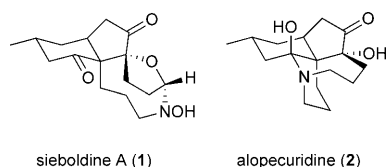


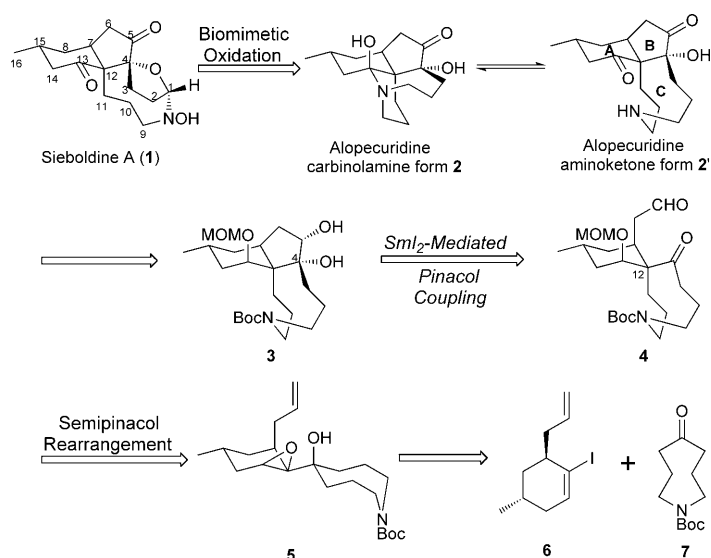
Total Synthesis of (±)-Alopecuridine and Its Biomimetic Transformation into (±)-Sieboldine A**

Xiao-Ming Zhang, Yong-Qiang Tu,* Fu-Min Zhang, Hui Shao, and Xing Meng

Lycopodium alkaloids often possess unusual polycyclic structures and wide-ranging biological activities.^[1] Their challenging skeletons and potential therapeutic applications have provoked broad interests in their total synthesis.^[1a,2] Among the lycopodium alkaloids, sieboldine A (**1**) and alopecuridine (**2**) are two appealing molecules.^[3,4] In particular, sieboldine A inhibits acetyl-



cholinesterase (AChE) significantly ($IC_{50} = 2.0 \mu M$) and is cytotoxic against murine lymphoma L1210 cells ($IC_{50} = 5.1 \mu g mL^{-1}$). Both molecules contain two contiguous quaternary stereocenters and sieboldine A even possesses an unprecedented skeleton with an *N*-hydroxyazacyclononane ring bridged to a tetrahydrofuran ring. Despite their unique structures and significant biological activity, few reports on their total synthesis have appeared. Recently, the Overman research group disclosed an elegant total synthesis of (+)-sieboldine A in 20 steps, in which an efficient gold(I)-catalyzed cyclization/pinacol sequence was used to construct the important *cis*-hydrindanone intermediate.^[2g] However, the total synthesis of alopecuridine and its biomimetic conversion into sieboldine A have not been achieved to date. Herein, we report the first total synthesis of (±)-alopecuridine and its biomimetic transformation into (±)-sieboldine A.



Scheme 1. Retrosynthetic analysis. Boc = *tert*-butoxycarbonyl.

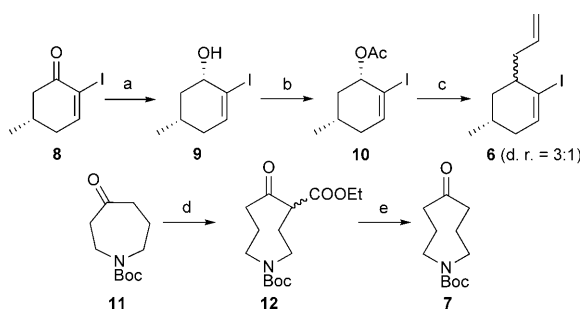
Our retrosynthetic analysis is presented in Scheme 1. Inspired by Kobayashi's proposed biogenetic pathway,^[4] we expected that a two-step oxidation of alopecuridine (**2**) would introduce the *N*-hydroxy group and construct the tetrahydrofuran ring in sieboldine A (**1**). Alopecuridine may exist in either a carbinolamine form **2** or an aminoketone form **2'**.^[3a] Unlike most of the synthesis performed on fawcettimine-type alkaloids, our strategy to obtain the tricyclic core of **2'** leaves the formation of the five-membered B ring until a late stage. A SmI_2 -mediated pinacol coupling^[5] of compound **4** might form ring B and simultaneously establish the oxa-quaternary stereocenter at C4. We further envisioned that the other all-carbon quaternary center at C12 and the aza-cyclononane ring could be constructed through a challenging semipinacol ring expansion^[6] of an eight-membered nitrogen-containing ring from hydroxy epoxide **5**. The precursor **5** could be readily prepared from iodoalkene **6** and carbamate **7** by coupling and epoxidation.

