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Enantioselective Total Synthesis of (+)-Sieboldine A

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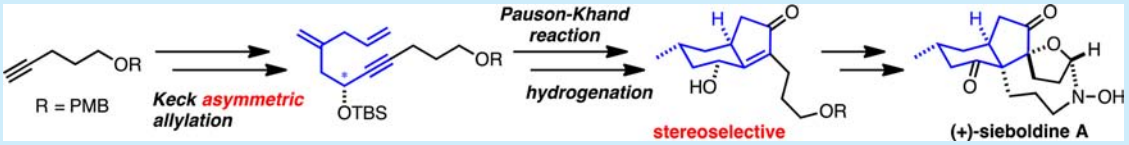
Supporting Information



ABSTRACT: The first total synthesis of (+)-sieboldine A was completed starting from 5-(*p*-methoxybenzyloxy)pentyne in 19 steps. The enantioselective Keck allylation provided the dienyne derivative, which was exposed to the Pauson–Khand conditions to afford the bicyclo[4.3.0]nonenone derivative with high stereoselectivity with an ee value of 93%. The following Ueno–Stork reaction formed the *cis*-hydrindane core with a quaternary carbon center. The late-stage Schmidt glycosylation led to the formation of the *N*-hydroxyazacyclononane ring.

The *Lycopodium* alkaloids consist of more than 200 structurally diverse natural products, which have attracted significant interest from biogenetic and biological points of view and provided challenging targets for their total synthesis.[1,2] (+)-Sieboldine A (**1**) is a fawcettimine-type *Lycopodium* alkaloid that was isolated from the club moss *Lycopodium sieboldii* along with (+)-alopecuridine (**2**) by Kobayashi et al. in 2003 (Figure 1).[3] (+)-Sieboldine A (**1**) has been found to inhibit

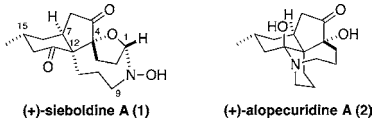


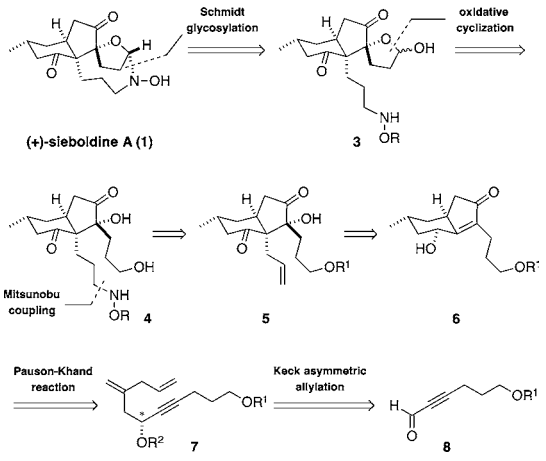
Figure 1. Structures of sieboldine A (**1**) and alopecuridine (**2**).

acetylcholinesterase (from the electric eel) with an IC_{50} value of 2.0 μM. This value was comparable to that of (±)-huperzine A[4] and exhibited cytotoxicity against murine lymphoma L1210 cells with an IC_{50} value of 5.1 μg/mL.[3]

(+)-Sieboldine A (**1**) contains an unprecedented fused tetracyclic skeleton consisting of (i) a *cis*-hydrindane ring system, the distinctive structural feature of the fawcettimine-type *Lycopodium* alkaloids, and (ii) an *N*-hydroxyazacyclononane ring embedded in bicyclo[5.2.1]decane-*N*,*O*-acetal. This unusual and unique skeleton with the unstable *N*,*O*-acetal moiety made **1** an important and attractive target molecule for its total synthesis. Two groups have already succeeded in the total synthesis of (+)-**1**. In 2010, the Overman group recorded the first total synthesis of (+)-**1** in 20 steps starting from the chiral tetrahydrocyclopenta[*b*]furan-2-one using a gold(I)-catalyzed pinacol-terminated 1,6-enyne cyclization for construction of the *cis*-hydrindanone core.[5] In the following year, Tu and co-workers reported the first total synthesis of (±)-alopecuridine (**2**) and its biomimetic transformation into (±)-**1**[6a] according to Kobayashi's proposed biogenetic pathway.[3] Tu and co-workers subsequently extended their methodology to the synthesis of these two optically active alkaloids in 2012.[6b]

