-Cermizine D (2) and its TFA salt

To a solution of bis-amide **31** (16 mg, 57 μmol) in THF (1.1 mL) was added $LiAlH_4$ (22 mg, 0.57 mmol) at 0 °C under argon atmosphere. The mixture was heated to reflux for 5 h. After dilution with Et_2O and careful addition of water at 0 °C, 1 M aqueous NaOH was added to the mixture. The mixture was stirred overnight at room temperature and then filtered with Celite. The filtrate was dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by silca gel chromatography ($CHCl_3$/MeOH/NH_4OH=80:18:2) to afford 8.6 mg (60%) of cermizine D (**2**) as a pale yellow oil. To a solution of the cermizine D (**2**) (4.3 mg) in MeOH (0.5 mL) was added TFA (one drop, excess). The mixture was concentrated under reduced pressure to afford 9.9 mg (quant.) of cermizine D TFA salt as a yellow oil. Compound **2:** $[\alpha]_D^{25}$ +80 (c 0.06, MeOH); IR (ATR) ν_{max} cm^{-1}: 3305, 2921, 1442, 1371, 725; ^{1}H NMR (CD_3OD, 600 MHz) δ ppm: 3.40 (1H, br d, J=14.0 Hz), 3.25 (1H, m), 3.13 (1H, m), 3.06 (1H, br d, J=10.7 Hz), 2.71 (1H, td, J=13.5, 2.5 Hz), 2.67 (1H, m), 2.64 (1H, td, J=12.1, 2.8 Hz), 2.00 (1H, qd, J=12.8, 4.1 Hz), 1.76–1.92 (3H, m), 1.62–1.73 (3H, m), 1.52–1.62 (2H, m), 1.43–1.51 (2H, m), 1.39 (1H, td, J=12.6, 5.0 Hz), 1.24–1.33 (3H, m), 1.14–1.24 (2H, m), 0.92 (3H, d, J=6.3 Hz), 0.87 (1H, q, J=12.0 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ ppm: 59.2, 54.9, 50.2, 47.3, 40.6, 40.4, 39.7, 34.1, 26.4, 26.2, 25.8, 25.42, 25.37, 22.6, 19.7; EIMS m/z (%): 250 (39, M^+), 178 (21), 166 (21), 166 (52), 152 (bp); HR-EIMS m/z: calcd for $C_{16}H_{30}N_2$ $[M]^+$: 250.2409, found: 250.2407.

(+)-Cermizine D TFA salt:[4] $[\alpha]_D^{20}$ +24 (c 0.50, MeOH); IR (ATR) ν_{max} cm^{-1}: 2954, 2871, 2719, 1665, 1457, 1429, 1125, 719; ^{1}H NMR (CD_3OD, 600 MHz) δ ppm: 3.96 (1H, br t, J=11.0 Hz), 3.65–3.73 (2H, m), 3.42 (1H, m), 3.31 (1H, m), 3.15 (1H, td, J=13.7, 3.1 Hz), 3.05 (1H, td, J=12.7, 2.9 Hz), 2.31 (1H, ddd, J=14.6, 8.7, 3.5 Hz), 2.21 (1H, m), 2.16 (1H, m), 2.01 (1H, m), 1.88–1.98 (4H, m), 1.52–1.82 (10H, m), 1.16 (1H, q, J=12.7 Hz), 0.98 (3H, d, J=6.3 Hz); ^{13}C NMR (CD_3OD, 100 MHz) δ ppm: 62.4, 54.2, 51.4, 50.0, 45.9, 38.9, 38.0, 36.3, 31.0, 24.9, 24.6, 23.7, 23.2, 23.1, 21.6, 18.6; EIMS m/z (%): 250 (10, M^+), 166 (12), 152 (95), 83 (bp); HR-EIMS m/z: calcd for $C_{16}H_{30}N_2$ $[M]^+$: 250.2409, found: 250.2408.

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