As depicted in Scheme 2, we began our synthesis by the preparation of fragment **6**. Luche reduction of known iodide **8**^[2f,7] afforded *cis*-allylic alcohol **9** quantitatively (d.r. > 20:1).^[8] After transforming the hydroxy group of **9** into its acetyl ester **10**, we attempted to introduce the allyl group by iodine-catalyzed allylation.^[9] However, this method failed to generate iodoalkene **6**; only a small amount of iodo-substituted products were isolated and large quantities of starting materials were recovered. To solve this problem, we attempted to replace the iodine with a Lewis acid. Fortu-

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Scheme 2. Reagents and conditions: a) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH , 0°C (100%), d.r. > 20:1; b) Ac_2O , Et_3N , DMAP, CH_2Cl_2 , 0°C to RT (97%), d.r. > 20:1; c) trimethylallylsilane, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, DCE, 58°C (75%), trans/cis = 3:1; d) $\text{N}_2\text{CHCOOEt}$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, Et_2O , -30°C (55%); e) aq K_2CO_3 , THF, reflux (75%). DMAP = 4-dimethylaminopyridine, THF = tetrahydrofuran.

nately, after some optimization, the reaction was found to proceed in 1,2-dichloroethane (DCE) at 58°C in the presence of excess $\text{BF}_3 \cdot \text{Et}_2\text{O}$. Iodoalkene **6** was obtained in 75% yield as an inseparable 3:1 mixture of diastereoisomers. Subsequent experiments revealed that the major isomer was the *trans*-product.

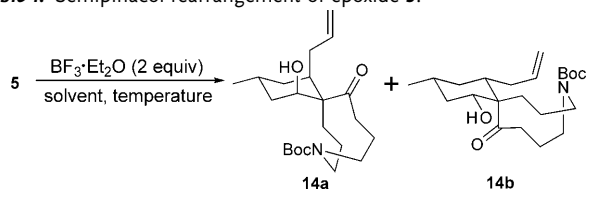
Ketone **7** was then prepared from commercially available azepine **11** through a Tiffeneau–Demjanov-type reaction and subsequent decarboxylation.^[10] Compound **12** was obtained from the rearrangement as the major isomer in 55% yield. Hydrolysis and decarboxylation of **12** proceeded well in one pot to give fragment **7** in 75% yield.

We next attempted to couple fragments **6** and **7** and achieve epoxidation in a regio- and stereoselective manner (Scheme 3). The lithium salt of **6** was first transformed into its cerium salt.^[11] Then **7** was added to afford the coupling product **13**. To avoid elimination, the crude coupling product **13** was directly subjected to the next reaction without purification. As we assumed in Scheme 3, to minimize the

steric interaction between the allyl group and eight-membered ring, the conformational isomers **13aa** and **13ba** would be more stable than **13ab** and **13bb**. As for the conformational isomers **13ac** and **13bc** with axial methyl groups, **13ac** would have similar energy to **13aa**, but **13bc** would be less stable than the corresponding **13ba**. Thus, the hydroxy group should direct epoxidation to occur in the electron-rich alkene with *syn* selectivity to the allyl group. After some attempts, we found that *meta*-chloroperoxybenzoic acid (*m*-CPBA) selectively epoxidized the crude coupling products. Epoxide **5** was then obtained as an inseparable mixture of isomers, which were considered to be the 4-methyl diastereoisomers (d.r. = 3.5:1).

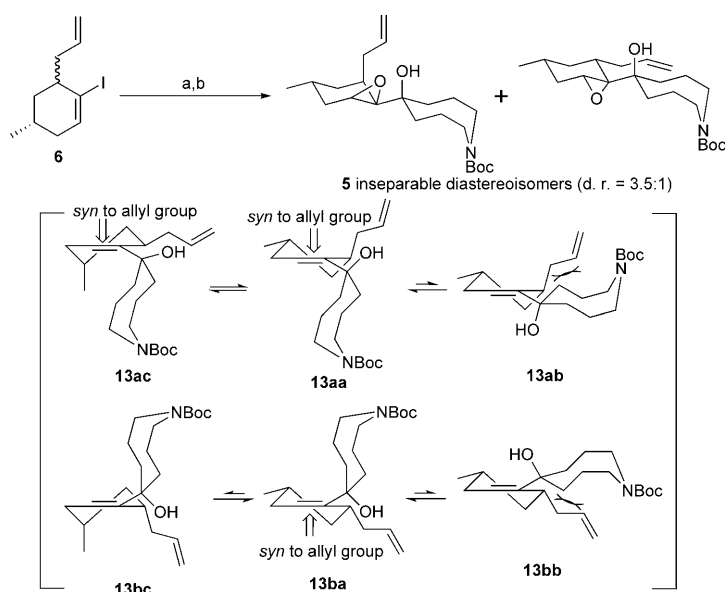
With **5** in hand, the key semipinacol reaction was investigated. Although this type of rearrangement of medium-sized rings has been reported earlier,^[6g] this method has rarely been applied to a total synthesis using a complex substrate. By examining a range of Lewis acids (e.g., TiCl_4 , SnCl_4 , ZnBr_2 , and $\text{BF}_3 \cdot \text{Et}_2\text{O}$), we found that $\text{BF}_3 \cdot \text{Et}_2\text{O}$

