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Total Synthesis of (+)-Sieboldine A

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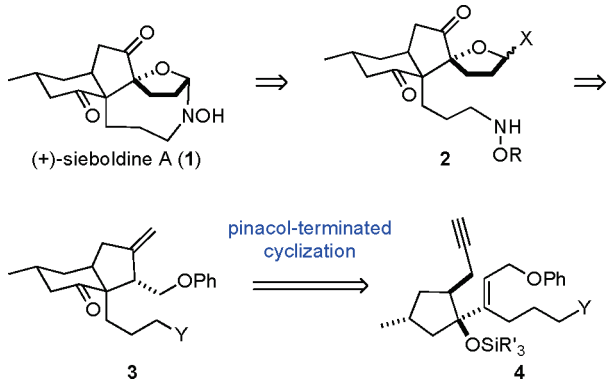
In 2003, Kobayashi and co-workers reported the isolation of (+)-sieboldine A (**1**) from the club moss *Lycopodium sieboldii*, securing its structure by 2D NMR and X-ray analysis.[1,2] Sieboldine A was reported to inhibit electric eel acetylcholinesterase with an IC_{50} value comparable to the *Lycopodium* alkaloid (±)-huperzine A,[3] although it was the uniqueness of its structure, rather than its biological properties that provoked our interest in its synthesis. Sieboldine A contains an unprecedented *N*-hydroxyazacyclononane ring embedded in a bicyclo[5.2.1]decane-*N*,*O*-acetal. To our knowledge, these functional group arrays were previously unknown not only in natural products but also in the chemical literature as a whole. We report herein the first total synthesis of (+)-sieboldine A (**1**).

Our retrosynthetic plan for preparing sieboldine A (**1**) is outlined in Scheme 1. The bicyclo[5.2.1]decane-*N*,*O*-acetal was expected to be sensitive, so we chose to fashion the *N*-hydroxyazacyclononane ring last by the coupling of a tethered hydroxylamine with a five-membered lactol or derivative.[4] The *cis*-hydrindanone core **3** was seen arising from a pinacol-terminated cyclization cascade.[5,6]

Scheme 1



The enantiomerically pure *cis*-hydrindanone intermediate **12** was assembled in 10 steps from readily available tetrahydrocyclopenta[*b*]furan-2-one **5** (>99:1 er) (Scheme 2).[7] Methylcuprate-promoted S_N2' alkylation of **5** and iodolactonization, as described by Curran for the racemate,[8] provided hexahydrocyclopentafuranone **6** in 93% yield (Scheme 2). Slow addition of this intermediate to a slurry of $LiAlH_4$ in refluxing THF afforded diol **7**.[9] Selective protection of the primary alcohol of **7**, followed by Dess−Martin oxidation, yielded (2*S*,4*R*)-cyclopentanone **8**. Conversion of (*E*)-vinyl iodide **9**[10,11] to the corresponding lithium reagent, addition of this species to a THF slurry of $CeCl_3 \cdot 2LiCl$, and addition of cyclopentanone **8** (all at −78 °C) delivered a single allylic alcohol product in 90% yield. Silylation of this intermediate with triethylsilyl triflate (TESOTf) delivered bis(triethylsilyl)ether **10** in 59% overall yield from cyclopentafuranone **5**.