Our retrosynthetic plan for the preparation of (+)-sieboldine A (**1**) is presented in Scheme 1. The elaboration of the sensitive

Scheme 1. Retrosynthetic Analysis of (+)-Sieboldine A



N,*O*-acetal functionality of (+)-**1** was planned to be formed during the late stage of the synthesis via the intramolecular displacement reaction of the lactol functionality of **3** by the *O*-protected hydroxylamine residue.[7] The spirolactol framework of **3** would be formed through oxidative cyclization of the diol **4**. Introduction of the nitrogen functionality could be achieved through the hydroboration–oxidation of the allyl side chain of **5**, followed by the Mitsunobu coupling with the protected hydroxylamine derivative. The *cis*-hydrindanone **5** with all-carbon units required for **1** would be obtained by the consecutive

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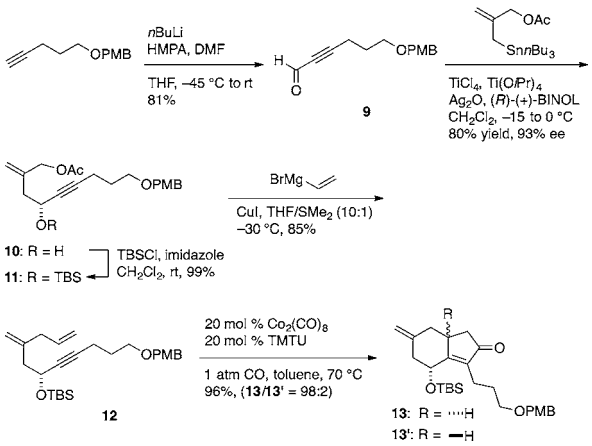
bromoacetalization, Ueno−Stork cyclization, and Wittig olefination of **6**. In our previous studies,[8] we definitely showed that the Pauson−Khand reaction (PKR) is a powerful and efficient synthetic tool to assemble bicyclo[4.3.0] frameworks. Based on our previous results, the PKR of the dienyne **7** would be expected to stereoselectively produce **6**. Thus, the highly enantioselective preparation of **7**, a substrate for the PKR, is mandatory. We envisioned that the optically active **7** would be available by the asymmetric allylation of aldehyde **8** with a suitable allyl derivative.[9]

The formylation of 5-(*p*-methoxybenzyloxy)pentyne[10] under conventional conditions[11] gave the aldehyde **9** in 81% yield (Scheme 2). The asymmetric allylation of aldehyde **9** is obviously

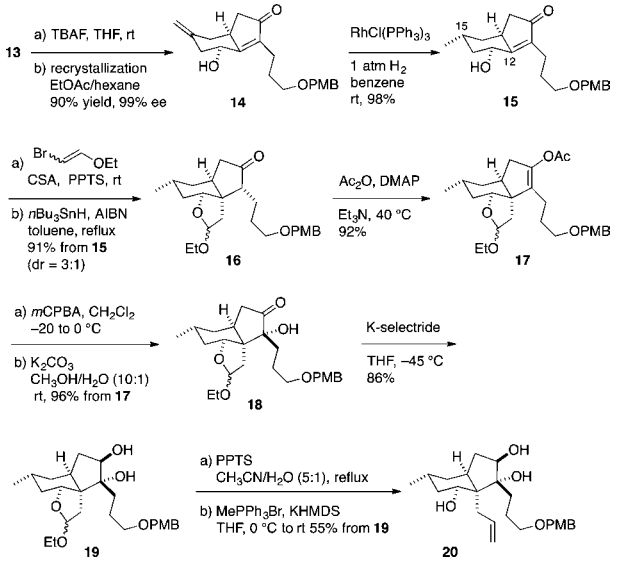
Scheme 2. Enantioselective Synthesis of the Bicyclo[4.3.0]nonenone 13



