Communication

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Enantioselective Total Synthesis of (–)-Alstoscholarisine A

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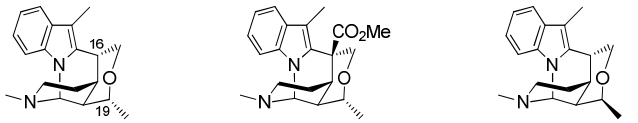
Supporting Information Placeholder

ABSTRACT: We report a concise and highly enantioselective total synthesis of (–)-alstoscholarisine A (**1**), a recently isolated monoterpenoid indole alkaloid that has significant bioactivity in promoting adult neuronal stem cells proliferation. A highly enantioselective (99% ee), intramolecular Ir-catalyzed Friedel-Crafts alkylation of indole **9** with a secondary allylic alcohol was utilized to establish the first stereogenic center upon which the other three contiguous chiral centers were readily set by a highly stereoselective tandem 1,4-addition and aldol reaction. The key tetrahydropyran was constructed through a hemiacetal reduction, and the final aminal bridge was forged by a one-pot reductive amination/cyclization. The conciseness of this approach was highlighted by building core bonds in each step with a minimalist protecting group strategy.

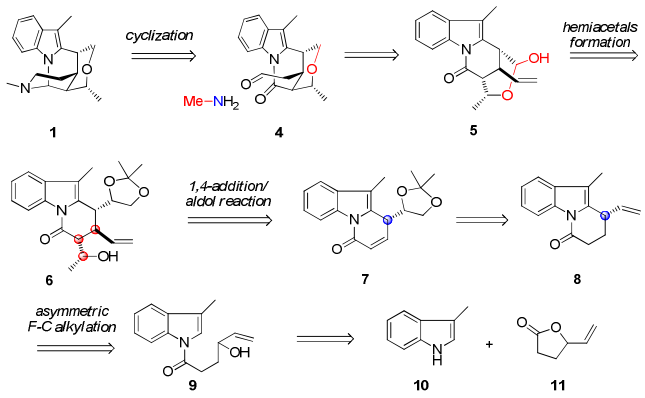


alstoscholarisine A alstoscholarisine B alstoscholarisine E

Figure 1. Monoterpenoid indole alkaloids alstoscholarisine A, B and E.

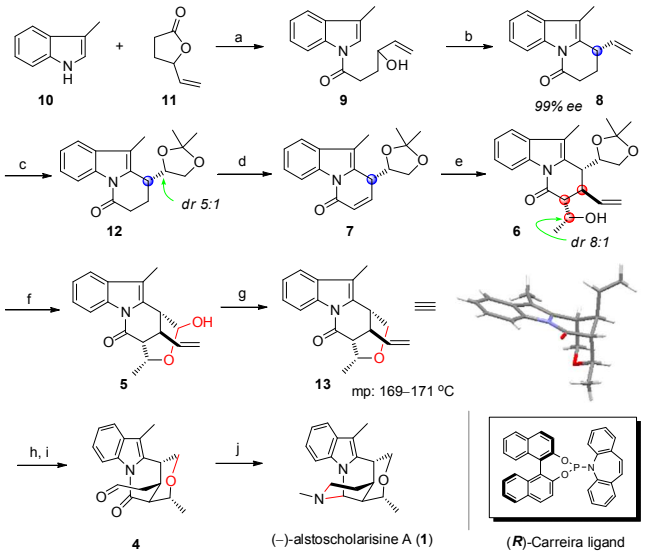
Neurodegenerative diseases, such as Alzheimer′s and Parkinson′s diseases, are characterized by a progressive loss of neuronal activity.[1] Novel methods aimed at restoration of neuronal viability or prevention of neuronal decline are in high demand. In this regard, identifying small molecules that modulate hippocampal neuronal stem cells (NSCs) is therefore therapeutic useful.[2] The alstoscholarisines[3] are five intriguing monoterpenoid indole alkaloids with a complex pentacyclic structure discovered by Luo and co-workers recently from *Alstonia scholaris* (Figure 1). Structurally, these alkaloids all share an identical synthetically challenging pentacyclic core arrayed with five contiguous stereogenic centers. The compounds differ only in the presence or absence of a carboxylic acid/ ester moiety on C16 and/or the configuration at C19. Biologically, they all show promising activity in promoting adult NSC proliferation, in which the most active alstoscholarisine A (**1**) functioned at low concentrations (0.1μg/mL). Considering that alstoscholarisine A (**1**) might be a valuable agent in the treatment of neurological disorders and its complex molecular architecture, we initiated a synthetic program, hoping to establish a concise and flexible route for future SAR study. During our preparation of this manuscript, an elegant 13-step racemic synthesis of (±)-**1** was just published online.[4] We report herein an enantioselective total synthesis of (–)-**1** in 10 steps.

