

## Total Synthesis of (+)-Sieboldine A

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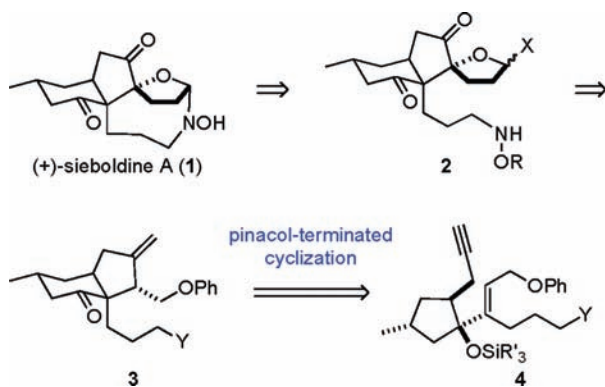
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In 2003, Kobayashi and co-workers reported the isolation of (+)-sieboldine A (**1**) from the club moss *Lycopodium sieboldii*, securing its structure by 2D NMR and X-ray analysis.<sup>1,2</sup> Sieboldine A was reported to inhibit electric eel acetylcholinesterase with an IC<sub>50</sub> value comparable to the *Lycopodium* alkaloid (±)-huperzine A,<sup>3</sup> 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.<sup>4</sup> The *cis*-hydrindanone core **3** was seen arising from a pinacol-terminated cyclization cascade.<sup>5,6</sup>

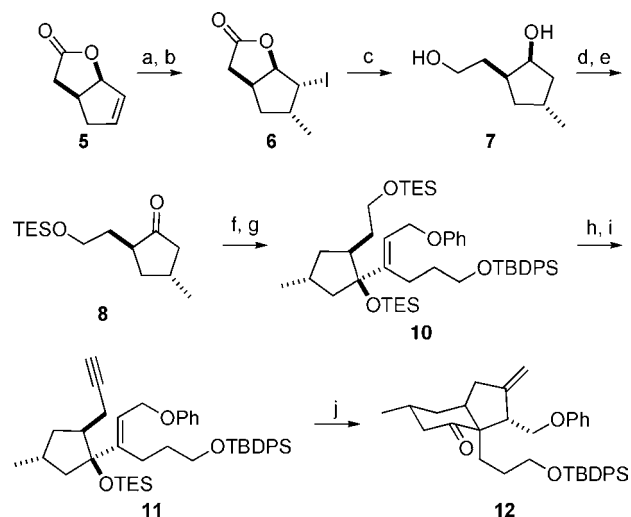
### Scheme 1



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).<sup>7</sup> Methylcuprate-promoted S<sub>N</sub>2' alkylation of **5** and iodolactonization, as described by Curran for the racemate,<sup>8</sup> provided hexahydrocyclopentafuranone **6** in 93% yield (Scheme 2). Slow addition of this intermediate to a slurry of LiAlH<sub>4</sub> in refluxing THF afforded diol **7**.<sup>9</sup> 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**<sup>10,11</sup> to the corresponding lithium reagent, addition of this species to a THF slurry of CeCl<sub>3</sub>·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**.

Orchestrating an efficient cyclization-pinacol sequence to deliver a *cis*-hydrindanone intermediate proved challenging. In early experiments, we discovered that standard Prins-pinacol reactions<sup>5</sup> of the dimethyl acetal analogue of **10** [CH(OMe)<sub>2</sub> in place of CH<sub>2</sub>OTES] yielded the corresponding *cis*-hydrindanone<sup>12</sup> in <45% yield. As a result, we turned to the related pinacol-terminated 1,6-enyne cyclization reaction reported recently by Kirsch and Rhee.<sup>6</sup> The cyclization precursor **11** was readily prepared in 77% overall yield from **10** by Swern oxidation of the primary silyl ether,<sup>13</sup> followed by condensation of the resulting aldehyde with the Ohira–Bestmann reagent.<sup>14</sup> Exposure of enyne **11** at room temperature in CH<sub>2</sub>Cl<sub>2</sub> to the cationic gold(I) catalyst described by Kirsch<sup>6b</sup> produced *cis*-hydrindanone **12** in 78% yield as a single stereoisomer.

### Scheme 2<sup>a</sup>



<sup>a</sup> (a) MeMgBr, CuBr·SMe<sub>2</sub>, THF/SMe<sub>2</sub> (4:1), –20 °C; (b) KI, I<sub>2</sub>, NaHCO<sub>3</sub>, THF, H<sub>2</sub>O (93% over 2 steps); (c) LiAlH<sub>4</sub>, THF, reflux (83%); (d) TESCl, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C (98%); (e) Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub> (97%); (f) i. (*E*)-PhOCH<sub>2</sub>CH=CH(CH<sub>2</sub>)<sub>3</sub>OTBDPS (**9**), *s*-BuLi, THF, –78 °C ii. CeCl<sub>3</sub>·2LiCl, THF, –78 °C iii. **8**, THF, –78 °C (90%); (g) TESOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C (90%); (h) Swern oxidation (86%); (i) N<sub>2</sub>=C(OMe)PO(OMe)<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, MeOH, 23 °C (90%); (j) 10 mol % (*t*-Bu)<sub>2</sub>P(*o*-biphenyl)AuCl, 5 mol % AgSbF<sub>6</sub>, 1.1 equiv *i*-PrOH, CH<sub>2</sub>Cl<sub>2</sub> (78%).

