A Concise Asymmetric Total Synthesis of (+)-Epilupinine

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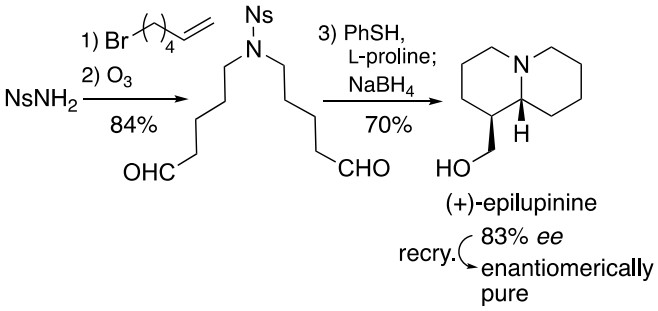
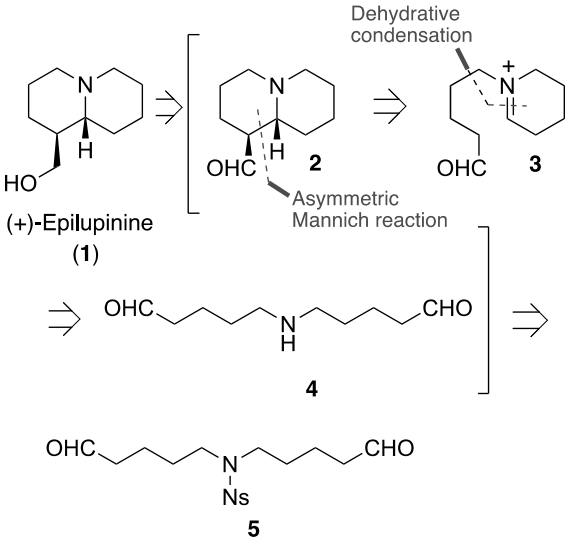


Asymmetric total synthesis of (+)-epilupinine was achieved in just 3 steps using only commercially available common reagents. The total synthesis involved alkylations of *N*-nosylamide, ozone oxidation, and sequential reactions of the removal of the nosyl group, intramolecular dehydrative condensation, intramolecular Mannich reaction catalyzed by L-proline, and a reduction.

Quinolizidine alkaloids, which have the octahydro-2*H*-quinolizine (quinolizidine) skeleton as a structural unit, are secondary metabolites found mostly in genus *Lupinus* and are known to exhibit various potent biological activities that are mainly cytotoxicity.[1] (+)-Epilupinine (**1**), structurally one of the simplest quinolizidine alkaloids, was initially considered the epimerized product of (+)-lupinine[2] but was later isolated as a natural secondary metabolite from various members of the lupin family.[3] **1** has been known to exhibit *in vitro* inhibitory activity against Leukaemia P-388 and lymphocytic Leukaemia L1210.[4] Recent studies elucidated that the structure of **1** incorporated into various drugs plays an important role as a pharmacophore.[5] For example, the (+)-epilupinine moiety of antiviral and antimalarial drugs is suggested to behave as a ligand of 5-HT_3, 5-HT_4, and sigma receptors.[6] Therefore, **1** has received a great deal of attention from synthetic organic chemists due to its potent and diverse biological activities and simple but synthetically cumbersome structure. So far, 15 asymmetric total syntheses of epilupinine[4,7] and more than 30 racemic total syntheses[8] have been reported. Although these include efficient chiral syntheses, there remain several points in need of improvement in the use of an expensive chiral auxiliary, other steps for the synthesis of starting materials, cumbersome separation from diastereomer and byproducts, longer number of steps, and so on, respectively. The biosynthetic pathway of (+)-epilupinine (**1**) is considered to include the cascade reaction of intramolecular dehydrative condensation and the Mannich reaction (**4**→**2** in Scheme 1),[9] and Van Tamelen and Foltz actually synthesized (±)-epilupinine based on the biomimetic cascade reaction in 1960.[8o] However, development of asymmetric version of this cascade reaction that would be the most efficient approach to (+)-epilupinine has not been achieved for around 60 years since their racemic total synthesis despite many successful examples of asymmetric total synthesis. Herein, we report a development of its asymmetric version and a remarkably simple total synthesis of (+)-epilupinine (**1**) in just 3 steps from commercially available common reagents as starting materials.

