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Approach to *cis*-Phlegmarine Alkaloids via Stereodivergent Reduction: Total Synthesis of (+)-Serratezomine E and Putative Structure of (−)-Huperzine N

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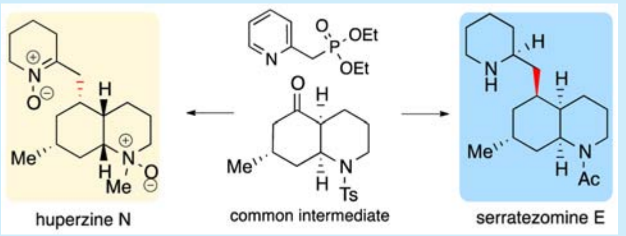
Supporting Information

ABSTRACT: A unified strategy for the synthesis of the *cis*-phlegmarine group of alkaloids is presented, leading to the first synthesis of serratezomine E (**1**) as well as the putative structure of huperzine N (**2**). A contrasteric hydrogenation method was developed based on the use of Wilkinson's catalyst, which allowed the facial selectivity of standard hydrogenation to be completely overturned. Calculations were performed to determine the mechanism, and structures for huperzines M and N are reassigned.

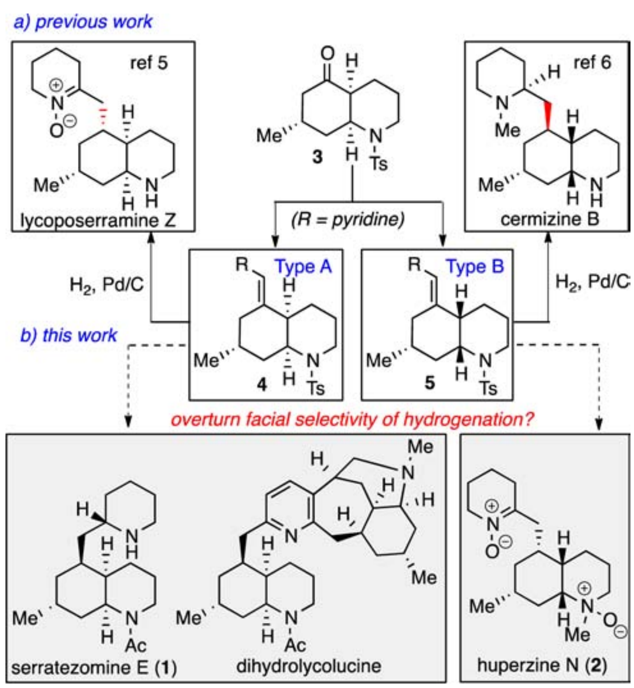


In the field of natural product synthesis there is a growing trend toward developing strategies that can prepare diverse molecular skeletons from a common intermediate.[1] Such "unified synthesis" approaches have an advantage in that they produce the maximum amount of molecular diversity in the most efficient manner possible, thereby facilitating structure−activity relationship studies. Our interest in this field stems from our research program to develop a unified synthesis of the *Lycopodium* alkaloids.[2] In particular, our efforts have focused on the phlegmarine alkaloid subset, since not only do their multiple stereochemical arrangements present synthetic challenges, but the core framework, embedded throughout the *Lycopodium* alkaloids, would constitute an ideal common scaffold in a unified synthesis of these compounds.[3,4]

Previously, we have developed an organocatalyzed tandem cyclization to access 5-oxodecahydroquinoline **3** bearing three stereogenic centers in a one-pot manner. Subsequent coupling generated the first point of diversification, providing vinylpyridines **4** or **5** depending on the conditions employed. Hydrogenation of the formed alkene led to a second point of diversity, which from **4** almost exclusively gave the stereochemistry required for the synthesis of lycoposerramine Z.[5] Similarly, hydrogenation of vinylpyridine **5**, under the same conditions, allowed the synthesis of cermizine B[6] (Scheme 1). Access to a wide range of C-5 epimeric *Lycopodium* alkaloids, such as those shown in Scheme 1,[7] would require the facial selectivity of this hydrogenation step to be completely overturned.[8] We herein report a highly efficient process to achieve this objective and its application to the first total synthesis of serratezomine E.[7a] Using this strategy, we also accomplished the total synthesis of the putative structure of huperzine N[7c] and its reassignment.

