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Total Synthesis of (+)-Sieboldine A

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Abstract

The first total synthesis of (+)-sieboldine A was completed in 20 steps from readily available (3a*S*, 6a*R*)-3,3a,4,6-atetrahydro-2*H*-cyclopenta[*b*]furan-2-one (**5**). Key steps are: (a) a pinacol-terminated 1,6-enyne cyclization reaction to form the *cis*-hydrindanone core (**11** → **12**), (b) formation of the spiro tetrahydrofuran ring by stereoselective DMDO oxidation of tricyclic dihydropyran intermediate **15**, and (c) formation of the unprecedented *N*-hydroxyazacyclononane ring by cyclization of a thioglycoside precursor (**18** → **19**).

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 IC₅₀ 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 not only previously unknown in natural products, but 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}

The enantiomerically pure *cis*-hydrindanone intermediate **12** was assembled in ten steps from readily available tetrahydrocyclopenta[*b*]furan-2-one **5** (>99:1 er) (Scheme 2).⁷ Methylcuprate-promoted S_N2' anti-opening 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 LiAlH₄ 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 CeCl₃·2LiCl, 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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Supporting Information Available: Experimental details and copies of ¹H and ¹³C NMR spectra of new compounds (80 pages)

Orchestrating an efficient cyclization-pinacol sequence to deliver a *cis*-hydrindanone intermediate proved challenging. In early experiments, we discovered that standard Prins-pinacol reactions⁵ of the dimethyl acetal analog of **10** [CH(OMe)₂ in place of CH₂OTES] yielded the corresponding *cis*-hydrindanone¹² 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 CH₂Cl₂ to the cationic gold(I) catalyst described by Kirsch^{6b} produced *cis*-hydrindanone **12** in 78% yield as a single stereoisomer.

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 ether¹⁵ 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 selective oxidation of this intermediate with dimethyldioxirane (DMDO), followed by exposure of the crude product to BF₃·OEt₂ 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 coupling¹⁸ 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 (Pr₄N⁺RuO₄[–])-catalyzed oxidation proved uneventful.²² The MOM protecting group was removed from the diketone product by reaction with an excess of Me₂BBr in CH₂Cl₂ at 0 °C to deliver (+)-sieboldine A (**1**) in 67% yield. Synthetic sieboldine A (**1**), [α]_D²³ +141 (c 0.4, MeOH), exhibited ¹H and ¹³C NMR spectra indistinguishable from those reported for the natural isolate.^{1,23}

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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23. The reported optical rotation for natural (+)-sieboldine A is $[\alpha]_{\text{D}} +139$ (c 0.3, MeOH).¹ A sample of natural sieboldine A is apparently no longer available.

Scheme 1.

Scheme 2a.

^a (a) MeMgBr, CuBr·SMe₂, THF:SMe₂ (4:1), -20 °C; (b) KI, I₂, NaHCO₃, THF, H₂O (93% over 2 steps); (c) LiAlH₄, THF, reflux (83%); (d) TESCl, 2,6-lutidine, CH₂Cl₂, -78 °C (98%); (e) Dess–Martin periodinane, CH₂Cl₂ (97%); (f) i. (*E*)-PhOCH₂CH=Cl(CH₂)₃OTBDPS (**9**), *s*-BuLi, THF, -78 °C ii. CeCl₃·2LiCl, THF, -78 °C iii. **8**, THF, -78 °C (90%); (g) TESOTf, 2,6-lutidine, CH₂Cl₂, 0 °C (90%); (h) Swern oxidation (86%); (i) N₂=C(COMe)PO(OMe)₂, K₂CO₃, MeOH, 23 °C (90%); (j) 10 mol % (*t*-Bu)₂P(*o*-biphenyl)AuCl, 5 mol % AgSbF₆, 1.1 equiv *i*-PrOH, CH₂Cl₂ (78%)

Scheme 3a.

^a Reagents: ; (a) i. O₃, MeOH/CH₂Cl₂, -78 °C ii. Me₂S, -78→23 °C iii. DBU, MeCN, 0 °C (75%); (b) 10 mol % Eu(fod)₃, ethyl vinyl ether, 23 °C (86%); (c) DIBALH, CH₂Cl₂, -78 °C; (d) i. DMDO, CH₂Cl₂, 0 °C ii. BF₃·OEt₂, EtSH, CH₂Cl₂, 0 °C (53% from **14**); (e) TBAF, THF, 23 °C (91%); (f) NsNH-OMOM (**17**), PPh₃, DEAD, C₆H₆, 5 °C (88%); (g) PhSH, K₂CO₃, DMF (95%); (h) DMTST, DTBMP, 4 Å MS, MeCN, -20 °C (51%); (i) 10 mol % TPAP, NMO, 4 Å MS, CH₂Cl₂, 23 °C (88%); (j) Me₂BBr, CH₂Cl₂, 0 °C (67%).