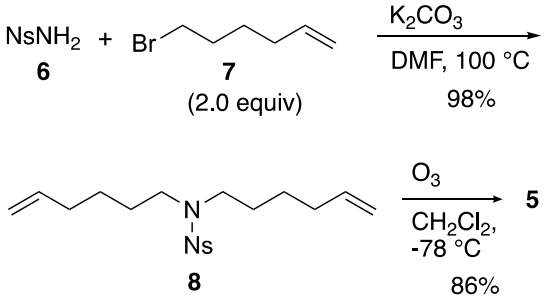
Scheme 1. Synthetic Plan of (+)-Epilupinine (1)



Our synthetic plan for **1** is outlined in Scheme 1. (+)-Epilupinine (**1**) will be readily obtained by the reduction of the aldehyde moiety of **2**. The aldehyde **2** would be obtained by the Mannich reaction of **3**. In this reaction, the addition of a chiral secondary amines as an organocatalyst is expected to give optically active **2** via an enamine aldol-type reaction. The iminium salt **3** would be formed by the intramolecular dehydrative condensation of either of the aldehydes of **4** with a secondary amine resulting from the deprotection of the nosyl group. It is noteworthy that removal of the nosyl group in the presence of asymmetric catalyst followed by reduction in one pot is expected to directly give (+)-**1** from **5** via the biomimetic cascade reaction.

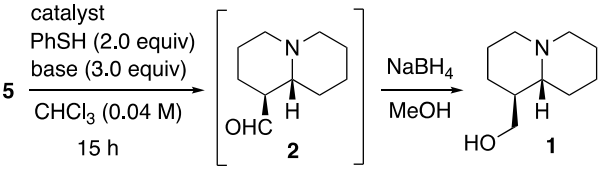
To investigate the optimal conditions for the cascade reaction, we synthesized the dialdehyde **5** as the precursor (Scheme 2). Treatment of *N*-nosylamide **6** with 2.0 equiv of 6-bromo-1-hexene **7** and K_2CO_3 in DMF at 100 °C afforded the diene **8** in 98% yield. Ozone oxidation of the diene **8** in dichloromethane at -78 °C proceeded smoothly to give the dialdehyde **5** in 86% yield. The dialdehyde **5** was sufficiently stable for purification by silica gel column chromatography.

Scheme 2. Synthesis of Cascade Reaction Precursor 5.



