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Stereoselective Total Synthesis of (±)-Alstoscholarisine E

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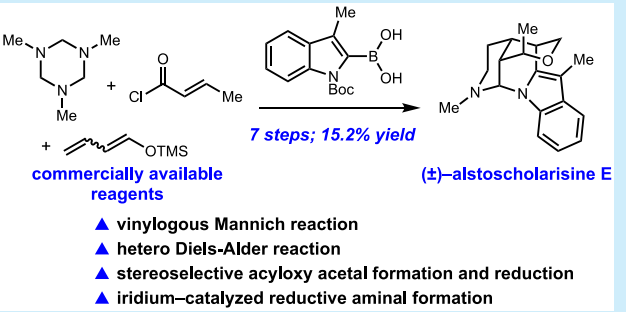
Supporting Information

ABSTRACT: The shortest synthesis to date of (±)-alstoscholarisine E was accomplished in seven linear steps from commercially available reagents and 15.2% overall yield. The approach features a tandem vinylogous Mannich reaction and hetero-Diels−Alder reaction to access the core. A novel tactic to induce diastereoselective reduction of the cyclic vinyl ether was discovered, and a mild procedure to form the bridged aminal ring by partial reduction of the lactam ring via iridium-catalyzed hydrosilylation was developed.



Progressive neuronal decline is a salient feature of Alzheimer's disease and other neurodegenerative disorders that lead to severe cognitive impairments and create significant healthcare challenges.[1] Despite extensive efforts, there are no effective treatments that prevent or reverse the neuronal deficits associated with these debilitating diseases.[2] One approach that has recently attracted significant attention as a potential disease-altering option is neural stem cell (NSC) therapy.[3] Because small molecules can be exploited to effect chemical control over stem cell proliferation, they have emerged as useful tools to develop new therapies to treat neurodegenerative processes.[4] It is therefore notable that the indole alkaloids alstoscholarisines A−E (**1**−**5**), which were isolated in 2014, promote NSC proliferation (Figure 1).[5]

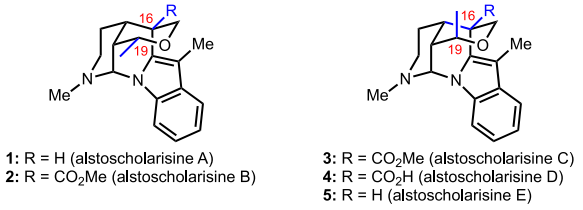


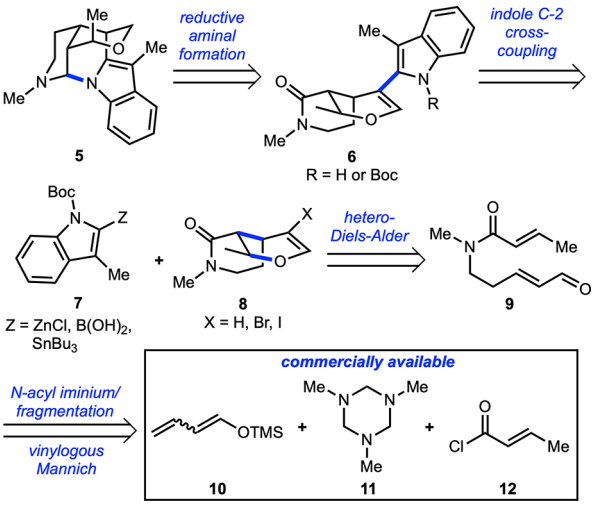
Figure 1. Structures of alstoscholarisines A−E.

Alstoscholarisine A (**1**) and E (**5**), respectively, are among the most potent members of the family, and **1** was found to promote neuronal fate commitment. Although they differ in substitution at C-16 and stereochemistry at C-19, **1**−**5** comprise a similar pentacyclic framework containing a *cis*-fused oxahydroisoquinolone ring bearing five contiguous stereocenters. The tetrahydropyran ring is bridged by an indole moiety that forms a cyclic aminal with the piperidine ring to create the novel caged structure.