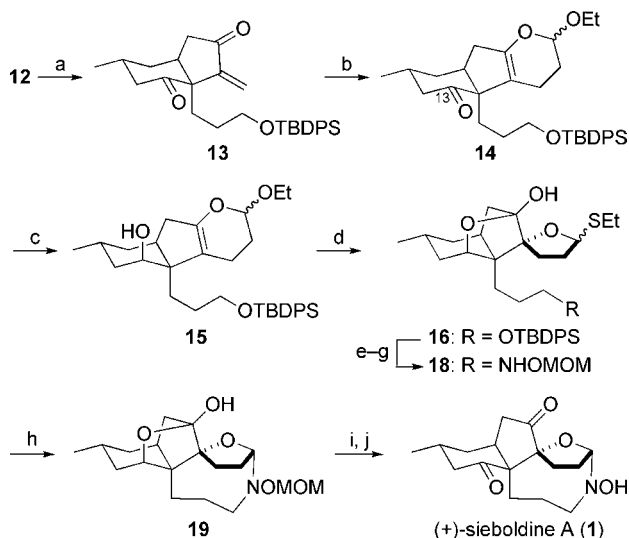
The sequence that we developed after much experimentation for elaborating hydrindanone **12** to (+)-sieboldine A (**1**) is summarized in Scheme 3. Cleavage of the exomethylene group of **12** with ozone, followed by base-promoted elimination of phenoxide provided enone **13**. A europium(III)-catalyzed cyclocondensation of this intermediate with ethyl vinyl ether<sup>15</sup> 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,<sup>16</sup> 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  $\text{BF}_3 \cdot \text{OEt}_2$  and  $\text{EtSH}$  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**,<sup>17</sup> Mitsunobu coupling<sup>18</sup> of the resulting primary alcohol with *N*-*N*-*O*-MOM hydroxylamine (**17**), and removal of the *N*s-group under conventional conditions<sup>19</sup> afforded the *O*-(methoxy)methyl (MOM)-protected hydroxylamine cyclization precursor **18**. Exposure of **18** to dimethyl(methylthio)sulfonium triflate (DMTST)<sup>20</sup> in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at  $-20^\circ\text{C}$  in acetonitrile provided pentacyclic product **19** in 51% yield.<sup>21</sup> Reintroduction of the C13 carbonyl group by TPAP ( $\text{Pr}_4\text{N}^+\text{RuO}_4^-$ )-catalyzed oxidation proved uneventful.<sup>22</sup> The MOM protecting group was removed from the diketone product by reaction with an excess of  $\text{Me}_2\text{BBr}$  in  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  to deliver (+)-sieboldine A (**1**) in 67% yield. Synthetic sieboldine A (**1**),  $[\alpha]_{\text{D}}^{23} +141$  (*c* 0.4, MeOH), exhibited  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra indistinguishable from those reported for the natural isolate.<sup>1,23</sup>

### Scheme 3<sup>a</sup>



<sup>a</sup> Reagents: (a) i.  $\text{O}_3$ ,  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$  ii.  $\text{Me}_2\text{S}$ ,  $-78 \rightarrow -23^\circ\text{C}$  iii. DBU, MeCN,  $0^\circ\text{C}$  (75%); (b) 10 mol %  $\text{Eu}(\text{fod})_3$ , ethyl vinyl ether,  $23^\circ\text{C}$  (86%); (c) DIBALH,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ; (d) i. DMDO,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  ii.  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{EtSH}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  (53% from **14**); (e) TBAF, THF,  $23^\circ\text{C}$  (91%); (f)  $\text{NsNH-OMOM}$  (**17**),  $\text{PPh}_3$ , DEAD,  $\text{C}_6\text{H}_6$ ,  $5^\circ\text{C}$  (88%); (g)  $\text{PhSH}$ ,  $\text{K}_2\text{CO}_3$ , DMF (95%); (h) DMTST, DTBMP, 4 Å MS, MeCN,  $-20^\circ\text{C}$  (51%); (i) 10 mol % TPAP, NMO, 4 Å MS,  $\text{CH}_2\text{Cl}_2$ ,  $23^\circ\text{C}$  (88%); (j)  $\text{Me}_2\text{BBr}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  (67%).

In summary, the first total synthesis of (+)-sieboldine A was accomplished in 20 steps from (3*aS*,6*aR*)-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,<sup>6</sup> rather than Lewis acid activation of an acetal,<sup>5</sup> 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  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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