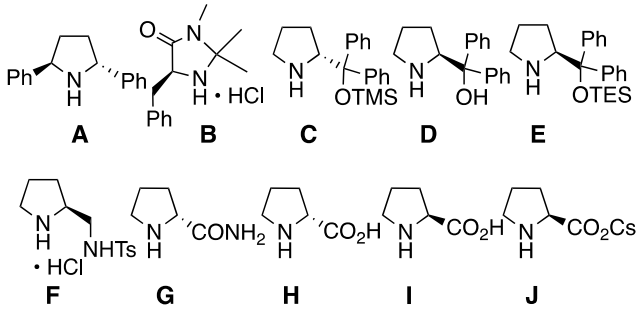
Having prepared precursor **5**, we next examined the cascade reaction from **5** to **2**. Since the cyclization product **2** is unstable and volatile, the aldehyde **2** was reduced directly to epilupinine **1** by adding $NaBH_4$ and methanol to the reaction mixture, and then the yield and *ee* were determined.[10] First, we tried various organocatalysts (**A**, **B**, **C**, **G**, **H, I**) in methanol, obtaining epilupinine **1** in low yield (6 ~ 29%) with modest *ee* (< 5 ~ 59%) after direct reduction of **2** (see Supporting Information). Although the cascade reaction proceeded as expected, optimization to increase yield and *ee* was required. When the solvent effect on the cascade reaction catalyzed by Jørgensen's catalyst **A** was investigated,[11] the use of $CHCl_3$ was found to increase the chemical yield, although almost no *ee* was appeared (Table 1, entry 1 and Supporting Information). Therefore, we further optimized the conditions of the cascade reaction in $CHCl_3$ (Table 1). Whereas the addition of MacMillan's catalyst **B**[7c,12] did not give **1** (entry 2), Hayashi-Jørgensen catalyst **C**[13] substantially increased the *ee* (61%) with good chemical yield (73%) (entry 3). However, increasing catalyst **C** to 50 mol% did not improve either yield or *ee* (entry 4). The related catalysts **D**[14] and **E**[15] showed declines in yield, and almost no *ee* was observed (entries 5 and 6). In addition, the reaction using catalyst **F**[16] or the prolineamide **G**[17] did not afford **1** (entries 7 and 8). On the other hand, the use of D-proline **H**[18] as the catalyst provided an enantiomer of **1** in 57% yield with 26% *ee* (entry 9), and increasing the amount of **H** to 100 mol% elevated both yield and *ee* (entry 10). Since the reaction using D-proline predominantly afforded (-)-epilupinine, L-proline was used in subsequent investigation. To further increase the *ee*, a similar reaction using L-proline was conducted at 0 °C, and the *ee* of (+)-**1** increased to 76% (entry 11). However, further decreasing the temperature to -15 °C induced declines in both yield and the *ee* (entry 12). Next, when we changed the base from K_2CO_3 to Cs_2CO_3, the *ee* fortunately increased to 83% (entry 13).[19] In addition, the use of previously prepared cesium salt **J** further improved the *ee* to 92% (entry 14).[19] However, several trials on multi-gram scale showed 84~86% *ee*, even when cesium salt **J** was used. Although the *ee* decreased in gram-scale synthesis, reproducibility over 83% *ee* was ensured. Thus, we adopted the condition of entry 13 for gram-scale synthesis in terms of chemical yield, *ee*, and convenience, because the 83% *ee* can be further increased by recrystallization. On the other hand, the use of Triton B as another base having a bulky counter cation decreased the *ee* (entry 15), and Li_2CO_3 and Me_4NOH did not give **1** (entries 16 and 17). Throughout the optimization study, we did not detect the formation of diastereomers. Probably, the diastereomers of **2** was readily epimerized under basic conditions. Although we further examined the reaction conditions such as additives, the *ee* could not be increased above 92% (Supporting Information).

Table 1. Optimization of the cascade reaction leading to (+)-epilupinine



entry[a]	catalyst (mol %)	base	temp (°C)	yield[b] (%)	*ee*[c] (%)
1	**A** (20)	K_2CO_3	rt	71	<5
2	**B** (20)	K_2CO_3	rt	-	-
3	**C** (20)	K_2CO_3	rt	73	61
4	**C** (50)	K_2CO_3	rt	61	59
5	**D** (20)	K_2CO_3	rt	33	<5
6	**E** (20)	K_2CO_3	rt	28	8[c]

7	**F** (20)	K_2CO_3	rt	trace	11
8	**G** (20)	K_2CO_3	rt	-	-
9	**H** (20)	K_2CO_3	rt	57	30[d,e]
10	**H** (100)	K_2CO_3	rt	68	69[d]
11	**I** (100)	K_2CO_3	0	61	76
12	**I** (100)	K_2CO_3	-15	38	28[e]
13[f]	**I** (100)	Cs_2CO_3	0	70	83
14	**J** (100)	Cs_2CO_3	0	35	92
15	**I** (100)	Triton B	0	53	25[e]
16	**I** (100)	Li_2CO_3	0	-	-
17	**I** (100)	Me_4NOH	0	-	-



