

Total Synthesis of (+)-Scholarisine A

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Supporting Information

ABSTRACT: An effective total synthesis and assignment of the absolute configuration of the architecturally challenging compound (+)-scholarisine A has been achieved via a 20-step sequence. Highlights include a reductive cyclization involving a nitrile and an epoxide, a modified Fischer indole protocol, a late-stage oxidative lactonization, and an intramolecular cyclization leading to the indolenine ring system of (+)-scholarisine A.

Scholarisine A (**1**), a monoterpenoid indole alkaloid first isolated in 2008 from the leaves of *Alstonia scholaris*, comprises an unprecedented scaffold containing a bridged lactone inscribed in a cagelike skeleton (Figure 1).¹ Although

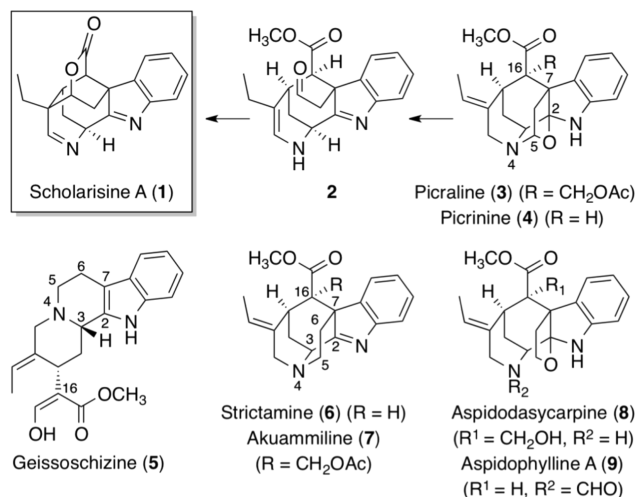


Figure 1. Biosynthesis of (+)-scholarisine A (**1**).

no information on the bioactivity of **1** is currently available, congeners of a putative biosynthetic precursor, picraline (**3**),² have been reported to be potent, selective inhibitors of SGLT2, a renal cortex membrane protein that regulates glucose reabsorption, which was recently validated as a target for type-II diabetes intervention.³

Alkaloids that are derived biosynthetically from geissoschizine (**5**) via a cyclization leading to a bond between C-7 and C-16⁴ are classified as the akuammiline alkaloids (Figure 1),⁵ named after akuammiline (**7**),⁶ which was first characterized in 1932.⁷ Loss of the acetoxymethyl moiety leads to strictamine (**6**).⁸ Hydrolysis and further functionalization is envisioned to provide alkaloids with a furoindoline core such as aspidodasycarpine (**8**)⁹ and aspidophylline A (**9**),¹⁰ the latter being the target of a recent elegant racemic total synthesis by Garg.¹¹ Alternatively, **7** could give rise to picrinine (**4**)¹² upon loss of the acetoxymethyl moiety from C-16 and oxidation at C-5. Scholarisine A (**1**), the target of this study, is proposed to arise from **4** via initial opening of the oxygen bridge at C-2 via participation of the indoline nitrogen and cleavage of the N-4–C-5 bond to furnish an aldehyde at C-5; migration of the double bond, nucleophilic attack by the resulting enamine carbon, and capture of the resulting hydroxyl group by the methyl ester would lead to the lactone ring of **1**.¹

Given the novel architectural features of **1**, in conjunction with the inherent synthetic challenge and the possibility of discovering a substrate that would permit a novel enantioselective route to the currently unobtainable akuammiline alkaloids via a late-stage “retro-biosynthetic” fragmentation,¹³ we initiated a synthetic program to construct **1** in 2008. We report here the first total synthesis of (+)-scholarisine A (**1**), comprising an enantiospecific strategy.

From the retrosynthetic perspective, we envisioned scholarisine A (**1**) to arise via cyclization and oxidation of indole lactone **10** (Figure 2). Construction of the latter would entail

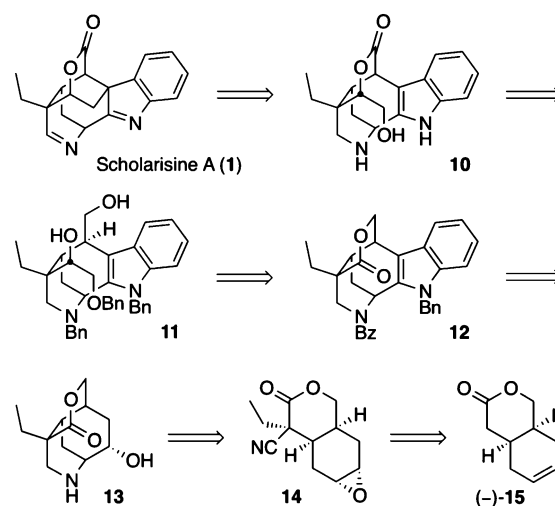


Figure 2. Retrosynthetic analysis of (+)-scholarisine A (**1**).