The structural complexity of the alstoscholarisines coupled with their interesting biological activity quickly captured the attention of the synthetic community.[6] Two racemic and two enantioselective syntheses of alstoscholarisine A,[7] as well as the synthesis of racemic B−D,[7c,8] have been achieved; the racemic and enantioselective syntheses of alstoscholarisine E were only recently disclosed.[7c,d] Despite these successes, the reported syntheses of **1**−**5** require 12−17 chemical steps[9] in their longest linear sequence (LLS) and proceed with modest overall yields that range from 1.0 to 4.6%. We now report a concise and high-yielding synthesis of (±)-alstoscholarisine E (**5**).

Our convergent approach to (±)-alstoscholarisine E (**5**) is outlined in retrosynthetic format in Scheme 1. We envisaged that the advanced intermediate **6** would be transformed into **5** via stereoselective reduction of the enol ether group in **6**,

Scheme 1. Retrosynthetic Analysis of Alstoscholarisine E



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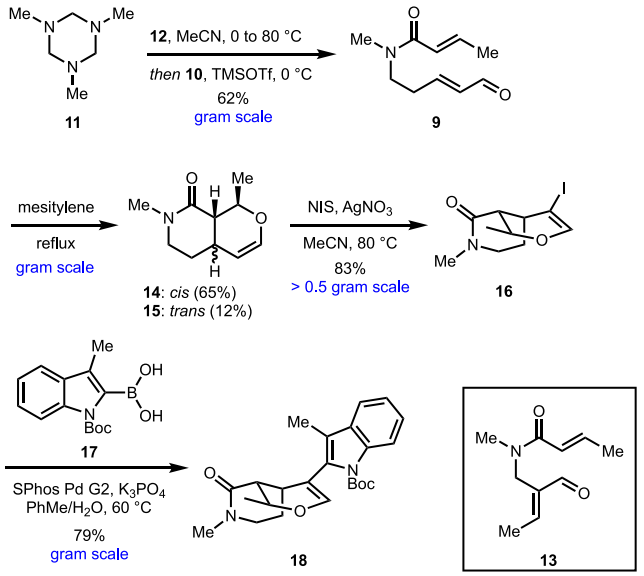
Org. Lett. XXXX, XXX, XXX−XXX

followed by partial reduction of the lactam moiety and spontaneous transannular cyclization to form the bridging aminal moiety in **5**. Access to **6** would be achieved by cross-coupling of a suitable 3-methylindole derivative **7** with the *cis*-oxahydroisoquinolone **8** (X = Br, I) using a Negishi, Suzuki, or Stille reaction. The synthesis of *cis*-oxahydroisoquinolones similar to **8** via intramolecular hetero-Diels–Alder reactions of heterodienes related to **9** is well precedented in our laboratories,[10] and we have implemented this cycloaddition in the syntheses of several natural products.[11] The vinylogous Mannich reaction,[12] a construction we pioneered and showcased in the syntheses of numerous alkaloids,[13] might be exploited to generate **9** in a single step via reaction of trimethylsilyloxydiene **10** with the *N*-acyliminium ion generated from *N*-acylation of hexahydrotriazine **11** with crotonyl chloride (**12**) and subsequent fragmentation.

The synthesis of alstoscholarisine E commenced with converting the hexahydrotriazine **11** directly to **9** (Scheme 2). The *N*-acylation of triazines such as **11** is known to