Table 1: Semipinacol rearrangement of epoxide **5**.



Entry	Solvent	Temperature	Products (yield [%] ^[a])
1	CH_2Cl_2	$-78 \rightarrow -50^\circ\text{C}$	trace amount
2	CH_2Cl_2	-40°C	14a (20), 14b (10)
3	THF	$-40 \rightarrow 0^\circ\text{C}$	trace amount
4	THF	RT	14a (11), 14b ^[b]
5	Et_2O	$-78 \rightarrow -40^\circ\text{C}$	trace amount
6	Et_2O	$-30 \rightarrow -15^\circ\text{C}$	14a (45), 14b (16)

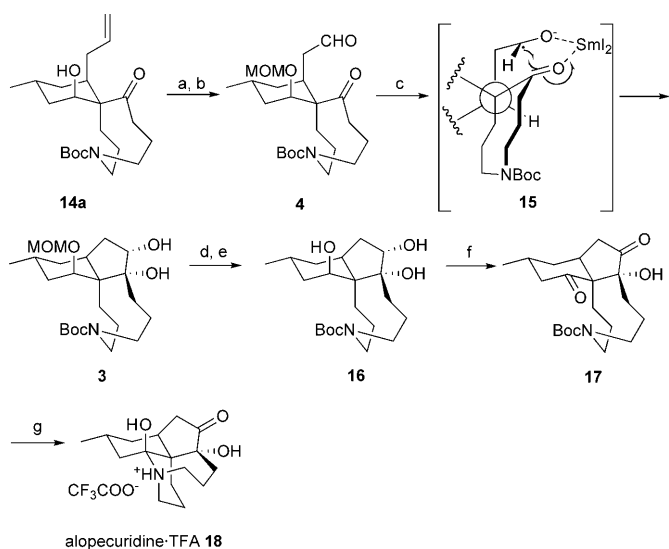
[a] Yield of isolated product. [b] Starting materials and **14b** were obtained as an inseparable mixture.



Scheme 3. Reagents and conditions: a) $t\text{BuLi}$, anhydrous CeCl_3 , then **7**, -78°C ; b) *m*-CPBA, NaHCO_3 , CH_2Cl_2 , 0°C (66% over two steps), d.r. = 3.5:1.

promoted this reaction in CH_2Cl_2 . Further studies showed that both solvent and temperature were crucial to the success of this rearrangement (see Table 1) and the reaction performed using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in Et_2O at $-30 \rightarrow -15^\circ\text{C}$ gave the best result (entry 6). The two desired epimers **14a** and **14b** were readily separated by column chromatography on silica gel. The relative configuration of **14b** was also assigned by X-ray analysis.^[12]

Having established the all-carbon quaternary center and the aza-cyclononane ring, we then focused on the construction of the B ring and the oxa-quaternary carbon center at C4 (Scheme 4). Protection of the hydroxy group with methyl chloromethyl ether (MOMCl), and subsequent ozonolysis, afforded aldehyde **4** in 86% overall yield from **14a**. Upon treatment of **4** with SmI_2 (0.1 mol L^{-1} in THF) at 0°C , stereoselective intramolecular pinacol coupling took place to give *cis*-diol **3** as a result of a chelation effect in the formation of ketyl radical **15**. The structure of **3** was



Scheme 4. Reagents and conditions: a) MOMCl, DIPEA, TBAI, CH₂Cl₂, RT; b) O₃, CH₂Cl₂, -78 °C; then PPh₃, RT (86% over 2 steps); c) HMPA, SmI₂ (0.1 mol L⁻¹), THF, 0 °C (60%); d) 6 N HCl, THF, 50 °C; e) (Boc)₂O, Et₃N, MeOH, RT (80% over 2 steps); f) TPAP, NMO·H₂O, M.S. (4 Å), CH₂Cl₂, RT (55%); g) TFA, CH₂Cl₂, RT, then NaHCO₃, CH₂Cl₂ (96%). DIPEA = *N,N*-diisopropylethylamine, HMPA = hexamethylphosphoramide, M.S. = molecular sieves, NMO·H₂O = *N*-methylmorpholine-*N*-oxide monohydrate, TBAI = tetrabutylammonium iodide, TPAP = tetrapropylammonium perruthenate.

unambiguously confirmed by X-ray crystallographic analysis.^[13] At this point, the key tricyclic core and two contiguous quaternary carbon atoms of alopcuridine (**2**) has been established. The only steps that remained were to remove the protecting groups and oxidize the secondary alcohols. Our initial attempts to selectively remove the MOM group failed, so a two-step procedure was adopted. Thus, compound **3** was treated with 6 M HCl in THF at 50 °C to remove both

protecting groups.^[14] The resulting crude amine was subjected to *N*-Boc protection to furnish **16** in 80% overall yield. The following oxidation with Dess–Martin periodinane, PCC, PDC, and CrO₃/pyridine reagents led to unexpected cleavage of the glycol unit. However, use of Ley conditions gave the desired diketone **17** in moderate yield.^[15] Finally, removal of the Boc group with trifluoroacetic acid (TFA) gave alopcuridine trifluoroacetate **18**.^[16]

To realize our biomimetic transformation to sieboldine A (**1**), we investigated a two-step oxidation based on Kobayashi's proposal (Scheme 5).^[4] Alopcuridine·TFA **18** would be probably oxidized to *N*-oxide **19** by a peroxide agent. Under suitable conditions, *N*-oxide **19** might isomerize to *N*-hydroxide **20** or eliminate to imine **21**, both of which would undergo further oxidation to give nitrone **22**. The final tetrahydrofuran ring in sieboldine A (**1**) could be formed by nucleophilic attack of the hydroxy group to the nitrone. To validate this hypothesis, we first attempted to oxidize alopcuridine·TFA **18** to *N*-oxide **19** with *m*-CPBA in CH₂Cl₂. This transformation proceeded easily in the presence of NaHCO₃. *N*-oxide **19** was unstable during purification, so was directly subjected to the next oxidation step. After screening some solvents, it was found that *N*-oxide **19** could be efficiently oxidized to sieboldine A with HgO in MeOH.^[17] The spectroscopic data (¹H and ¹³C NMR, IR, and HRMS analysis) for synthetic sieboldine A were identical to those reported for the natural product.

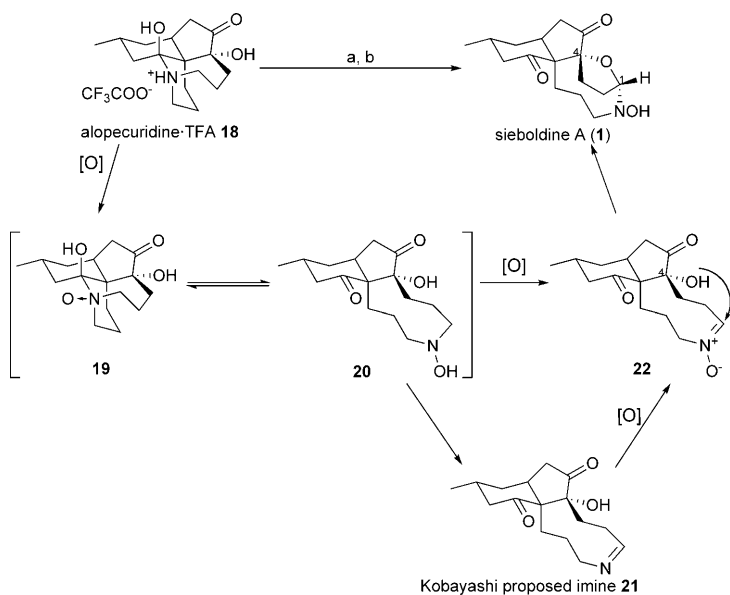
In conclusion, we have achieved the first total synthesis of (±)-alopcuridine in 13 steps and a biomimetic synthesis of (±)-sieboldine A in 15 steps through a common convergent route from known iodide **8**. Key features of this synthesis include a semipinacol rearrangement of a functionalized medium-sized ring and an intramolecular pinacol coupling mediated by SmI₂. The biogenetic pathway from alopcuridine to sieboldine A is also validated for the first time.

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Scheme 5. Reagents and conditions: a) *m*-CPBA, CH₂Cl₂, RT; b) HgO, MeOH, 35 °C (60% over 2 steps).

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