one of the crucial steps in our synthesis. Several allyl derivatives and different asymmetric reaction conditions were evaluated to optimize the allylation process in terms of the chemical yield and enantiomeric excess (ee).[12] As a result, the Keck asymmetric allylation using the modified Ti(IV) catalyst described by Maruoka et al.[13] was found to be the most satisfactory one. Indeed, the treatment of **9** with 2-((tributylstannyl)methyl)allyl acetate[14] using Maruoka's conditions afforded the hydroxyenyne (+)-**10** in 80% yield with 93% ee.[15] The TBS protection of **10** was followed by treatment with vinylmagnesium bromide to furnish **12** in 85% yield from **10**.[16] A highly diastereoselective PKR of **12** was realized under catalytic conditions using 20 mol % of $Co_2(CO)_8$ and 20 mol % of tetramethylthiourea in toluene at 70 °C under 1 atm of CO[17] to afford the indenone **13** and its epimer **13′** in 96% yield in the ratio of 98:2.

Deprotection of the TBS group of **13** with TBAF provided **14**, which was recrystallized from EtOAc/hexanes to furnish the optically pure (−)-**14** (>99% ee; Scheme 3).[18] The efficient construction of the *cis*-hydrindane framework possessing the C_{15}-methyl group[19] and the quaternary carbon center at the C_{12}-position[19] was realized as follows. The hydrogenation of **14** in the presence of Wilkinson's catalyst proceeded in a highly chemo- and stereoselective manner to form **15**, having the C_{15}-methyl group with the desired stereochemistry in 98% yield. According to the procedures developed during our previous investigations,[8g,j] the Ueno−Stork reaction was applied to **15** to produce **16** in 91% yield as a mixture of two diastereomers in the ratio of 3:1.[20] Upon exposure to acetic anhydride in the presence of Et_3N and DMAP at 40 °C, **16** underwent regioselective enolization to provide the vinyl acetate derivative **17** in 92% yield. The

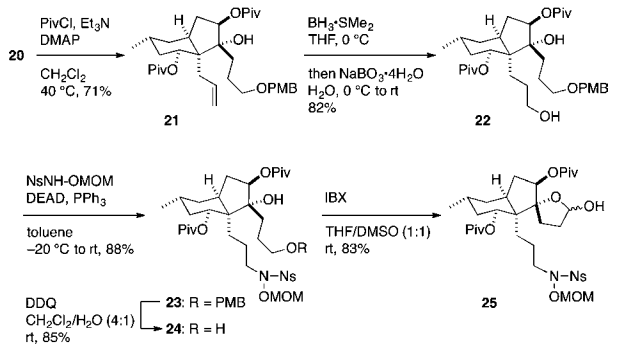
Scheme 3. Construction of the *cis*-Hydrindane Framework with a Quarternary Carbon Center



oxidation of **17** with *m*CPBA occurred from the sterically less-hindered α face, and the resulting acetoxy epoxide moiety was hydrolyzed to give the α-hydroxy ketone derivative **18** in 96% yield.[21] The ketone derivative **18** was temporarily converted to the *trans*-diol derivative **19** in 86% yield by the stereoselective K-selectride reduction to avoid any side reactions during further chemical elaboration.[22] Compound **19** was treated with PPTS, and the resulting hemiacetal was subsequently subjected to the Wittig olefination with $MePPh_3Br$ to form the allyltriol (−)-**20** in 55% yield.

Having established all the carbon units with the proper stereochemistry, we focused on the introduction of the nitrogen functionality and formation of the spirotetrahydrofuran ring (Scheme 4). The two secondary hydroxyl groups of the triol

Scheme 4. Introduction of the Nitrogen Functionality and Formation of the Spirotetrahydrofuran Ring



derivative **20** were protected by the pivaloyl group to provide **21** in 71% yield, which was subjected to hydroboration with BH_3·SMe_2, followed by oxidation using $NaBO_3$ to afford **22** in 82% yield.[23] The Mitsunobu reaction of **22** with NsNH−OMOM effected the introduction of the nitrogen atom to give **23** in 88% yield.[24] The PMB group of **23** was then removed with DDQ to afford the diol **24** in 85% yield. The optimized oxidation condition of **24** was required to exclusively obtain the spirolactol **25** in a satisfactory yield without overoxidation to the corresponding lactone species. After testing different oxidation