Scheme 2. Synthesis of the Indolyl Oxahydroisoquinolone

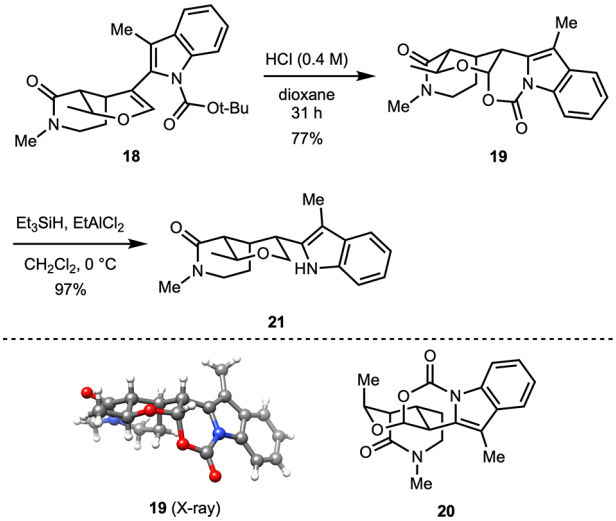


generate transient *N*-acyliminium ions that can be captured by a variety of nucleophiles, including enol ethers,[14] but we are not aware of any application of such a process to a vinylogous Mannich reaction using π-nucleophiles such as **10**. Gratifyingly, we discovered that stirring a solution of hexahydrotriazine **11** and crotonyl chloride in MeCN at 80 °C, followed by reaction with diene **10** (ca. 9:1 *E*/*Z*) at 0 °C in the presence of TMS-OTf provided the desired ene–aldehyde **9** in 62% yield together with 10% of the regioisomer **13**. Consistent with our earlier studies,[10,11b,c] heating **9** in mesitylene under reflux afforded a readily separable mixture (5.4:1) of the *cis*- and *trans*-fused cycloadducts **14** and **15** in 77% combined yield.[11a,15] Treating **14** with *N*-iodosuccinimide (NIS) in the presence of a catalytic amount of $AgNO_3$ (10 mol %), according to a slight modification of a protocol reported by Vankar[16] furnished the vinyl iodide **16** in 83% yield.

The stage was then set for the cross-coupling of **16** with a suitable derivative of 3-methylindole to give **18**. After numerous attempted Negishi couplings failed, we turned to a Suzuki reaction using the known indole boronic acid **17**.[17] A variety of catalysts were screened to couple **16** and **17**, but competitive protodeborylation, a well-known side reaction of 2-heterocyclic boronic acids in Suzuki reactions, resulted in low yields.[18] We turned to the SPhos Pd G2 precataylst,[19] which is reported to promote Suzuki couplings of challenging substrates and was contemporaneously shown to induce the cross-coupling of **17** with a similar oxahydroisoquinolone.[7d] Although initial efforts gave **18** in only 18% yield because of persistent protodeborylation of **17**, we eventually discovered that increasing the catalyst loading from 5 to 10 mol % and using 4 equiv of **17** afforded **18** in 79% yield on a gram scale.

Our original plan to induce the stereoselective reduction of **18** in one step to provide **21** anticipated an ionic reduction initiated by diastereoselective, axial protonation of the enol ether moiety in **18** from the less hindered face followed by hydride reduction of the intermediate carbocation (Scheme 3).

Scheme 3. Stereoselective Reduction of Enol Ether Moiety



Somewhat surprisingly, treatment of **18** with Et_3SiH in the presence of CF_3CO_2H furnished a mixture (1:1, 60% yield) of the bicyclic acetal **19** and a diastereomer that has been tentatively identified as **20**; none of the desired product **21** was obtained. Armed with this unexpected result, we queried whether we might optimize this cyclization to selectively furnish **19**. After some experimentation, we discovered that treating **18** with 0.4 M HCl in dioxane delivered **19** as a single diastereomer in 77% yield. The structure of **19** was confirmed by X-ray crystallography.

The bicyclic acetal moiety in **19** proved to be remarkably resistant toward reductive opening under acidic conditions. Hydride reduction in the presence of a variety of Lewis acids that were known to promote reductive opening of bicyclic lactone acetals returned only starting material.[20] Eventually, we discovered that use of $EtAlCl_2$ in the presence of Et_3SiH led to smooth reductive opening and decarboxylation to deliver **21** in 97% yield. The diastereoselectivity achieved in this two-step reduction sequence is notable given that catalytic hydrogenation of an indolyl oxahydroisoquinolone similar to **18** in Liao's synthesis of (−)-alstoscholarisine E gave a mixture (2.2:1) of diastereomers.[7d]