[a]The reaction was performed by using 35 mg (0.095 mmol) of **5**. [b]Isolated yield. [c]*Ee* was measured by the integral ratio of ^{19}F NMR after converting **1** to the corresponding Mosher's ester according to the conventional method. [d]*Ee* of (-)-epilupinine (enantiomer) is described. [e]*Ee* was determined from specific optical rotation. [f]5.0 g (13.5 mmol) of **5** was used.

Next, we tried to increase the *ee* by recrystallization. Due to the low recovery rate of free **1** from recrystallization, we tried to recrystallize **1** in a salt form. Among various acids such as carboxylic, sulfonic, and hydrochloric acids,[20] we found that triphenylacetic acid forms a good solid salt with epilupinine. Then, (+)-epilupinine triphenylacetic acid salt was sufficiently recrystallized from $CHCl_3$ and diethyl ether, and the resulting crystals were treated with acid-base distribution to afford salt-free (+)-epilupinine **1** in 53% yield as an enantiomerically pure form.[21] Thus, enantiomerically pure (+)-epilupinine (**1**) was obtained by our three-step total synthesis[22]and the efficient single step construction of (+)-epilupinine **1** from dialdehyde **5** was established.

We studied the enantioselectivity of a proline-catalyzed intramolecular Mannich reaction under Cs_2CO_3 condition by Density Functional Theory (DFT) calculation (Figure 1 and supporting information). Taking the adduct of proline-activated Cs-salt of iminium cation (A, A' and A'') as a model substrate, we calculated the transition states for the intramolecular asymmetric Mannich reaction to form a C1-C2 bond. Our calculation result showed that the attack from the less-hindered *Si*-face of the sp^2 carbon C2 in the 6-membered ring of the iminium cation through TS_{Si} is favored and the reaction is exergonic, resulting in (+)-epilupinine. However, its opposite enantiomer resulting from the *Re*-face attack at C2 needed a high-energy barrier of 5.36 kcal/mol through TS_{Re} (Figure 1). The transition state TS_{Si} is stabilized by the formation of low-energy 6-membered ring with an O--H interaction between H of C2 and O of carboxylate group of the catalyst I (Figure 1). The transition state lacks such interaction in the case of opposite enantiomer. In addition, the transition state for formation of one of its diastereomer (TS') has lower energy barrier of 3.63 kcal/mol compared to TS_{Re}, however, we obtained only enantiomer 1' and 1 may be due to the epimerization of aldehyde to the most stable conformer that leads to the formation of (+) epilupinine **1**. We also compared the reaction profile taking K-salt. The calculation showed that the distance between C1 and C2 in the transition state TS_{Si} is 2.55 Å (Cs-salt) and 2.50 Å (K-salt) respectively; and the gap of activation energy between TS_{Re} and TS_{Si} is higher in the case of Cs-salt than K-salt due to stronger O--H interaction (O-H distance for Cs-salt is 2.88 Å and for K-salt is 3.22 Å respectively) (Figure 1 and supporting information). This resulted in slow and highly enantioselective reaction during our study.