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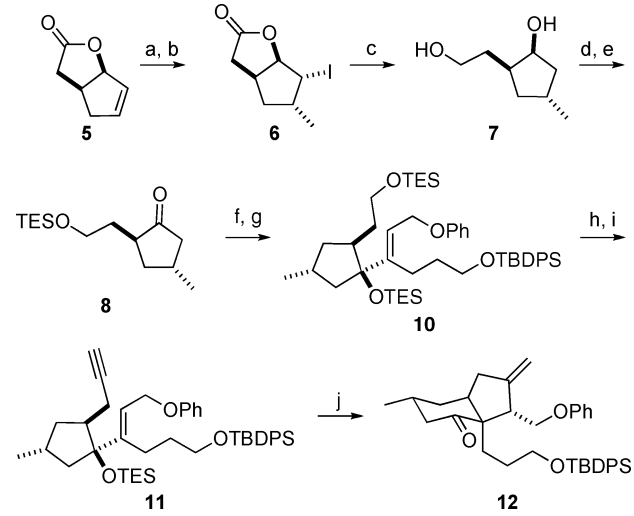
Orchestrating an efficient cyclization-pinacol sequence to deliver a *cis*-hydrindanone intermediate proved challenging. In early experiments, we discovered that standard Prins-pinacol reactions[5] of the dimethyl acetal analogue of **10** [$CH(OMe)_2$ in place of CH_2OTES] yielded the corresponding *cis*-hydrindanone[12] in <45% yield. As a result, we turned to the related pinacol-terminated 1,6-enyne cyclization reaction reported recently by Kirsch and Rhee.[6] The cyclization precursor **11** was readily prepared in 77% overall yield from **10** by Swern oxidation of the primary silyl ether,[13] followed by condensation of the resulting aldehyde with the Ohira−Bestmann reagent.[14] Exposure of enyne **11** at room temperature in CH_2Cl_2 to the cationic gold(I) catalyst described by Kirsch[6b] produced *cis*-hydrindanone **12** in 78% yield as a single stereoisomer.

Scheme 2[a]



[a] (a) MeMgBr, CuBr·SMe_2, THF/SMe_2 (4:1), −20 °C; (b) KI, I_2, $NaHCO_3$, THF, H_2O (93% over 2 steps); (c) $LiAlH_4$, THF, reflux (83%); (d) TESCl, 2,6-lutidine, CH_2Cl_2, −78 °C (98%); (e) Dess−Martin periodinane, CH_2Cl_2 (97%); (f) i. (*E*)-$PhOCH_2CH{=}CI(CH_2)_3OTBDPS$ (**9**), *s*-BuLi, THF, −78 °C ii. $CeCl_3 \cdot 2LiCl$, THF, −78 °C iii. **8**, THF, −78 °C (90%); (g) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (90%); (h) Swern oxidation (86%); (i) $N_2{=}C(COMe)PO(OMe)_2$, K_2CO_3, MeOH, 23 °C (90%); (j) 10 mol % (*t*-Bu)$_2$P(*o*-biphenyl)AuCl, 5 mol % $AgSbF_6$, 1.1 equiv *i*-PrOH, CH_2Cl_2 (78%).

The sequence that we developed after much experimentation for elaborating hydrindanone **12** to (+)-sieboldine A (**1**) is summarized in Scheme 3. Cleavage of the exomethylene group of **12** with ozone, followed by base-promoted elimination of phenoxide provided enone **13**. A europium(III)-catalyzed cyclocondensation of this intermediate with ethyl vinyl ether[15] gave tricyclic dihydropyran **14** in 65% overall yield from precursor **12**. After establishing that the C13 carbonyl group would require protection during the cyclization to form the *N*-hydroxyazacyclononane ring,[16] ketone **14** was reduced with DIBALH to provide axial alcohol **15**. Facial

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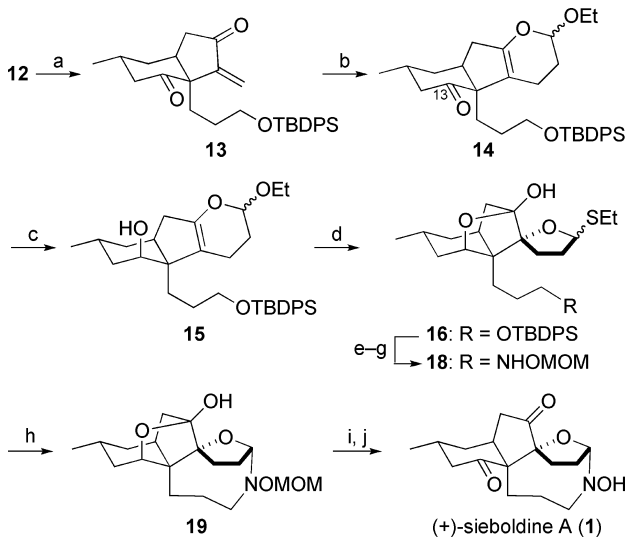
selective oxidation of this intermediate with dimethyldioxirane (DMDO), followed by exposure of the crude product to $BF_3 \cdot OEt_2$ and EtSH gave rise to thioglycoside **16** in 53% overall yield from **14**.