an oxidative lactonization of diol **11** with subsequent deprotection. Diol **11** in turn could be derived from lactone **12** via homologation and reduction, the latter being obtained

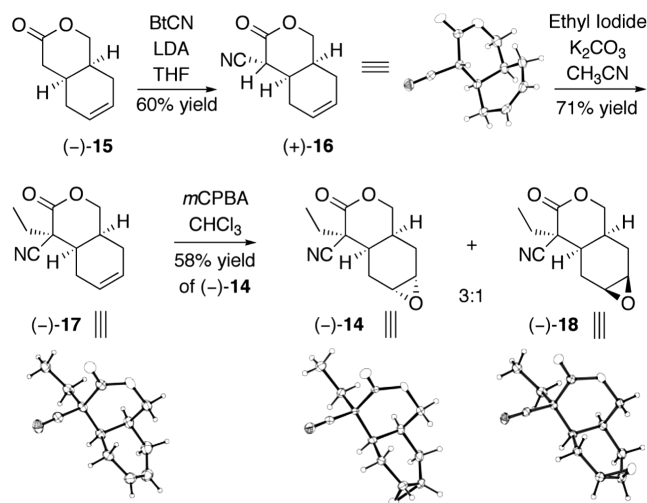
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from tricyclic amine **13** upon amine protection, oxidation, and a Fischer indole annulation. Amine **13**, the cornerstone construct of this synthetic venture, was envisioned to be the product of a reductive cyclization involving the nitrile and epoxide functionalities present in lactone **14**, which could be prepared from known bicyclic lactone (–)-**15**.¹⁴

Toward this end, cyanation of (–)-**15** with cyanobenzotriazole (Scheme 1) using basic conditions¹⁵ provided nitrile

Scheme 1



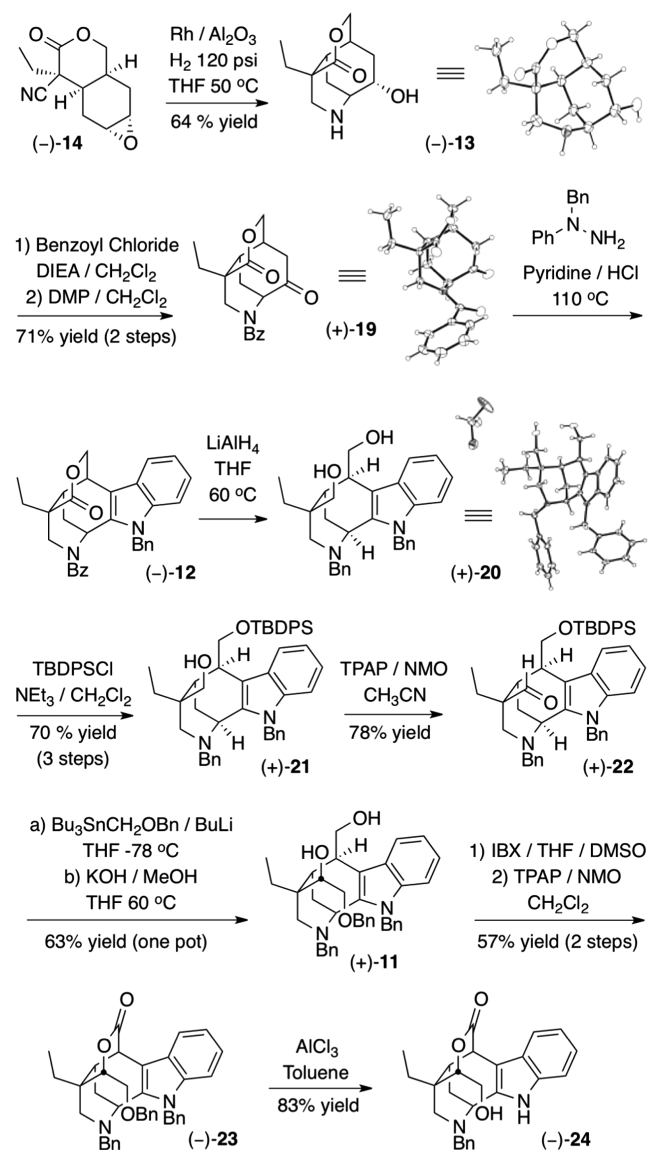
lactone (+)-**16**¹⁶ in 60% yield after an extractive workup. Alkylation occurring from the convex face utilizing ethyl iodide furnished cyanolactone (–)-**17**¹⁶ in 71% yield, which upon epoxidation with *m*-chloroperoxybenzoic acid (*m*CPBA) in chloroform led to a mixture of epoxides.¹⁷ The desired epoxide (–)-**14**¹⁶ was formed selectively over the undesired (–)-**18**;¹⁶ the ratio was 3:1. Crystallization from toluene provided pure (–)-**14** in 58% yield.

Reductive cyclization of epoxide (–)-**14** was then achieved employing rhodium on alumina¹⁸ via hydrogenation with in situ epoxide ring opening to generate tricyclic compound (–)-**13**¹⁶ (Scheme 2). Benzoyl protection of the amine in tricycle (–)-**13** followed by oxidation of the hydroxyl group with Dess–Martin periodinane (DMP)¹⁹ then led to ketone (+)-**19**.¹⁶

We next turned to installation of the indole ring.²⁰ A Fischer synthesis utilizing 1-benzyl-1-phenylhydrazine (pyridine–HCl, 110 °C)²¹ furnished the protected indole lactone (–)-**12**. We found that 1-benzyl-1-phenylhydrazine proved highly effective, whereas use of phenylhydrazine led to complete decomposition.²² Indole (–)-**12** was next reduced with LiAlH₄ to furnish diol (+)-**20**,¹⁶ which cocrystallized with chloroform, permitting confirmation of the absolute configuration by X-ray analysis. Diol (+)-**20** was next selectively protected as the TBDPS ether (+)-**21**,²³ which in turn was oxidized with tetrapropylammonium perruthenate (TPAP) using *N*-methylmorpholine *N*-oxide (NMO) as a co-oxidant²⁴ to furnish aldehyde (+)-**22**. Pleasingly, this four-step sequence proved highly effective, proceeding in 55% yield. Earlier studies had indicated that protection of both nitrogen atoms was required in order to prevent side reactions during the oxidation process.

With aldehyde (+)-**22** in hand, treatment with benzyloxymethyl lithium, derived from benzyloxymethyltributylstannane and *n*-BuLi,²⁵ led to diol (+)-**11** as the major product after workup with methanolic KOH to remove the TBDPS group;

Scheme 2



this one-pot, two-step sequence proceeded in 63% yield. Nuclear Overhauser effect NMR spectroscopy (NOESY) studies suggested the average conformation of the carbonyl in (+)-**22** to be that illustrated in Figure 3. External nucleophilic attack of (+)-**22** would explain the high selectivity observed during the formation of diol (+)-**11**.

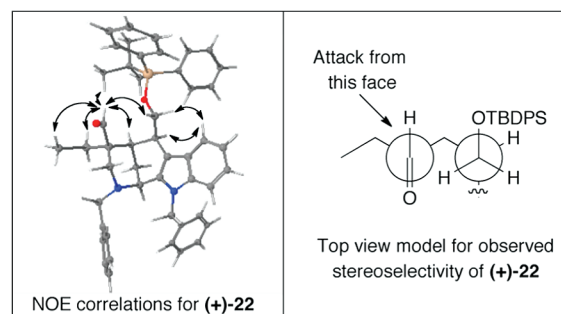
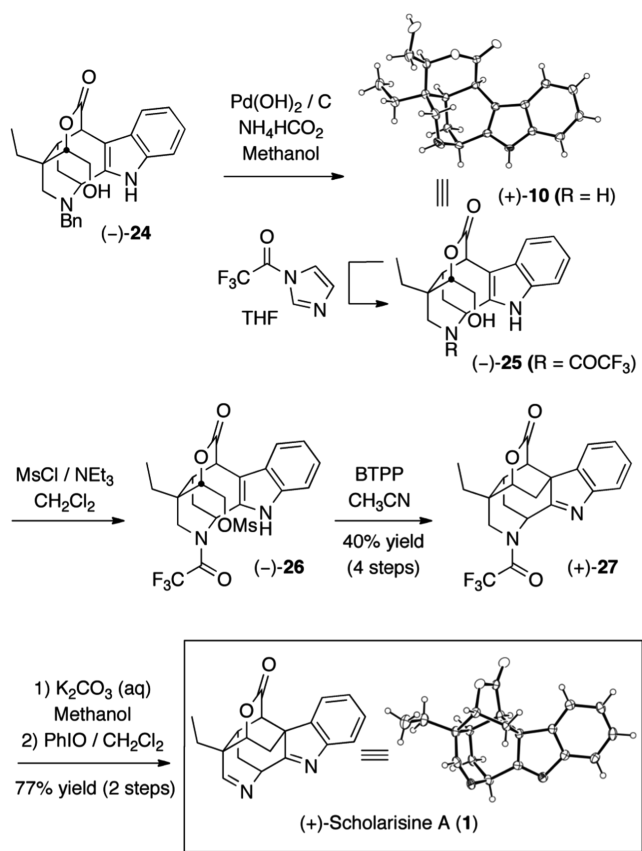


