Natural Product Synthesis

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Protecting-Group-Free Total Synthesis of (*E*)- and (*Z*)-Alstoscholarine**

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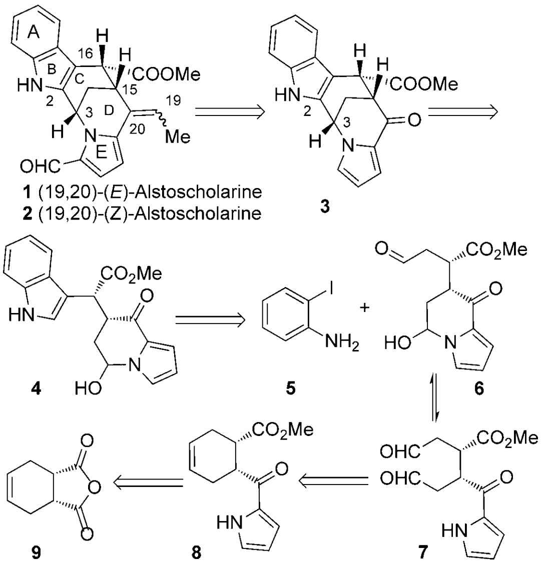
Monoterpenoid indole alkaloids, for their structural complexity and important bioactivities, have fascinated chemists for over a century.[1] The complexity of some of these alkaloids is such that they stand as molecular benchmarks to test new synthetic strategies and methodologies.[2] In spite of the skeletal diversity of these alkaloids, all of them are believed to be biosynthetic products from tryptamine and secologanine.[3] It is therefore not surprising that the tryptamine unit is readily recognized in most of these indole alkaloids.[4]

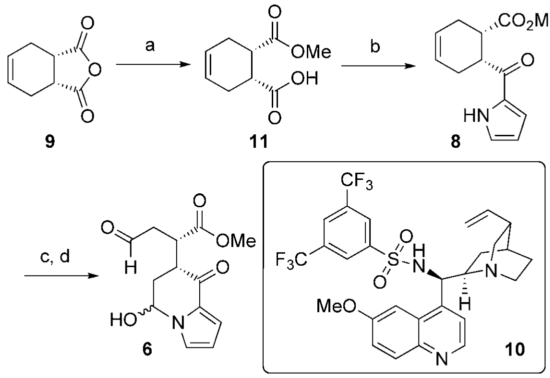
Recently, Luo and co-workers isolated (*E*)-alstoscholarine (**1**) and (*Z*)-alstoscholarine (**2**), from leaves of *Alstonia scholaris*, a plant used in traditional medicine in South and Southeast Asia (see Scheme 1 for structures).[5] Compounds **1** and **2** have an atypical pentacyclic structure characterized by: 1) a bridged [3.1.3] bicycle fused with an indole ring on one side and a pyrrole ring on the other, a structural feature absent in all other indole alkaloids, 2) a lack of an apparent tryptamine subunit, despite the existing belief that these are derived from tryptamine, and 3) two additional carbon atoms compared to other monoterpenic indole alkaloids. Herein, we report the first enantioselective total synthesis of **1** and **2** by a route that is sufficiently concise and easily diverted at a late stage to access natural product analogues.



Scheme 1. Retrosynthetic analysis of alstoscholarines.

Our retrosynthetic analysis of **1** and **2** is outlined in Scheme 1. We envisioned reaching the natural products by installing the olefin and formyl groups on pentacycle **3**, which could in turn be prepared by the Pictet–Spengler reaction of **4**. As no obvious, simple, and readily available indole derivative could be used for the construction of **4**, we thought to build the indole unit at this stage, using the palladium-catalyzed heteroannulation of *ortho*-iodoaniline (**5**) with aldehyde **6**. Dialdehyde **7**, the ring-opened form of **6**, could be obtained by oxidative cleavage of cyclohexene derivative **8**, which could in turn be prepared by deracemization of *meso*-anhydride **9**.

Our synthesis began with the desymmetrization of *meso*-anhydride **9** (Scheme 2). Treatment of *cis*-1,2,3,6-tetrahydrophthalic anhydride in diethyl ether with MeOH (10.0 equiv) in the presence of catalyst **10** (0.05 equiv) following the protocol developed by Song afforded hemiester **11** in 95% yield with 93% *ee*.[6] Conversion of the carboxylic acid function in **11** into 2-pyridylthioester (PyS−SPy, PPh_3,



Scheme 2. Preparation of intermediate **6**. Reagents and conditions: a) **10** (0.05 equiv), MeOH (10.0 equiv) in Et_2O (c = 0.1 M), RT, 95%, 93% *ee*; b) 2,2′-dipyridyldisulfide, PPh_3, THF, RT; then pyrrylmagnesium bromide, THF, −20°C, 76%; c) OsO_4 (0.1 equiv), *N*-methylmorpholine-*N*-oxide, *t*BuOH/THF/H_2O (13:9:1), RT; d) $NaIO_4$, acetone/H_2O (1.7:1), RT, 78% over two steps. THF = tetrahydrofuran.