The selectivity of the hydrogenation of vinylpyridine **4** (Figure 1) using either Pd−C or Raney nickel is believed to be governed by an axially positioned methyl group, which blocks the approach from the lower face of the molecule, leading to the kinetic decahydroquinoline **6b** (Table 1, entries 1 and 2). A priori, compound **7** appeared to be a convenient precursor of **8a**, since its different conformation (Figure 1) could allow a

Scheme 1. Stereochemistries of *cis*-Phlegmarine Alkaloids



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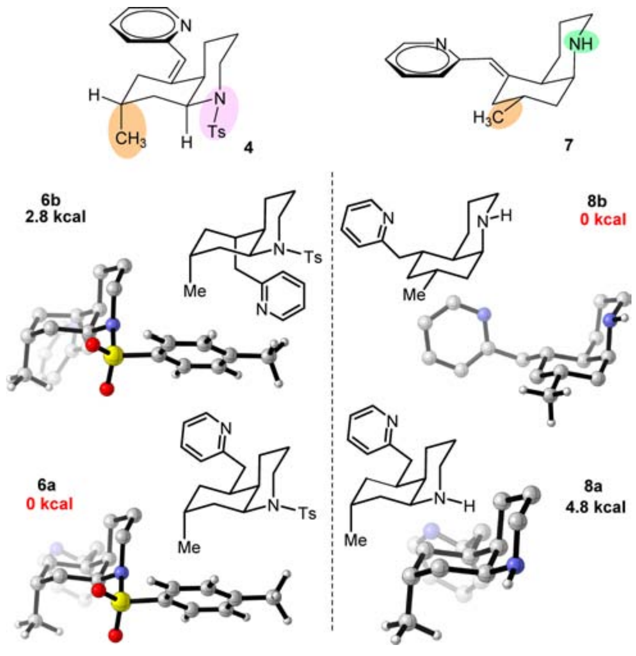
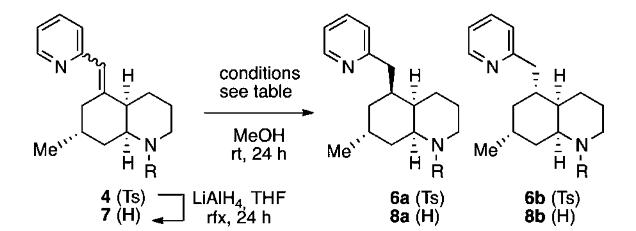


Figure 1. Structural conformations and relative stabilities of **6a**/**b** and **8a**/**b**, computed at B3LYP/6-311G** (LANL2DZ) level of theory.

Table 1. Screening of Conditions for the Reduction Reaction[a]



entry	compd	method[a]	yield[b] (%)	dr[c] a:b
1	4	H_2, Pd–C	100	3:97
2	4	H_2, Ra–Ni	75	14:86
3	7	H_2, Pd–C	100	36:64
4	4	$Mn(dpm)_3$, $PhSiH_3$, TBHP	63	73:27
5	7	$Mn(dpm)_3$, $PhSiH_3$, TBHP	0	
6[d]	4	$Fe_2(ox)_3 \cdot H_2O$, $NaBH_4$, H_2O	10	75:25
7[e]	4	$Co(acac)_2$, Et_3SiH, TBHP	7	nd
8[d]	4	$Fe(acac)_3$, $PhSiH_3$	49	67:33
9	4	H_2, $[Ir(PCy_3)\ (cod)\ (py)]PF_6$	100	68:32
10	4	H_2, $[RhCl(PPh_3)_3]$	100	96:4

[a]For detailed reactions conditions, see the Supporting Information. Reactions were performed on a mixture of *E*/*Z* isomers (4:1). [b]Yield of hydrogenated compounds refers to the conversion determined from ^{1}H NMR spectra. [c]The ratio was determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture. [d]EtOH used as solvent. [e]^{i}PrOH used as solvent and 1,4-cyclohexadiene as additive.

kinetic hydrogenation from the bottom face and lead to the thermodynamically more stable epimer **8a**. However, hydrogenation of the secondary amine **7** (entry 3) did not give the expected reversal of selectivity. An explanation is that the haptophilicity[9] of the secondary amino function binds it to the catalyst surface and thus directs the delivery of the hydrogen from the top face of **7** to give **8b** as the major epimer.