All that remained to complete the synthesis of (±)-alstoscholarisine E was partial reduction of the lactam moiety of **21** followed by cyclization to form the bridging aminal ring in accord with similar cyclizations in the prior art.[7c,d,8] However,

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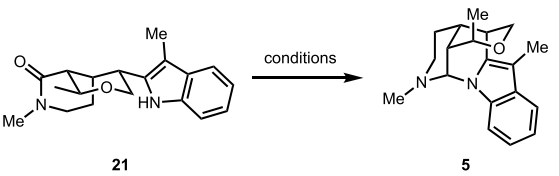
Org. Lett. XXXX, XXX, XXX–XXX

only trace quantities of **5** were observed in early attempts using known conditions to achieve this transformation (Table 1, entries 1−3). We then turned to hydrosilylation of the amide as an alternative tactic.[21] In the event, attempted reduction of **21** using Ph_2SiH_2 under conditions developed by Buchwald produced a mixture containing only small quantities of **5** (entry 4).[22] Alternatively, reaction of **21** with 1,1,3,3-tetramethyldisiloxane (TMDS) and Ti(O*i*-Pr)$_4$ at 50 °C according to a modification of a protocol reported by Lemaire produced **5** in 56% yield (entry 5).[23] When **21** was treated with TMDS in the presence of a catalytic amount of Vaska's complex (2 mol %) in PhMe following conditions reported by Nagashima,[24] **5** was isolated in similar yields, but some overreduction to the amine was observed (entry 6). However, simply switching the solvent for the reduction to CH_2Cl_2 delivered (±)-alstoscholarisine E (**5**), which exhibited spectral properties consistent with those previously reported,[5,7c,d] in 77% yield (entry 7). Although partial reduction of amides using Vaska's complex and TMDS followed by nucleophilic trapping of the intermediate iminium ion is known,[25] to our knowledge this represents the first example in which the intermediate is captured by a nitrogen nucleophile to generate an aminal. Hence, it is a useful extension of existing methodology for reductive refunctionalization of tertiary lactams and amides.

Table 1. Completion of the Synthesis of (±)-Alstoscholarisine E via Reductive Cyclic Aminal Formation



21 5

entry	conditions	yield (%)
1	DIBAL-H, CH_2Cl_2, −78 °C	trace[a]
2	Cp_2ZrHCl, THF, 70 °C	trace[a]
3	Bu_3SnH, Tf_2O, MeCN, −40 °C to rt	trace[a]
4	Ph_2SiH_2, Ti(O*i*-Pr)$_4$, THF, 50 °C	trace[a]
5	TMDS, Ti(O*i*-Pr)$_4$, PhMe, 50 °C	56[b]
6	TMDS, $IrCl(CO)(PPh_3)_2$, PhMe, rt	56[c]
7	TMDS, $IrCl(CO)(PPh_3)_2$, CH_2Cl_2, rt	77[b]

[a]Small, nonquantifiable formation of **5** was observed in LCMS of crude reaction mixture. [b]Isolated yield after chromatographic purification. [c]Yield determined by ^{1}H NMR spectroscopy with an internal standard.

In summary, we completed a concise and efficient synthesis of (±)-alstoscholarisine E (**5**) that requires only seven chemical steps (LLS) from commercially available reagents and proceeds in 15.2% overall yield. The synthesis features a novel variant of the vinylogous Mannich reaction and an intramolecular hetero-Diels−Alder reaction to quickly access the *cis*-oxahydroisoquinolone core, a subunit common to a large number of indole alkaloids. Another key step in the synthesis is the unprecedented and highly diastereoselective reduction of the vinyl ether moiety in **18** by a stereoselective acid-catalyzed cyclization and Lewis acid promoted hydride reduction sequence. A new and mild procedure to form cyclic aminals was also developed and applied to complete the synthesis of (±)-alstoscholarisine E (**5**) by a route that is considerably shorter and more efficient than previous syntheses of members of the alstoscholarisine family of natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04093.

Experimental procedures and spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 1947103 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX