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Alstoscholarisines H–J, Indole Alkaloids from *Alstonia scholaris*: Structural Evaluation and Bioinspired Synthesis of Alstoscholarisine H

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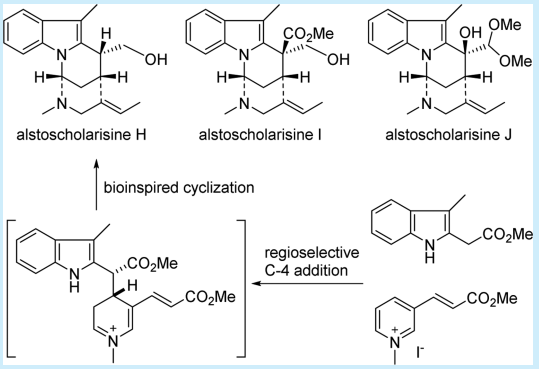
Supporting Information

ABSTRACT: Alstoscholarisines H–J (**1**–**3**), new monoterpenoid indole alkaloids with an unprecedented skeleton created via the formation of a C-3/N-1 bond, were isolated from *Alstonia scholaris*. Their structures were established by extensive spectroscopic analyses and the assessment of single-crystal X-ray diffraction data. The total synthesis of alstoscholarisine H was achieved via the regioselective nucleophilic addition of pyridinium through a bioinspired iminium ion intermediate followed by Pictet–Spengler-like cyclization.



Monoterpenoid indole alkaloids (MIAs) of *Alstonia* comprise nearly 400 compounds and are very attractive due to their complex structures and diverse biological bioactivities.[1] In our continuing investigations of indole alkaloids, we have reported the isolation of a series of new MIAs from different parts of *A. scholaris*.[2] Among these MIAs, (*E*/*Z*)-alstoscholarine, scholarisine A, alstolactine A, and alstoscholarisine A have been introduced as "Hot off Press",[3] and (*E*/*Z*)-alstoscholarine, scholarisine A, picrinine, and scholarisine G have been synthesized by outstanding chemists after our report.[4] Moreover, MIAs from *A. scholaris* leaves have demonstrated antitussive, antiasthmatic, anti-inflammatory, analgesic, and expectorant activities both *in vitro* and *in vivo*.[5] Subsequently, a defined mixture of alkaloids from *A. scholaris* leaves was registered as an investigational new botanical drug (No. 2011L01436) and approved for clinical trials (phases I and II) by the China Food and Drug Administration (CFDA). Then, a monocenter, randomized, double-blind, and placebo phase I clinical trial has been finished, and the results will support further phase II clinical trials. Moreover, in our investigation examining *A. scholaris* leaves that had been stored for seven years, alstolactines A–C derived from picrinine via oxidation and cyclization and alstoscholarisines A–E, which promote adult neuronal stem cell (NSC) proliferation, were reported.[6] During our ongoing studies involving chemical investigations of *A. scholaris*, alstoscholarisines H–J (**1**–**3**, Figure 1) with unprecedented skeletons generated via the formation of C-3/N-1 bonds were isolated. Here, we report the isolation and structural elucidation of alstoscholarisines H–J and the total synthesis of alstoscholarisine H.

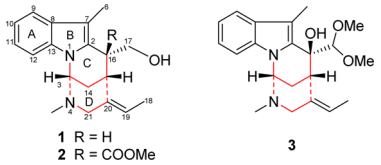


Figure 1. Structures of alkaloids **1**–**3**.

Alstoscholarisine H (**1**), which was obtained as a colorless crystal, was assigned a molecular formula of $C_{19}H_{24}N_2O$ based on its molecular ion peak at *m*/*z* 296.1886 $[M]^+$ in HREIMS in conjunction with its ^{13}C NMR spectral data (Table S1, Supporting Information), which indicated nine degrees of unsaturation. The ^{13}C NMR and DEPT spectra revealed 19 carbon signals generated by a substituted indole ring [δ_C 132.0 (s, C-2), 106.6 (s, C-7), 128.9 (s, C-8), 117.7 (d, C-9), 119.2 (d, C-10), 121.0 (d, C-11), 109.6 (d, C-12), and 136.9 (s, C-13)], two olefinic carbons [δ_C 135.0 (s) and 122.1 (d)], three methine (δ_C 67.2, 40.2, and 28.0), three methylene (δ_C 63.0, 56.5, and 33.9), and three methyl groups (δ_C 43.9, 12.9, and 10.1). The aforementioned functionalities accounted for seven degrees of unsaturation, and the structure required two additional rings for the structural elucidation of **1**.

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In the HMBC spectrum, the correlations between δ_H 2.38 (3H, s, Me-6) and δ_C 132.0 (s, C-2), 106.6 (s, C-7), and 128.9 (s, C-8) suggested an uncommon methyl group (Me-6) at C-7 of the indole ring (Figure 2). Moreover, the correlations of δ_H 5.34

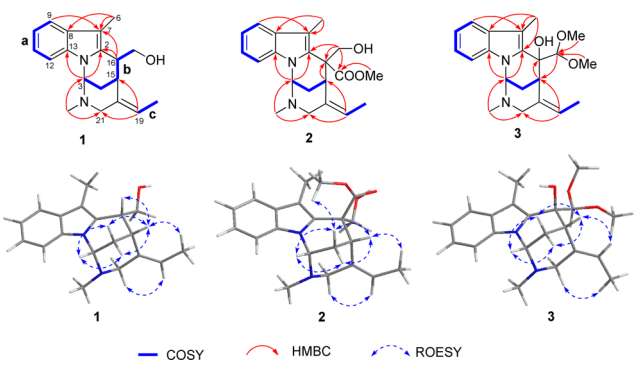

Figure 2. Key 2D NMR correlations of **1**−**3**.

(t, J = 2.6 Hz, H-3) with δ_C 132.0 (C-2) and 136.9 (C-13), and δ_H 3.60 (H-16) with δ_C 132.0 (C-2) and 106.6 (C-17) suggested connections of C-3/N-1 and C-2/16. Furthermore, the correlation among δ_H 5.34 (H-3)/2.31 (H-14)/3.52 (H-15)/3.60 (H-16)/4.30 (H-17) in the ^{1}H−^{1}H COSY spectrum, indicated the presence of spin-coupling structural unit **b**; thus, the six-membered ring C with a methanol group was constructed. In the HMBC spectrum, the correlations of δ_H 2.45 (3H, N4-Me) with δ_C 56.5 (C-21) and 67.2 (C-3) as well as δ_H 5.67 (H-19) with δ_C 28.0 (C-15) and 56.5 (C-21) led to the construction of the six-membered ring D with a ethylidene group. In the ROESY spectrum, NOE correlations of δ_H 1.84 (3H, Me-18)/3.52 (H-15) and δ_H 5.67 (H-19)/2.99 and 2.90 (2H, H-21) resulted in the assignment of the C-19/20 as *E*, whereas NOE correlations of δ_H 5.34 (H-3)/2.31 and 2.02 (H-14a and H-14b), δ_H 3.52 (H-15)/2.31 and 2.02 (H-14a and H-14b), and δ_H 3.52 (H-15)/3.60 (H-16) placed these atoms on the same side of the structure. H-3 appeared as a triplet with a small coupling constant (J = 2.8 Hz) in the ^{1}H NMR spectrum, suggesting that it was equatorially located. H-3, 15, and 16 were then positioned equatorially on the top side of ring C to conform to the rigid structure indicated by a molecular model. Finally, a single-crystal X-ray diffraction experiment confirmed the structure of **1** and indicated that rings C and D were in the boat and chair conformations, respectively (Figure 3).

Alstoscholarisine I (**2**) had the molecular formula of $C_{21}H_{26}N_2O_3$, as indicated by its HREIMS (m/z 354.1940, M^+) and ^{13}C NMR spectral data, which revealed that **2** contained an additional $-C_2H_2O_2$ unit compared with **1**. From careful comparisons of the ^{1}H and ^{13}C NMR spectral data (Table S1, Supporting Information) for **2** and **1**, **2** had an additional

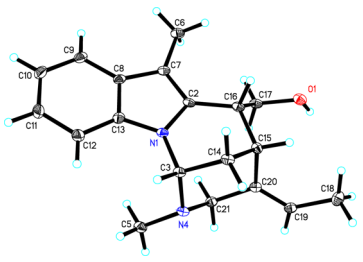

Figure 3. X-ray crystallographic structure of **1**.

methoxycarbonyl group at δ_C 175.1 (s) and 52.8 (q) and corresponding protons at δ_H 3.66 (3H, s). Moreover, the absence of a methine (δ_C 40.2, C-16) and the presence of a quaternary carbon at δ_C 54.0 (C-16) in the ^{13}C NMR spectrum of **2** positioned the methoxycarbonyl group at C-16, a conclusion supported by HMBC correlations between δ_H 4.65 (H-17a) and δ_C 54.0 (C-16) and 175.1 (−COOMe). In other regions, **2** was identical to **1**, as indicated by a detailed analysis of 2D NMR spectral data.