Scheme 1



As illustrated in Scheme 1, our retrosynthetic analysis of (–)-alstoscholarisine A (**1**) calls for a late stage construction of the aminal bridge by the one-pot reductive amination/cyclization[5] of tetracyclic aldehyde **4** with methylamine. Tetracyclic aldehyde **4** contains a tetrahydropyran moiety, which was envisioned to arise from the reduction of the hemiacetal **5**.[6] Further inspection of the four contiguous stereogenic centers in the hemiacetal precursor **6**, surprisingly, reveals that they can be installed strategically via a stereoselective tandem 1,4-addition and aldol reaction from the unsaturated tricyclic amide **7**. The pivotal stereogenic center could be established easily in the formation of tricycle **8**. The stereogenic center harbored in the tricycle **7** or **8** is strategically useful for our synthesis because it could exert influence on setting other three stereogenic centers. In spite of no precedent, we were audacious to propose that tricycle **8** could be generated via an asymmetric intramolecular Friedel-Crafts alkylation[7] of indole **9** with a secondary allylic alcohol by taking advantage of Carreira's iridium catalysis system.[8] The requisite Friedel-Crafts alkylation substrate **9** could be prepared directly from two simple starting materials, 3-methylindole (**10**) and 4-vinylbutyrolactone (**11**).[9]

Scheme 2[a]



[a]Reagents and conditions: (a) $AlMe_3$, DCM, 40 °C, 75%; (b) [{Ir(cod)Cl}$_2$] (3 mol%), (***R***)-Carreira ligand (12 mol%), Sc(OTf)$_3$ (20 mol%), DCE, rt, 75%; (c) OsO_4 (5 mol%), NMO (5.0 equiv), THF-H_2O, rt, then *p*-TSA (0.1 equiv), 2,2-dimethyoxypropane, DMF, rt, 75% major, 15% minor; (d) LiHMDS (3.0 equiv), PhSeBr (1.5 equiv), THF, −78 °C, then H_2O_2, NH_4Cl, DCM, 70%; (e) CuI (3.0 equiv), vinyl magnesium bromide (6.0 equiv), acetaldehyde (6.0 equiv), THF, −78 °C, 75%; (f) HCl (4 *N*), $NaIO_4$ (3.0 equiv), MeOH, rt, 86%; (g) Et_3SiH (1.5 equiv), BF_3•Et_2O (2.0 equiv), DCM, −78 °C to rt, 85%; (h) BH_3•THF (2.0 equiv), THF, 0 °C to rt, $NaBO_3$ (4.0 equiv), 78%; (i) DMP (2.0 equiv), DCM, rt, 81%; (j) $MeNH_2$•HCl (20 equiv), Et_3N (20 equiv), $Ti(OiPr)_4$ (20 equiv), THF, rt, then $LiAlH_4$ (20 equiv), 40 °C, 58%.

The synthetic pathway toward (−)-alstoscholarisine A (**1**) is outlined in Scheme 2. Acylation of 3-methylindole (**10**) with known 4-vinylbutyrolactone (**11**) was promoted by trimethylaluminium,[10] leading to secondary allylic alcohol **9** in 75% yield. Catalytic asymmetric Friedel-Crafts alkylation of **9** using the combination of [{Ir(cod)Cl}$_2$], (*R*)-Carreira ligand[8] and Lewis acid Sc(OTf)$_3$ successfully provided tricycle **8** in 75% yield with 99% *ee*. The resulting terminal olefin of **8** was dihydroxylated, and then protected as the corresponding acetonide **12**. Without the addition of any exogenous stereodirecting agents, the osmium-catalyzed dihydroxylation produced a 5:1 diastereomeric mixture that could be separated cleanly after acetonide formation. Furthermore, the diastereomeric ratio was inconsequential given that both stereoisomers are viable precursors to the desired natural product. Treatment of the major acetonide isomer with a standard selenenylation-elimination protocol[11] afforded a conjugated tricyclic amide **7**. With amide **7** in hand, the stage was set to the key installation of the contiguous stereogenic centers in a cascade manner. Gratifyingly, copper iodide-promoted 1,4-addition of a vinyl Grignard reagent to the unsaturated amide **7** followed by aldol reaction with acetaldehyde, stereospecifically delivered β-hydroxyl amide **6** in 75% yield.[12] The 8:1 diastereomeric ratio was deemed sufficient for our purposes. After removal of the acetonide protecting group in **6** followed by cleavage of the diol with $NaIO_4$ and concomitant cyclization, a mixture of 1:1 diastereomeric hemiacetals **5** was obtained. Reduction of this mixture with triethylsilane–BF_3•Et_2O gave **13** (85%, mp: 169–171°C) as a crystalline compound, whose structure was confirmed by both 2-D NMR and a single crystal X-ray crystallographic analysis. Hydroboration-oxidation of the terminal olefin **13** followed by oxidation of the resulting primary alcohol using the Dess-Martin periodinane gave aldehyde **4** in 81% yield. Finally, aldehyde **4** was converted to (−)-alstoscholarisine A (**1**) via a one-pot reductive amination/cyclization procedure.[5,13] Our synthetic material was analytically identical to the authentic sample donated by Professor Luo.

In summary, we have developed the first concise route for the enantioselective total synthesis of (−)-alstoscholarisine A (**1**), a newly discovered monoterpenoid alkaloid that is potent in promoting adult NSC proliferation. The synthesis was accomplished in 10 steps. Each step is productive in building molecular complexity with a minimalist protecting group strategy.[14] Ir-catalyzed intramolecular Friedel-Crafts alkylation of indole with a secondary allylic alcohol, tandem 1,4-additon-aldol reaction, facile construction of the tetrahydropyran and the one-pot reductive amination/cyclization endgame strategy were all particularly effective for this synthesis. It is worthy to note that the five components utilized in this flexible strategy, namely, indole **10**, lactone **11**, vinyl-copper species, acetaldehyde and methylamine are not only inexpensive but also can be modified easily to prepare various alstoscholarisine analogues, which will be immensely beneficial for future SAR study.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications website at DOI:
Full characterization, analysis of enantioselectivity, spectral data, experimental procedures (PDF)
X-ray crystallographic data for **13** (CIF)

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Notes

The authors declare no competing financial interests.

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