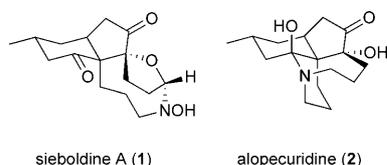


Alkaloid Synthesis

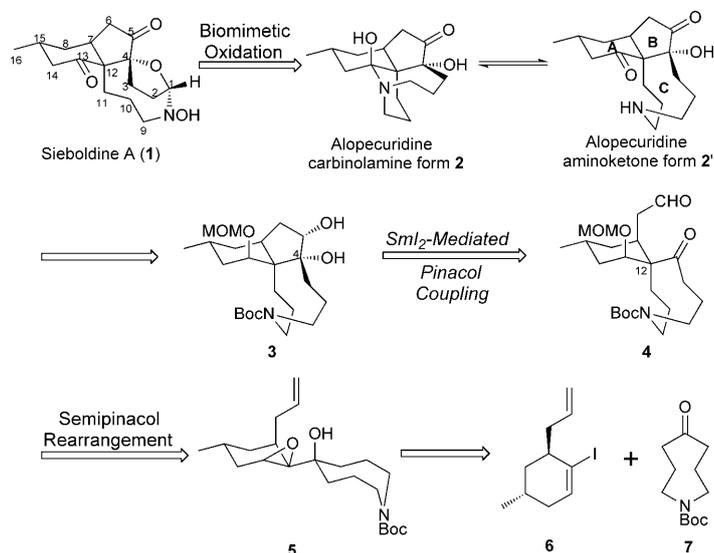
Total Synthesis of (\pm)-Alopecuridine and Its Biomimetic Transformation into (\pm)-Sieboldine A**

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 (\pm)-alopecuridine and its biomimetic transformation into (\pm)-sieboldine A.



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

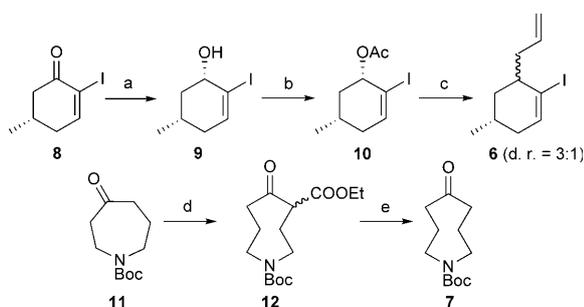
Our retrosynthetic analysis is presented in Scheme 1. Inspired by Kobayashi's proposed biogenetic pathway,^[4] we expected that a two-step oxidation of alopecuridine (**2**) would introduce the *N*-hydroxy group and construct the tetrahydrofuran ring in sieboldine A (**1**). Alopecuridine may exist in 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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[**] This work was supported by the NSFC (Nos. 20921120404, 20672085, 20732002, and 20972059), the National Basic Research Program of China "973" program (2010CB833200), the "111" program of MOE, and the fundamental research funds for the central universities (lzujbky-2010-k09, lzujbky-2009-76, lzujbky-2009-158). We thank Prof. Yuan-Jiang Pan of Zhejiang University for high-resolution mass spectrometry analysis of compounds **9**, **10**, and **6**.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201008147>.



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

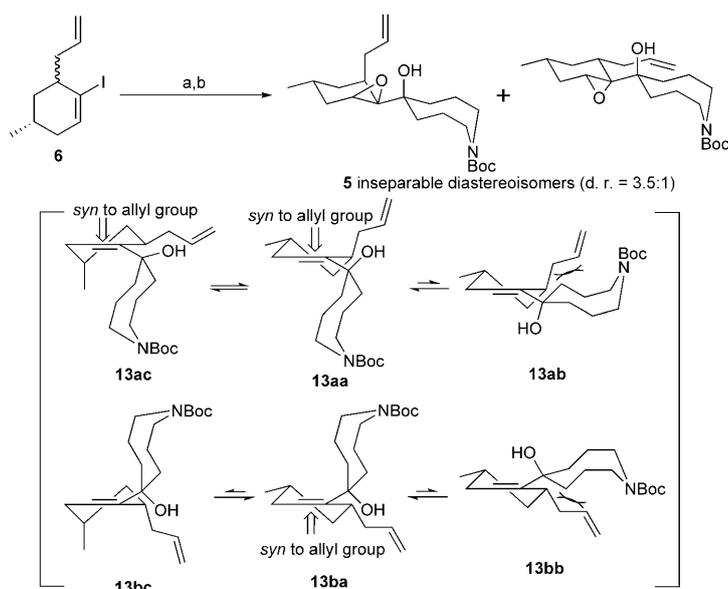
steric interaction between the allyl group and eight-membered ring, the conformational isomers **13aa** and **13ba** would be more stable than **13ab** and **13bb**. As for the conformational isomers **13ac** and **13bc** with axial methyl groups, **13ac** would have similar energy to **13aa**, but **13bc** 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)

