Alkaloid Synthesis

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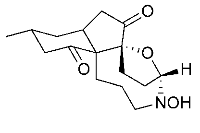
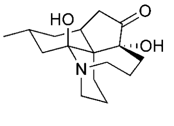
Total Synthesis of (±)-Alopecuridine and Its Biomimetic Transformation into (±)-Sieboldine A**

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

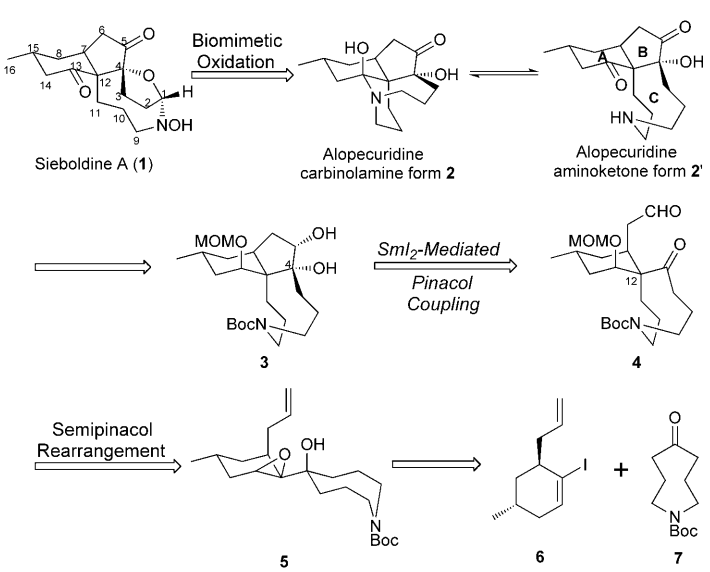
Lycopodium alkaloids often possess unusual polycyclic structures and wide-ranging biological activities.[1] Their challenging skeletons and potential therapeutic applications have provoked broad interests in their total synthesis.[1a,2] Among the lycopodium alkaloids, sieboldine A (**1**) and alopecuridine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



sieboldine A (**1**)



alopecuridine (**2**)



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-quarternary stereocenter at C4. We further envisioned that the other all-carbon quarternary 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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[*] X.-M. Zhang, Prof. Dr. Y.-Q. Tu, Prof. Dr. F.-M. Zhang, H. Shao, X. Meng
Department of Chemistry
State Key Laboratory of Applied Organic Chemistry
Lanzhou University, Lanzhou 730000 (China)
Fax: (+86) 931-891-5557
E-mail: tuyq@lzu.edu.cn

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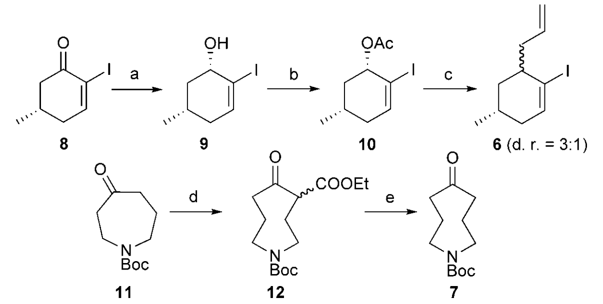


Scheme 2. Reagents and conditions: a) $NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH, 0 °C (100 %), d.r. > 20:1; b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C to RT (97 %), d.r. > 20:1; c) trimethylallylsilane, $BF_3\cdot Et_2O$, DCE, 58 °C (75 %), trans/cis = 3:1; d) $N_2CHCOOEt$, $BF_3\cdot Et_2O$, Et_2O, −30 °C (55 %); e) aq K_2CO_3, THF, reflux (75 %). DMAP = 4-dimethylaminopyridine, THF = tetrahydrofuran.

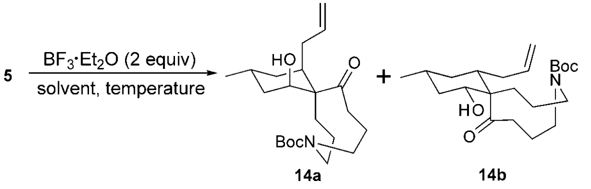
nately, after some optimization, the reaction was found to proceed in 1,2-dichloroethane (DCE) at 58 °C in the presence of excess $BF_3\cdot Et_2O$. Iodoalkene **6** was obtained in 75 % yield as an inseparable 3:1 mixture of diastereoisomers. Subsequent experiments revealed that the major isomer was 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 $BF_3\cdot Et_2O$), we found that $BF_3\cdot Et_2O$ 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 $BF_3\cdot Et_2O$ in Et_2O at −30→−15 °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]

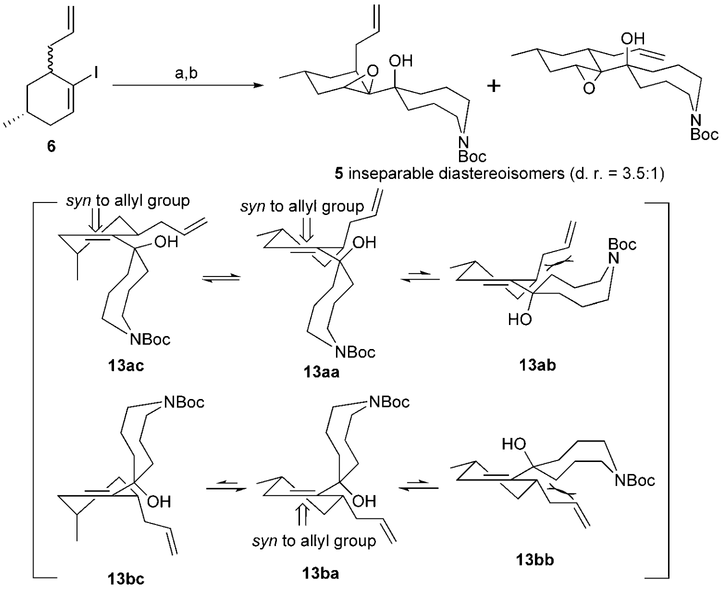
Table 1: Semipinacol rearrangement of epoxide **5**.