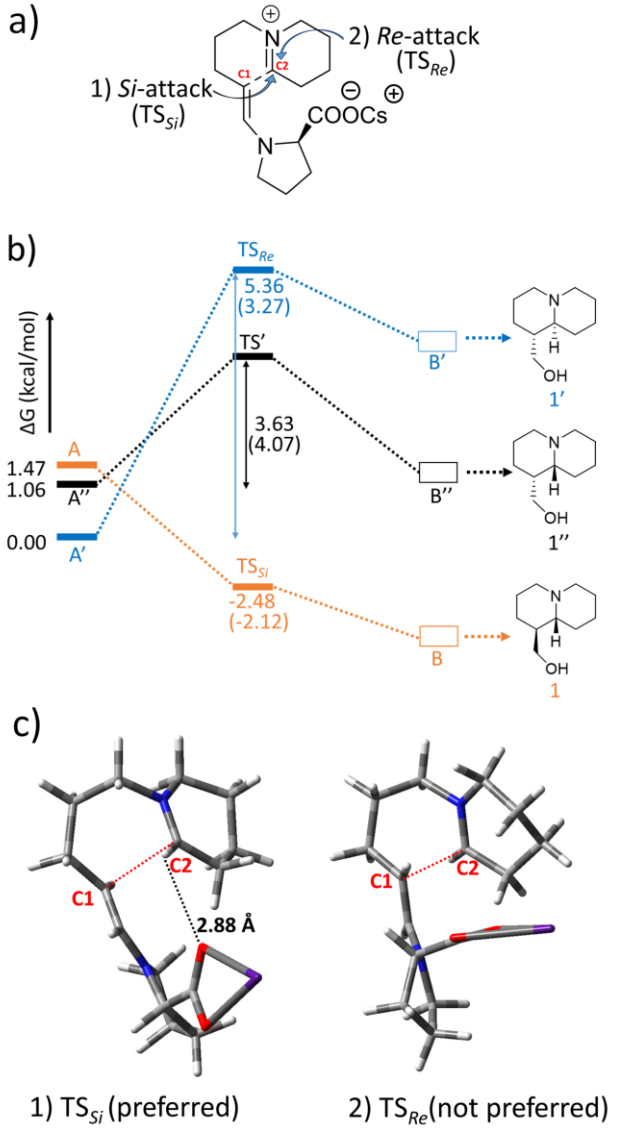
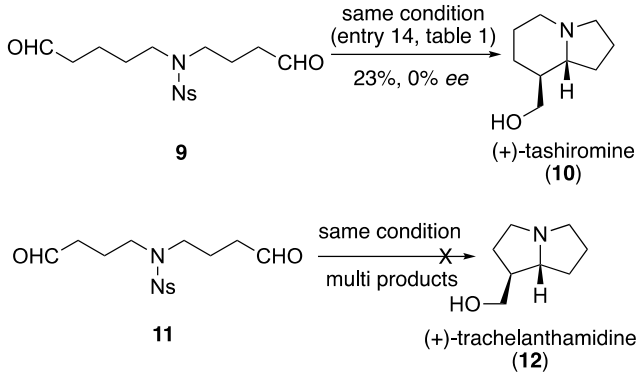


Figure 1. a) Mode of attack on C2 by nucleophilic C1. b) Energy profile diagram for formation of enantiomers and diasteromers of Epilupinine using catalyst I. c) optimized transition states for the Mannich reaction.

Finally, we applied the established condition for (+)-epilupinine (**1**) to the synthesis of related natural products such as (+)-tashiromine (**10**) and (+)-trachelanthamidine (**12**) that include azabicyclo [4,3,0] and [3.3.0] skeletons, respectively. However, although the similar reaction of **9** afforded racemic tashiromine **10** in 23% yield.[23] In addition, multi products were obtained in the case of **11**, and the isolation of (+)-trachelanthamidine (**12**) was difficult. Further optimization is needed for these related natural products.

Scheme 3. Application of the cascade reaction to related quinolizidine alkaloids.