We then evaluated the reductive radical conditions recently reported by Shenvi,[10] known to give more thermodynamically favored products. Calculations showed that the targeted **6a** was 2.8 kcal more stable than its epimer **6b** (Figure 1), and indeed, it was obtained as the main compound in a ratio of 73:27 (entry 4), although it was difficult to separate from significant amounts of byproducts (>30%).[11] When the same conditions were applied to the N–H compound **7**, there was no reaction and the starting material was completely recovered (entry 5). Similar radical-based methods based on other protocols,[12] either directly or modified, were also evaluated, but with no significant improvements (entries 6–8). We then assessed homogeneous hydrogenation catalysts and were pleased to observe that Crabtree's catalyst provided the same stereoselectivity as $Mn(dpm)_3$ but without any byproducts (entry 9). Finally, Wilkinson's catalyst proved more successful, enabling us to achieve almost complete diastereoselectivity (96:4) in a clean quantitative manner using only 2 mol % of catalyst (entry 10).[13]

Given the sterically impeded nature of the *β*,*β* disubstituted vinylpyridine and large size of Wilkinson's catalyst, we presumed the reaction proceeded via a coordination of the catalyst.[14] Indeed, when the analogous benzene analogue of **4** (not shown) lacking the pyridine nitrogen was prepared, no reduction was observed.

To understand the reaction and account for the excellent stereocontrol observed, calculations were performed, and the proposed reaction mechanism is outlined in Scheme 2. The hydrogenated Wilkinson's catalyst (**I**) forms an initial complex **A** by coordination to the double bond and the pyridine nitrogen atom of the substrate, releasing two molecules of phosphine in the process, which can occur through both faces of the double bond. In complex **A**, the Rh atom is coordinated to the pyridine ring and the double bond with short interatomic Rh–N (2.4 Å) and Rh–alkene (2.3 Å) distances, inducing a slight deconjugation of the double bond and the pyridine ring, which is partially responsible for its 10 kcal/mol higher energy than the initial hydrogenated Wilkinson catalyst. Thus, the initial equilibrium between the starting materials and A is shifted toward the former (Scheme 2). However, the very low activation energy required for the hydro-rhodation (**TS-down** is only 4 kcal/mol above **A**) makes the whole process feasible, triggering an easy formation of **C**, and the consumption of the starting material. After the insertion of hydrogen into **C**, the reaction proceeds through reductive elimination, liberating the final product **D**. As mentioned, the hydro-rhodation step can occur on either face of the double bond, through two diastereoisomeric transition states, **TS-down** and **TS-up** (**E** → **G**). The computed activation energies predict that **TS-down** is favored by 2.8 kcal/mol over **TS-up**, justifying the experimental formation of the major diastereoisomer **6a**. The main difference between the two diasteromeric transition states consists of the different orientation of the *N*-tosyl moiety of the substrate. In **B**, the phenyl ring of the tosyl group forms at least three strong *π*-stacking interactions, with one of the rings of the PPh_3 group, and with two different H atoms of the bicyclic skeleton (see Supporting Information). During the transition state, the Rh-alkene bond is even tighter than in **A** (2.1 Å), inducing a weakening of the Rh–N coordination (2.5 Å).

With the optimum reduction method in hand, transformation of **4** (prepared in six steps from the commercially available 5-aminopentanoic acid) led to a concise synthesis of serratezomine E (**1**, Scheme 3). Hydrogenation with Wilkinson's catalyst and removal of the tosyl group of **6a** led to the secondary amine **8a** in a pure form and the introduction