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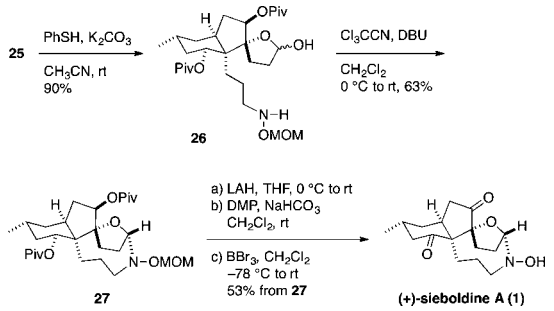
conditions, we found that the oxidation of the diol **24** with 1.5 equiv of IBX in THF/DMSO (1:1) at room temperature provided a clean conversion to the spirolactol **25** in 83% yield.[25]

With the spirolactol **25** in hand, our efforts moved toward constructing the azacyclononane ring and removing the nosyl, pivaloyl, and MOM groups to complete the total synthesis of (+)-sieboldine A (**1**) (Scheme 5). The denosylation of **25** with

Scheme 5. Completion of the Total Synthesis of (+)-Sieboldine A (1)



thiophenolate smoothly proceeded to afford the aminolactol **26** in 90% yield. The *N*-(methoxymethyloxy)azacyclononane ring formation via the intramolecular condensation reaction of **26** was carefully examined using a wide variety of combinations of thermal, dehydrative, Lewis acidic, Brønsted acidic, and even Mitsunobu conditions. However, all these efforts were found to be unsuccessful. We finally reached the conclusion that the Schmidt glycosylation condition was the best one for our purpose. Thus, the aminolactol **26** was treated with Cl_3CCN and DBU in CH_2Cl_2 at 0 °C to room temperature to produce the desired tetracyclic derivative **27** in 63% yield.[26] The LAH reduction of **27** was followed by oxidation with Dess–Martin periodinane to furnish the diketone derivative. Finally, the MOM protecting group of the diketone derivative was removed by the commercially available BBr_3, delivering (+)-sieboldine A (**1**) in 53% yield.[27] The synthetic (+)-**1** exhibited indistinguishable spectral data (^{1}H NMR, ^{13}C NMR, IR, and HRMS) as well as optical rotation (observed $[\alpha]_D^{24}$ +140, *c* = 0.33, MeOH); lit. $[\alpha]_D$ +139, *c* = 0.3, MeOH) from the natural isolate.[3,28]

In conclusion, we have completed the highly enantioselective total synthesis of (+)-sieboldine A (**1**) from 5-(*p*-methoxybenzyloxy)pentyne in 19 steps with a 1.9% overall yield. The key features of this synthesis include (i) enantioselective Keck allylation to form the optically active enyne **10**; (ii) PKR to build the bicyclo[4.3.0]nonenone fragment **13** with a high diastereoselectivity; (iii) Ueno–Stork cyclization to construct the *cis*-hydrindane skeleton with a carbon quaternary center; (iv) regioselective formation of the vinyl acetate moiety followed by oxidation with *m*CPBA to form the oxa-quaternary center; (v) oxidative cyclization to prepare the spirolactol **25**; and (vi) Schmidt glycosylation for assembly of the *N*-hydroxyazacyclononane ring. The enantioselective route for construction of the *cis*-hydrindane core is convergent and flexible, thus providing new avenues to access other fawcettimine-type *Lycopodium* alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03416.

Experimental procedures, characterization for new compounds including NMR spectra and HPLC charts (PDF)
X-ray crystallographic data for **14** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(18) The structure of **14** was determined by spectral evidence and unambiguously confirmed by a single crystal X-ray diffraction analysis. CCDC 1482946 (**14**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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(28) (a) See the Supporting Information for details. (b) The optical rotations of synthetic (+)-sieboldine A reported by Overman and Tu were $[\alpha]_D^{23}$ +141 (*c* = 0.4, MeOH) and $[\alpha]_D^{20.2}$ +135.7 (*c* = 0.28, MeOH), respectively.[5a,6b]

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