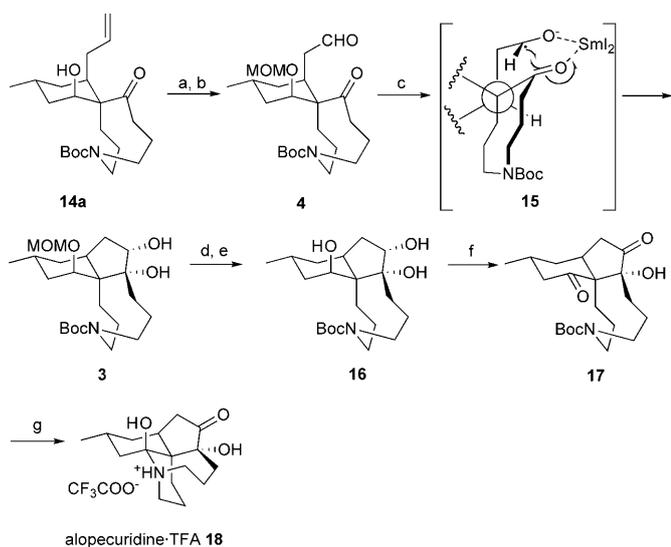
[a] Yield of isolated product. [b] Starting materials and **14b** were obtained as an inseparable mixture.



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.

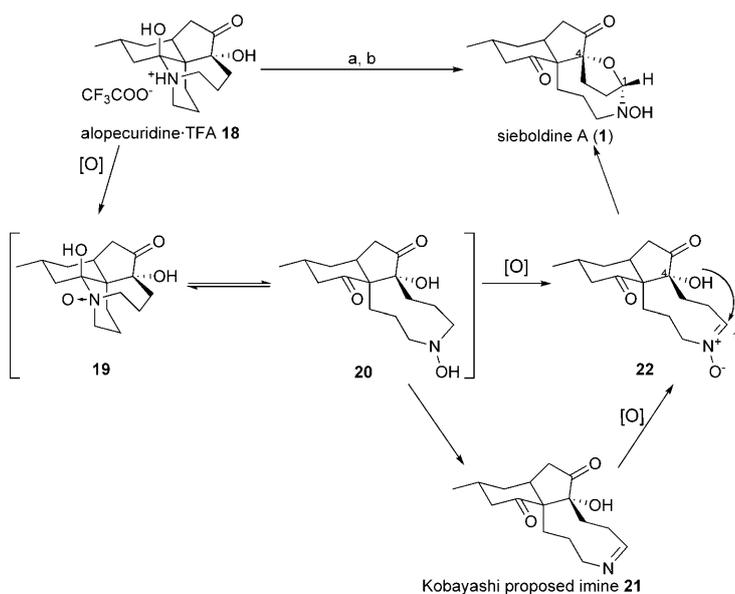
promoted this reaction in CH_2Cl_2 . Further studies showed that both solvent and temperature were crucial to the success of this rearrangement (see Table 1) and the reaction performed using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in Et_2O at $-30 \rightarrow -15^\circ\text{C}$ gave the best result (entry 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 oxo-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 quarternary 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



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

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 nitron **22**. The final tetrahydrofuran ring in sieboldine A (**1**) could be formed by nucleophilic attack of the hydroxy group to the nitron. 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.

Received: December 23, 2010

Revised: February 14, 2011

Published online: March 22, 2011

Keywords: alkaloids · biomimetic synthesis · semipinacol rearrangement · total synthesis

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