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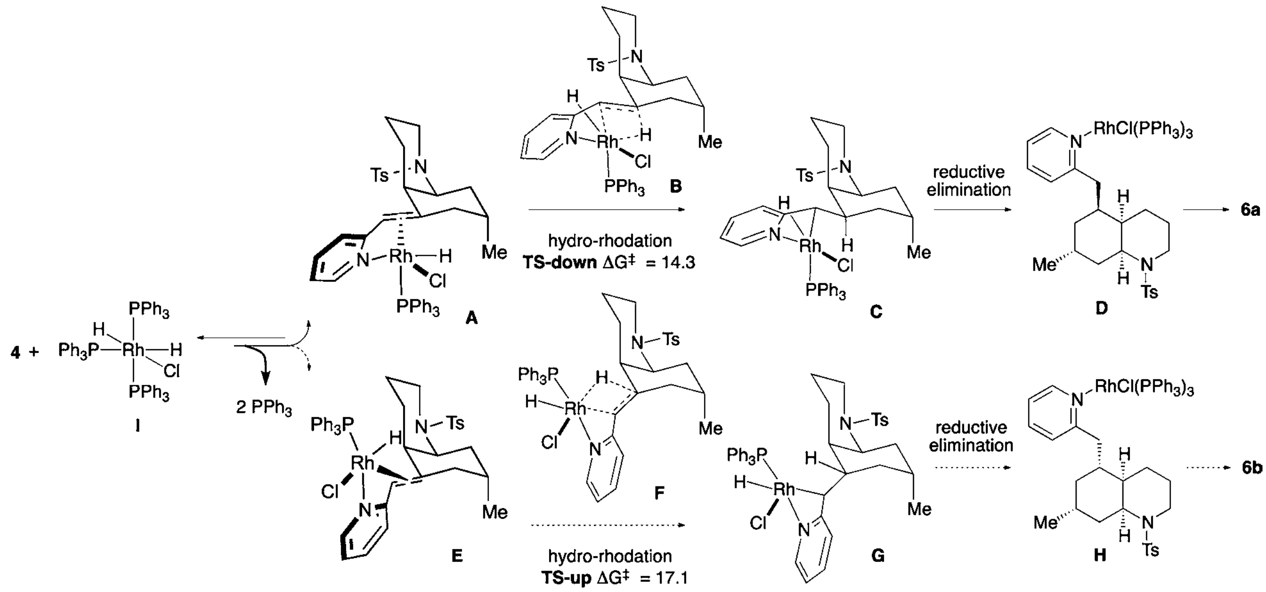
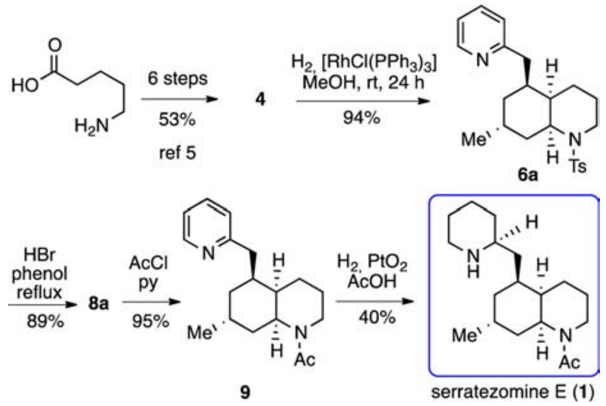
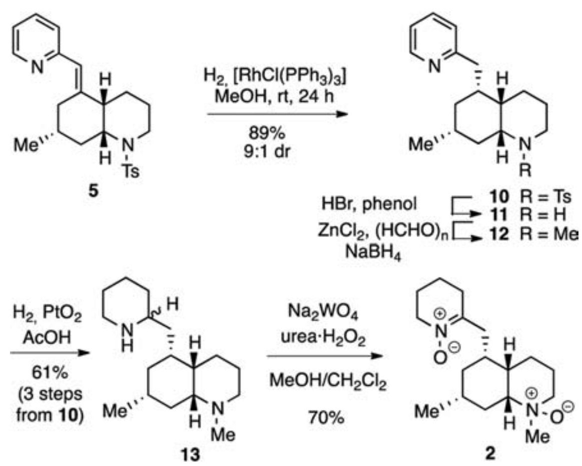
Scheme 2. Proposed Mechanism for the Rh-Catalyzed Hydrogenation of 4



Scheme 3. Synthesis of Serratezomine E (1)