HREIMS for alstoscholarisine J (**3**) yielded the molecular formula $C_{21}H_{28}N_2O_2$, which represented a molecular mass 60 mass units greater than the molecular mass of **1**. The high similarity of 1D NMR spectral data for **3** and **1** suggested that alkaloid **3** was an analogue of **1**. Relative to the ^{13}C NMR spectrum of **1**, the corresponding spectrum for **3** lacked the δ_C 40.2 (d, C-16) and 63.0 (t, C-17) signals but included signals at δ_C 76.9 (s, C-16) and 111.5 (d, C-17) as well as two additional methoxyls at δ_C 3.38 and 3.59 (each 3H, s). HMBC correlations of δ_H 3.38 and 3.59 ($-OCH_3$) with only one carbon at δ_C 111.5 (C-17) and of δ_H 3.26 (H-15) with δ_C 76.9 (C-16), placed two methoxyls at C-17, while a hydroxyl at C-16. Based on ROESY, the configurations of **3** were the same as those of **1**. Similarly to the previously reported alstoscholarisines A−E, compounds **1**−**3** were generated from a common precursor, 19,20-*E*-vallesamine, through an iminium ion intermediate (Scheme S1, Supporting Infromation).[6b]

In our previous studies, alstoscholarisines A−E promoted adult neuronal stem cell proliferation.[6b] However, the three new alkaloids alstoscholarisines H−J (**1**−**3**) did not affect adult neuronal stem cells proliferation, as well as PC12 cells differentiation (neurite outgrowth-promoting activity) in their bioactivities evaluation. Moreover, alstoscholarisines H−J without any cytotoxic activity in our test, suggested that the new metabolites (**1**−**3**) may not affect the safety of medicine during storage, which was in accordance with our acute toxicity evaluation on total alkaloids from seven-year-stored leaf of *A. scholaris*.

Based on the NMR spectroscopic and X-ray crystallographic analyses described above, alstoscholarisine H (**1**), which is a compact tetracyclic indole alkaloid, consists of a bridged-ring system. Pyridiniums are useful precursors in syntheses of alkaloids by functionalization through the addition of nucleophiles and electrophiles as well as by transition metal-mediated C−H functionalization.[7] We previously developed a cross-dehydrogenation reaction for pyridinium through a transition-metal-free intramolecular functionalization reaction that efficiently generates rhynchophylline-type skeletons utilized in the facile total synthesis of corynoxine and corynoxine B.[8] As shown in Scheme 1, the total synthesis of alstoscholarisine H (**1**) also utilized pyridinium as a key building block. We proposed that alstoscholarisine H (**1**) could be generated from ester **4** through several functional group interconversions. Ester **4** would be accessible from dienamine intermediate **6**, which could be converted to biomimetic iminium ion intermediate **5** under acidic conditions via a Pictet−Spengler-like mechanism to construct the C ring.[9] To differentiate between the two possible cyclization positions of enamine, the placement of an electron-withdrawing group (R) on the dienamine **6** would be needed to direct the regioselective cyclization reaction.[9c,10] This dienamine intermediate **6** could be established through the nucleophilic selective addition of 1*H*-indole **7** to the C-4 position of *N*-methylpyridinium salt **8**.[11]

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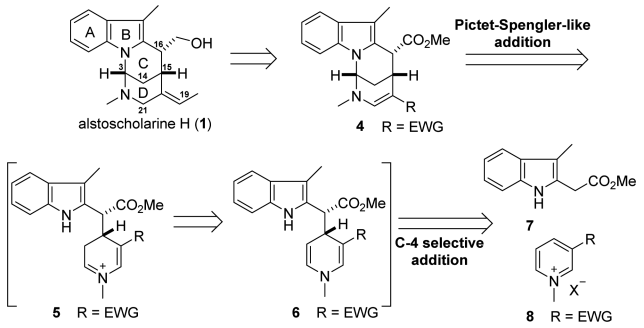
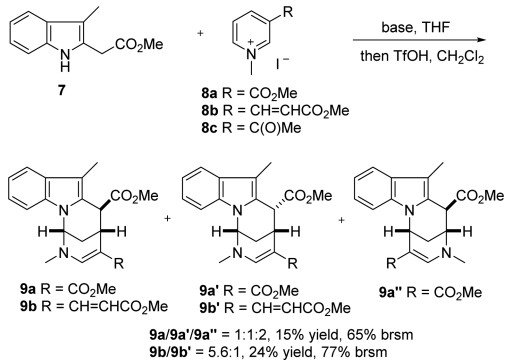
Scheme 1. Retrosynthetic Analysis of Alstoscholarisine H (1)



The regioselectivity and yield of the addition of enolates to *N*-alkylpyridinium depended on the presence and type(s) of C-3 electron-withdrawing groups on the pyridinium.[12] To facilitate the regioselective addition at C-4 of the pyridinium, three different C-3 substitution groups were examined: ester (**8a**), α,β-unsaturated ester (**8b**),[13] and ketone (**8c**) (Scheme 2). After