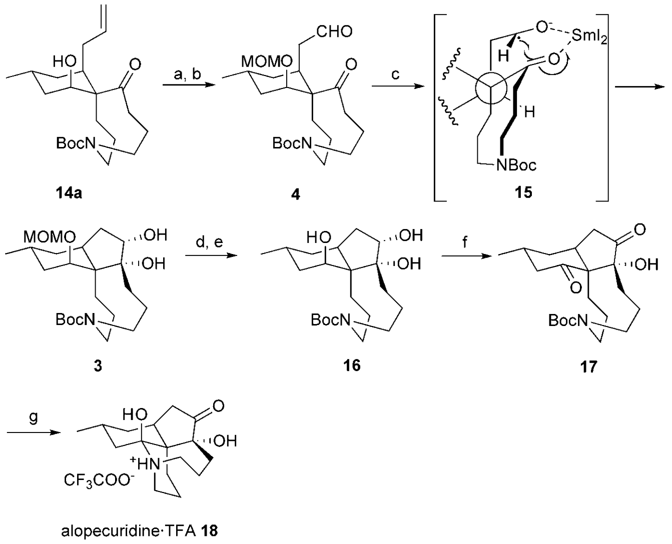
Entry	Solvent	Temperature	Products (yield [%][a])
1	CH_2Cl_2	−78→−50 °C	trace amount
2	CH_2Cl_2	−40 °C	**14a** (20), **14b** (10)
3	THF	−40→0 °C	trace amount
4	THF	RT	**14a** (11), **14b**[b]
5	Et_2O	−78→−40 °C	trace amount
6	Et_2O	−30→−15 °C	**14a** (45), **14b** (16)

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

Having established the all-carbon quarternary 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

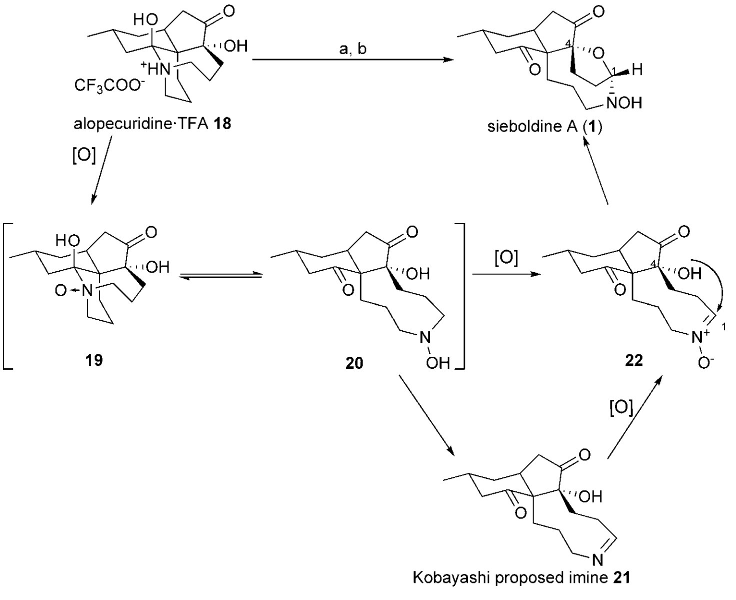


Scheme 3. Reagents and conditions: a) *t*BuLi, anhydrous $CeCl_3$, then **7**, −78 °C; b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C (66 % over two steps), d.r. = 3.5:1.



Scheme 4. Reagents and conditions: a) MOMCl, DIPEA, TBAI, CH$_2$Cl$_2$, RT; b) O$_3$, CH$_2$Cl$_2$, −78 °C; then PPh$_3$, RT (86% over 2 steps); c) HMPA, SmI$_2$ (0.1 mol L^{-1}), THF, 0 °C (60%); d) 6 N HCl, THF, 50 °C; e) (Boc)$_2$O, Et$_3$N, MeOH, RT (80% over 2 steps); f) TPAP, NMO·H$_2$O, M.S. (4 Å), CH$_2$Cl$_2$, RT (55%); g) TFA, CH$_2$Cl$_2$, RT, then NaHCO$_3$, CH$_2$Cl$_2$ (96%). DIPEA = *N*,*N*-diisopropylethylamine, HMPA = hexamethylphosphoramide, M.S. = molecular sieves, NMO·H$_2$O = 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 alopecuridine (**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 CrO$_3$·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 alopecuridinium trifluoroacetate **18**.[16]



Scheme 5. Reagents and conditions: a) *m*-CPBA, CH$_2$Cl$_2$, RT; b) HgO, MeOH, 35 °C (60% over 2 steps).

To realize our biomimetic transformation to sieboldine A (**1**), we investigated a two-step oxidation based on Kobayashi's proposal (Scheme 5).[4] Alopecuridine·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 alopecuridine·TFA **18** to N-oxide **19** with *m*-CPBA in CH$_2$Cl$_2$. This transformation proceeded easily in the presence of NaHCO$_3$. 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 (^{1}H and ^{13}C 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 (±)-alopecuridine 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 a intramolecular pinacol coupling mediated by SmI$_2$. The biogenetic pathway from alopecuridine to sieboldine A is also validated for the first time.

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