Scheme 4. Synthesis of Putative Huperzine N (2)



of the required acetyl group gave **9**. Subsequent reduction of the pyridine provided serratezomine E (**1**) as a white solid,[15] whose structure was unequivocally confirmed by X-ray analysis (Figure 2), having the absolute configuration (*S*) at the C2 piperidine ring and (*R*) at the C7 decahydroquinoline ring, characteristic of phlegmarine alkaloids.[16,17]

An analogous procedure allowed for the synthesis of huperzine N (**2**, Scheme 4). Hydrogenation of **5** with Wilkinson's catalyst gave the desired epimer **10** in a 9:1 ratio. Removal of the tosyl group, formation of the *N*-methyl via reductive amination with $ZnCl_2$,[18] and reduction of the pyridine gave **11** in good overall yield. Finally, oxidation with Na_2WO_4/urea·H_2O_2[5] gave the reported structure of huperzine N, although the NMR spectra of **2** did not match those described (see the Supporting Information). Instead, the ^{13}C NMR data of natural huperzine N would be explained by structure **14** (Figure 3), whose NMR data are consistent with the *N*-oxide form of the previously isolated lycoposerramine Y.[19] Indeed, the closely related alkaloid huperzine M (**15**)[7c] should also be

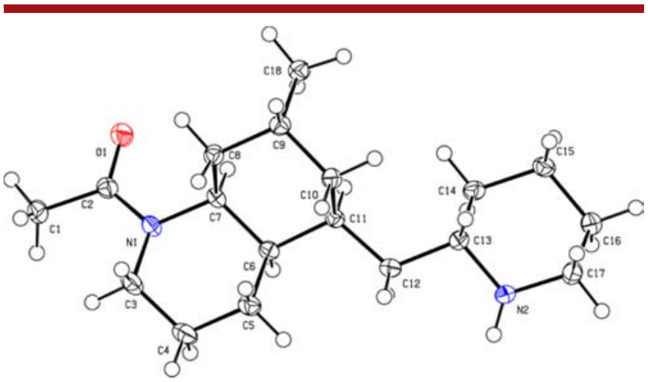


Figure 2. X-ray structure of (+)-serratezomine E (**1**).

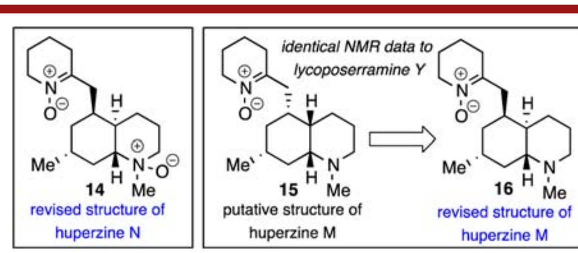


Figure 3. Revised structure for huperzines M and N.

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reassigned, its NMR data being identical to those of lycoposerramine Y (**16**).

In summary, a divergent hydrogenation protocol was developed that provides access to a range of *Lycopodium* compounds unattainable by standard hydrogenation of common vinylpyridine intermediates. Via rhodium complexation with the pyridine nitrogen and selective facial delivery, it was possible to invert the course of hydrogenation from 97:3 to 4:96 dr. This method was successfully applied for the first total synthesis of serrazomine E as well as huperzine N. The latter turned out to be a putative structure, and the natural one was structurally reassigned. The application of this strategy to other *cis* and *trans Lycopodium* alkaloids is now in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02581.

Experimental procedures, spectroscopic and analytical data, and NMR spectra of new compounds; Cartesian coordinates and energies for all species considered in Scheme 2 (PDF)

X-ray data for **1**(CIF)

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Notes

The authors declare no competing financial interest.

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(13) The use of the *E* isomer alone gave the same result. It should also be noted that the free N−H compound **7** did not react with either catalyst.

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(15) The remaining mass comprised the epimer in the form of an oil, which enabled its simple separation from the desired product, despite the two compounds having identical R_f values.

(16) The NMR data for the piperidine ring atoms are slightly different from those reported for the natural product. However, partial protonation of our synthetic **1** afforded NMR data identical to those described for natural **1**. For a similar titration of a free base with TFA, see: Altman, R. A.; Nilsson, B. L.; Overman, L. E.; Read de Alaniz, J.; Rohde, J. M.; Taupin, V. *J. Org. Chem.* **2010**, *75*, 7519.

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