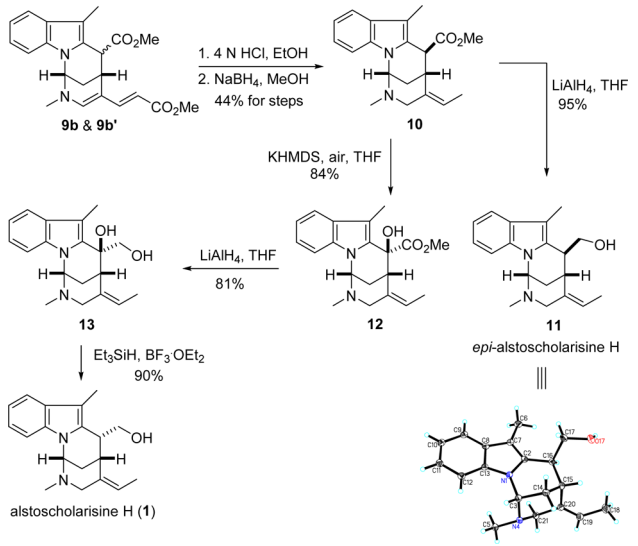
Scheme 2. Regioselective Nucleophilic Addition of Pyridiniums



deprotonation of the nucleophile **7** using LDA, the reaction mixture was treated with **8a** followed by TfOH. Three tetracyclic compounds (**9a**, **9a**′, and **9a**″) were isolated and structurally characterized in a ratio of 1/1/2 (15% yield, 65% brsm). The exo product **9a** and endo product **9a**′ were generated via C-4 nucleophilic addition and possessed the desired skeleton of alstoscholarisine H (**1**), whereas compound **9a**″ was generated via C-6 addition. No C-2 addition products were detected. Changing the base from LDA to LiHMDS, NaHMDS, or KHMDS did not improve the reaction. When pyridinium **8b** was subjected to this reaction, only the desired C-4 nucleophilic addition products **9b** and **9b**′ (5.6/1, 24% yield, 77% brsm) were isolated. However, when ketone **8c** was subjected to this reaction, none of the desired products were generated. These experimental results suggested that the C-3 substitution groups on pyridinium affected both the regioselectivity and the efficiency of the addition.

Subsequently, the tetracyclic products **9** were subjected to acid-mediated decarboxylation. We observed that when **9b** and **9b**′ were treated with refluxing hydrochloric acid followed by $NaBH_4$ reduction, the same exo product **10** was obtained (Scheme 3). The treatment of ester **10** with base (such as *t*BuOK or DBU) did not isomerize the ester group to the endo position. These results indicated that the ester was much more stable in the exo position than in the endo position. After ester **10** was reduced to a hydroxyl compound with $LiAlH_4$, we obtained **11**,

Scheme 3. Total Synthesis of Alstoscholarisine H (1)



an epimer of alstoscholarisine H, in 95% yield. We reasoned that if a hydroxyl group occupied the exo position, the ester group would be fixed in the endo position. When the hydroxyl group was removed under acidic conditions, the reductant would attack the carbenium ion from the less hindered exo position; thus, the hydroxymethylene would continue to be located in the endo position. Ester **10** was treated with KHMDS under air conditions to induce the hydroxyl group. As expected, the hydroxyl group of compound **12** was located in the exo position. The ester was then reduced with $LiAlH_4$ to afford diol **13**. Finally, treatment of diol **13** with Et_3SiH under acidic conditions afforded alstoscholarisine H (**1**) in 90% yield. The structure of synthetic alstoscholarisine H was unambiguously confirmed by comparing to this compound's NMR spectra to those of the naturally isolated product. By oxidation of the alcohol **13** with IBX, the corresponding aldehyde was obtained in moderate yield. However, after treatment of the aldehyde under different conditions, such as trimethyl orthoformate, the aldehyde was very inertial and failed to afford the dimethyl acetal as alstoscholarisine J (**3**). It might be reasonable to the significant hindrance around the aldehyde.

In summary, three new MIAs, alstoscholarisines H–J (**1**–**3**), were isolated from *A. scholaris*. These compounds possessed an unprecedented skeleton generated via the formation of a C-3/N-1 bond. The total syntheses of alstoscholarisine H (**1**) and (±)-16-*epi*-alstoscholarisine H (**11**) were accomplished in 7 steps and 5 steps, respectively, from commercially available materials, without the use of protecting groups. The presented synthesis features a formal [3 + 3] annulation to construct the tetracyclic core skeleton of alstoscholarisines in a single step and an epimerization to assemble the sterically hindered hydroxymethylene group in the desired configuration.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03583.

Experimental procedures (PDF)
Compound characterization (CIF)
Compound characterization (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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