The final *N*-hydroxyazacyclononane ring was fashioned as follows. Removal of the TBDPS group from intermediate **16**,[17] Mitsunobu coupling[18] of the resulting primary alcohol with *N*-Ns-*O*-MOM hydroxylamine (**17**), and removal of the Ns-group under conventional conditions[19] afforded the *O*-(methoxy)methyl (MOM)-protected hydroxylamine cyclization precursor **18**. Exposure of **18** to dimethyl(methylthio)sulfonium triflate (DMTST)[20] in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at −20 °C in acetonitrile provided pentacyclic product **19** in 51% yield.[21] Reintroduction of the C13 carbonyl group by TPAP ($Pr_4N^+RuO_4^-$)-catalyzed oxidation proved uneventful.[22] The MOM protecting group was removed from the diketone product by reaction with an excess of Me_2BBr in CH_2Cl_2 at 0 °C to deliver (+)-sieboldine A (**1**) in 67% yield. Synthetic sieboldine A (**1**), $[\alpha]^{23}_D$ +141 (*c* 0.4, MeOH), exhibited ^1H and ^{13}C NMR spectra indistinguishable from those reported for the natural isolate.[1,23]

Scheme 3[a]



[a] Reagents: (a) i. O_3, $MeOH/CH_2Cl_2$, −78 °C ii. Me_2S, −78→23 °C iii. DBU, MeCN, 0 °C (75%); (b) 10 mol % $Eu(fod)_3$, ethyl vinyl ether, 23 °C (86%); (c) DIBALH, CH_2Cl_2, −78 °C; (d) i. DMDO, CH_2Cl_2, 0 °C ii. $BF_3 \cdot OEt_2$, EtSH, CH_2Cl_2, 0 °C (53% from **14**); (e) TBAF, THF, 23 °C (91%); (f) NsNH-OMOM (**17**), PPh_3, DEAD, C_6H_6, 5 °C (88%); (g) PhSH, K_2CO_3, DMF (95%); (h) DMTST, DTBMP, 4 Å MS, MeCN, −20 °C (51%); (i) 10 mol % TPAP, NMO, 4 Å MS, CH_2Cl_2, 23 °C (88%); (j) Me_2BBr, CH_2Cl_2, 0 °C (67%).

In summary, the first total synthesis of (+)-sieboldine A was accomplished in 20 steps from (3a*S*,6a*R*)-tetrahydrocyclopenta-[*b*]furan-2-one **5**. Our construction of the *cis*-hydrindanone intermediate using Au(I)-catalyzed activation of an alkyne to promote a cyclization-pinacol sequence,[6] rather than Lewis acid activation of an acetal,[5] illustrates the potential advantages in demanding contexts of this mild catalytic procedure. Of particular note was the surprisingly efficient cyclization to form the unprecedented *N*-hydroxyazacyclononane ring from a thioglycoside precursor.

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Supporting Information Available: Experimental details and copies of ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Introduction of the side chain as a protected alcohol allowed various *N*- and *O*-protected hydroxylamine functionalities to be incorporated at this point. This diversification proved important, as defining the optimal nature of the hydroxylamine nucleophile for the final cyclization reaction required significant experimentation. For example, 1,2-oxazacyclodecane formation was observed under alternative cyclization conditions when the hydroxylamine oxygen was unprotected.
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