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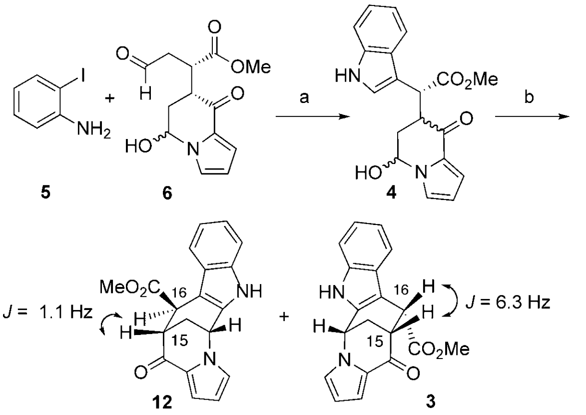
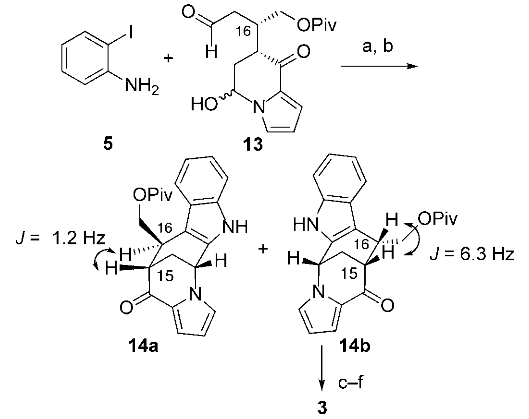
RT), and subsequent addition of pyrrylmagnesium bromide according to the method developed by Nicolaou provided the 2-ketopyrrole **8** as the only regioisomer in 76% yield.[7] The use of acyl chloride instead of pyridin-2-yl thioester led to the formation of a significant amount of 3-ketopyrrole derivative. Dihydroxylation of **8** afforded the corresponding diol when subjected to Upjohn conditions.[8] The diol was submitted, without purification, to oxidative cleavage ($NaIO_4$, Me_2CO/H_2O (1.7:1), RT) to provide bis(aldehyde) **7**. Compound **7** cyclized spontaneously in situ to give the desired six-membered hemiaminal **6** as a mixture of two diastereoisomers (78% overall yield). The lack of stereoselectivity in the hemiaminal formation is of no consequence, as this stereogenic center will be destroyed transiently in the subsequent C–C bond-forming event. Notably, this highly regioselective hemiaminal-forming process served three functions in our synthesis: 1) to form the D ring of the natural product through formation of a C–N bond, 2) to differentiate two sterically and electronically similar aldehydes, thus setting the required functionality for construction of the indole ring, and 3) to build the latent iminium functionality (hemiaminal) necessary for the subsequent construction of the C ring.

The key palladium-catalyzed heteroannulation between *ortho*-iodoaniline (**5**) and aldehyde **6** took place under our standard conditions ($Pd(OAc)_2$ (0.1 equiv), DABCO (3.0 equiv), DMF, 85 °C)[9,10] to provide indole **4** as a mixture of diastereoisomers (Scheme 3). The hemiaminal function, known to participate in the palladium-catalyzed heteroannulation with *ortho*-iodoaniline,[11] was found to be stable. Treatment of **4** under optimized conditions for the Pictet–Spengler reaction (HCOOH, RT) furnished pentacycles **3** and **12** (ratio 1:1) resulting from the partial epimerization of stereogenic center(s) in this two-step sequence. Submitting each diastereomerically pure form of compound **4** to the Pictet–Spengler reaction conditions afforded the diastereomerically pure pentacycle **12** or **3**, thus indicating that epimerization was not occurring under acidic Pictet–Spengler conditions. Therefore we concluded that the basic heteroannulation conditions are responsible for the observed epimerization in the preparation of pentacycle **12**/**3** from **5** and **6**.



Scheme 3. Reagents and conditions: a) $Pd(OAc)_2$ (0.3 equiv), DABCO (2.0 equiv), DMF, 85 °C, 40 min; b) HCO_2H, RT, 60% over two steps, ratio **12**/**3** = 1:5. DABCO = 1,4-diazabicyclo[2.2.2]octane, DMF = *N*,*N*-dimethylformamide.