Figure 3. NOE analysis of (+)-**22** and stereoselectivity in the formation of (+)-**11**.

A two-step oxidative lactonization employing 2-iodoxybenzoic acid (IBX) in a 1:1 mixture of tetrahydrofuran (THF) and dimethyl sulfoxide (DMSO) followed by TPAP/NMO in methylene chloride was next achieved to access lactone (–)-23 from diol (+)-11 in 57% yield. Stepwise oxidation to generate the lactol employing IBX²⁶ prevented the formation of the undesired side products that were observed when diol (+)-11 was subjected directly to the TPAP/NMO conditions. Subsequent treatment of lactone (–)-23 with AlCl₃ in toluene under sonication conditions then selectively removed the protecting groups on the oxygen and the indole nitrogen to furnish alcohol (–)-24 in 83% yield.²⁷

Various attempts to activate the hydroxyl group in (–)-24 for cyclization with the indole ring resulted in decomposition, most likely as a result of intramolecular cyclization involving the basic tertiary amine. An exchange of nitrogen protection was therefore required in order to attenuate the reactivity of the piperidine nitrogen. The latter was achieved via transfer hydrogenolysis to give amine (+)-10¹⁶ followed by treatment with trifluoroacetylhydrazide in THF²⁸ to furnish trifluoroacetamide (–)-25 (Scheme 3). Activation of the 1° alcohol with

Scheme 3



methanesulfonyl chloride then provided the stable sulfonate ester (–)-26, which upon cyclization triggered by indole deprotonation with *tert*-butylimino-tri(pyrrolidino)-phosphorane (BTTP)²⁹ furnished indolenine (+)-27 in 40% yield over four steps. Removal of the trifluoroacetyl group in (+)-27 with a 1:2 mixture of saturated aqueous K₂CO₃ and methanol, followed by aliphatic amine oxidation with iodosobenzene (PhIO) in methylene chloride,³⁰ completed the synthesis of (+)-scholarisine A (1),¹⁶ which displayed

spectral properties identical in all respects to those reported for the natural product [i.e., ¹H and ¹³C NMR (500 and 125 MHz, respectively), HRMS parent ion identification, and chiroptic properties].¹

In summary, the first total synthesis and assignment of the absolute configuration of (+)-scholarisine A has been achieved with a longest linear reaction sequence of 20 steps from known lactone (–)-15.³¹ Highlights of the synthesis include a reductive cyclization involving a nitrile and an epoxide, a modified Fischer indole protocol, a late-stage oxidative lactonization, and an intramolecular cyclization leading to the indolenine ring system of (+)-scholarisine A.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectra, complete ref 3b, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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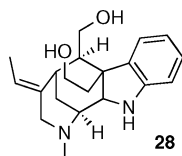
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(13) Oxidation state manipulation and/or functionalization would most likely be required for such a fragmentation. Indoline **28**, a reported degradation derivative of aspidodasycarpine (see ref 9), possesses the carbon scaffold contained in the akuammiline alkaloids. All members of this class can be considered as oxidized and functionalized analogues of this scaffold.



(14) Lactone (–)-**15** was prepared via the reported four-step enzyme-mediated asymmetric functionalization of meso-cyclohex-4-ene-1,2-dimethanol. See: (a) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *J. Org. Chem.* **1995**, *60*, 2506–2513. (b) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *Tetrahedron* **1994**, *50*, 8837–8852. (c) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *Tetrahedron: Asymmetry* **1990**, *1*, 793–800. See the Supporting Information for a modified preparation amenable to scale-up.

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(16) The structures of (+)-**10**, (–)-**13**, (–)-**14**, (+)-**16**, (–)-**17**, (–)-**18**, (+)-**19**, (+)-**20**, and totally synthetic scholarisine A (**1**) were confirmed by single-crystal X-ray analysis.

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(31) The assignment of the absolute configuration of (+)-scholarisine A (**1**) was derived from the known absolute configurations of (–)-**15** and (+)-**20**.