In conclusion, a three-step total synthesis of (+)-epilupinine from commercially and readily available common reagents was established. The total synthesis consists of two alkylations of *N*-nosylamide, ozone oxidation, the cascade reaction of two cyclizations, and a reduction. The cascade reaction includes deprotection of the nosyl group, intramolecular iminium cation formation, and the intramolecular asymmetric Mannich reaction. In the asymmetric Mannich reaction, L-proline cesium salt was found to give the highest enantiomeric excess. Although a stoichiometric amount of L-proline was needed for high *ee*, L-proline is not an expensive organocatalyst and is recoverable from the reaction mixture. Furthermore, we discovered the recrystallization condition of **1** so that enantiomerically pure (+)-epilupinine is readily obtained by this synthesis. Although there have been over 45 examples of the synthesis of epilupinine, there are fewer steps in this synthesis than in any conventional synthesis, even including racemic total synthesis. On the other hand, the application of this asymmetric cascade reaction to other related natural products from genus *Lupinus* is next challenge, because the application to the synthesis of (+)-tashiromine and (+)-trachelanthamidine did not give good results. Further development of the resulting quinolizidine analogs as the functional molecules is currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental details and ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(10) The enantiomeric excess of epilupinine **1** was determined by the integral ratio of ^{19}F NMR after converting **1** to the corresponding Mosher's ester according to the conventional method, as the separable condition using HPLC could not be established.

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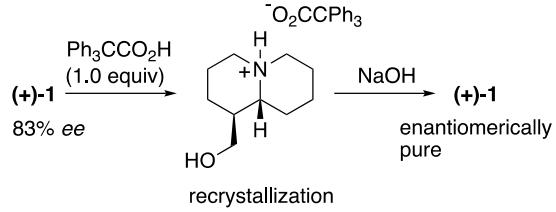
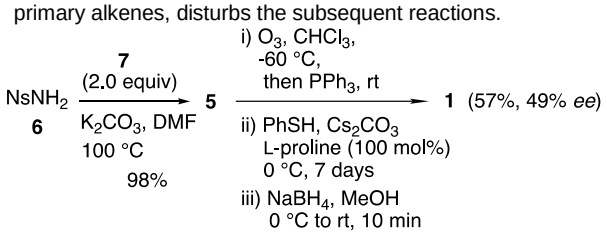
(19) The use of 20 mol% of **J** gave the 66% *ee* and 38% yield, and the prepared potassium salt of L-proline did not affect the *ee*.

(20) HCl, $(COOH)_2$, AcOH, L-tartalic acid, TFA, L-malic acid, D-mandelic acid, benzoic acid, TsOH, and 10-campher sulfonic acid did not afford good solid salt for recrystallization.

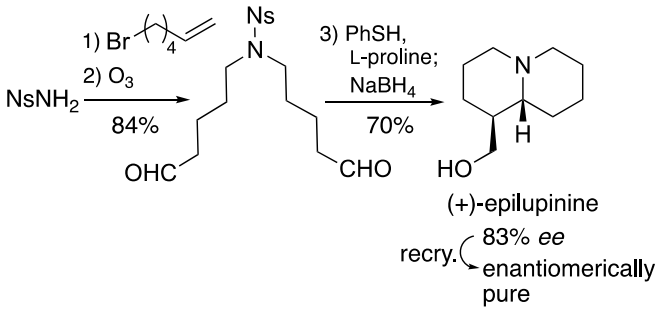


(21) The peak of enantiomer was not detected by ^{19}F NMR, and the value of $[\alpha]_D$ was identical to that of the literature.

(22) We tried to develop to two-step total synthesis. After ozonolysis of **5** in $CHCl_3$ at -60 °C, the reaction mixture was directly subjected to the cascade reaction to give **1**. In this one-pot operation, although long reaction time was needed, **1** was actually obtained in 57% yield from **5**. However, the *ee* of **1** was substantially decreased to 49%. After various examination, we found that the formaldehyde, derived from ozone oxidation of primary alkenes, disturbs the subsequent reactions.



(23) The formation of tashiromine (**10**) was confirmed by comparison with the data of ref. 7c.


1) Br
4
2) O3
NsNH2
84%
Ns
N
OHC
CHO
3) PhSH,
L-proline;
NaBH4
70%
N
H
HO
(+)-epilupinine
recry.
83% ee
enantiomerically
pure