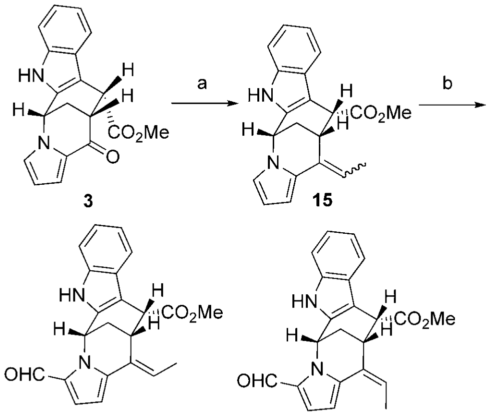
The relative stereochemistry of C15 and C16 (natural product numbering) was deduced from coupling constants between H15 and H16 in **3** and **12** ($J_{H15\text{-}H16} = 6.3$ Hz for **3** and $J_{H15\text{-}H16} = 1.1$ Hz for **12**). To fully determine the stereochemical identity of **3**, aldehyde **13** (for which epimerization at C16 is impossible) was synthesized by a similar strategy as that detailed for **6**. Palladium-catalyzed heteroannulation between aniline **5** and **13**, and subsequent acid-promoted Pictet–Spengler reaction afforded two diastereomers **14a** and **14b** resulting from the epimerization at C15 (Scheme 4). By following a four-step sequence, the protected primary alcohol in **14b** was converted into the corresponding methyl ester, which was found to be identical to **3** in all respects including the sign of the optical rotation. These results allowed us to conclude that the absolute configuration of **3** was 3*S*,15*R*,16*R* and that partial epimerization during the heteroannulation of **5** and **6** occurred only at C15.



Scheme 4. Alternative synthesis of **3** confirming its stereochemical integrity. Reagents and conditions: a) $Pd(OAc)_2$ (0.05 equiv), DABCO (3.0 equiv), DMF, 85 °C, 40 min; b) HCO_2H, RT, 55% over two steps, ratio **14a**/**14b** = 1:1; c) nBu_4NOH, THF, H_2O, 60 °C, 4 h, 93%; d) IBX (1.0 equiv), DMSO, 2 h; e) $NaClO_2$, NaH_2PO_4, amylene, *t*BuOH, THF, H_2O, RT, 1.5 h; f) $TMSCHN_2$, CH_2Cl_2, MeOH, 30 min, 82% over three steps. DMSO = dimethylsulfoxide, IBX = 2-iodoxybenzoic acid, Piv = pivaloyl, TMS = trimethylsilyl.

With the stereochemistry of pentacycle **3** now assigned, we came back to the total synthesis endeavor and proceeded to optimize the conditions for the palladium-catalyzed synthesis of indole **3** from **5** and **6**. It was found that epimerization could be minimized by shorten the reaction time. Finally, under optimized conditions ($Pd(OAc)_2$ (0.3 equiv), DABCO (2.0 equiv), DMF, 85 °C, 40 min), the desired pentacycle **3** was obtained in 50% yield over two steps (Scheme 3). Interestingly, the Fischer indole synthesis using *N*-phenyl hydrazine and aldehyde **6** as reaction partners under a variety of acidic conditions led to the complete degradation of aldehyde **6**.[12]

Conversion of the ketone moiety into an ethylidene turned out to be quite challenging. Ethyltriphenylphosphonium halide was found to be inactive toward **3** under a variety of reaction conditions. Nucleophilic addition of ethylmagnesium bromide to the ketone of *N*-Boc-protected **3**, followed by dehydration, did install the olefin unit. However, this was accompanied by complete epimerization at C16. Finally, ethylidenation of **3** using Takeda's reagent took place smoothly to provide the desired compound **15** (Scheme 5).[13] Due to the low stability of **15**, it was submitted, after a rapid filtration of the reaction mixture, to Vilsmeier–Haack formylation conditions to afford (*Z*) and (*E*)-alstoscholarine (3:1 ratio) in 40% yield over two steps. The two isomers were readily separated by preparative thin layer chromatography on silica gel (eluent: EtOAc/heptane = 1:4). The physical and spectroscopic data of these two synthetic alstoscholarines were identical to those reported for the natural products.[14] Therefore, the absolute configuration of (*E*)- and (*Z*)-alstoscholarine is 3*S*,15*R*,16*R*, which was proposed on the basis of their biogenetic origin, is confirmed by the present synthesis.



3 **15**

1 (19, 20)-(*E*)-Alstoscholarine **2** (19, 20)-(*Z*)-Alstoscholarine

Scheme 5. Total synthesis of alstoscholarines. Reagents and conditions: a) 1,1-bis(phenylthio)ethane (4.0 equiv), [Cp$_2$TiCl$_2$] (10.0 equiv), P(OEt)$_3$ (20.0 equiv), Mg (12.0 equiv), molecular sieves (4 Å), THF, 70°C, 6 h; b) DMF, POCl$_3$, DCE, RT, 31% yield of **1** and 9% yield of **2** over two steps. Cp = cyclopentadienyl, DCE = 1,2-dichloroethane.

In summary, we have completed the first enantioselective total synthesis of (*E*)- and (*Z*)-alstoscholarines, accomplished in 14% yield over eight steps. We believed that the late-stage construction of the indole ring has greatly simplified the present synthesis design, thus allowing the use of simple and readily accessible starting materials. The synthesis is protecting-group free,[15] with desirable atom-, step-, and redox-economies.[16–18] Indeed, there is no concession step in this synthesis since each transformation creates new C–C and C–N bonds found in the target molecules.[19] Furthermore, the construction of the indole unit at a late stage of the synthesis should allow us to access natural product analogues easily.[20] Efforts aimed at solving the epimerization problem in the palladium-catalyzed heteroannulation step as well as the moderate yield of the ethylidenation step are ongoing.

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