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Formal Synthesis of Aspidospermidine via the Intramolecular Cascade Transannular Cyclization

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Received: 28.02.2013; Accepted after revision: 30.03.2013

Abstract: A formal synthesis of aspidospermidine is reported through a novel preparation of Stork's penultimate tricyclic ketone intermediate. The key steps of the synthesis consist of an intramolecular cascade transannular cyclization, triggered by the removal of Boc group, which simultaneously forms the C, D, and E rings of aspidospermidine and conveniently setting up the quaternary stereocenter via decarboxylative alkylation reaction of the β-keto ester.

Key words: alkaloid, total synthesis, palladium, cross-coupling, cyclization

The *Aspidosperma* alkaloids have received much attention from the synthetic community due to their structural complexity and interesting biological activities. To date, over 250 alkaloids in this family have been isolated[1] and many of them incorporate the core exemplified by aspidospermidine (**1**, Figure 1). Unlike the more complicated vinblastine and vincristine, which are frontline drugs in cancer therapy,[2] aspidospermidine is not of pharmacological interest and is lacking in sensitive functional groups. Also for this reason, **1** has often been used as an attractive target for the development of new routes to these alkaloids, thereby culminating in a cornucopia of synthetic studies in the literature.[3,4] A pioneering work in this area, Stork and Dolfini first synthesized the alkaloids aspidospermine (**2**) and quebrachamine (**3**) nearly 50 years ago.[5] In their classic synthesis, a late-stage Fischer indole synthesis to introduce the indole moiety onto a tricyclic ketone intermediate **5a** was successfully adopted. Moreover, this work established that all of the stereocenters in the final target were responsive to a single, nonepimerizable quaternary center in ketone **5** (Scheme 1). Since then, many others have reported the formal syntheses based on Stork's tricyclic ketone. In addition, the diasteromer of **5a** could be used in the preparation of aspidospermidine.[3c,g,4j,n]

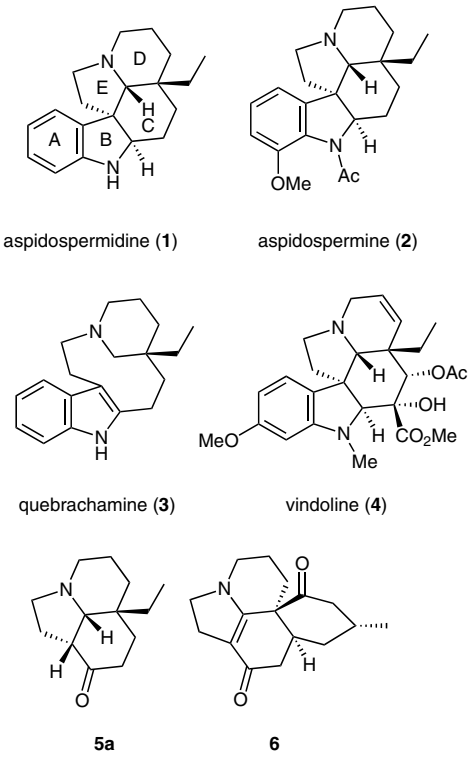
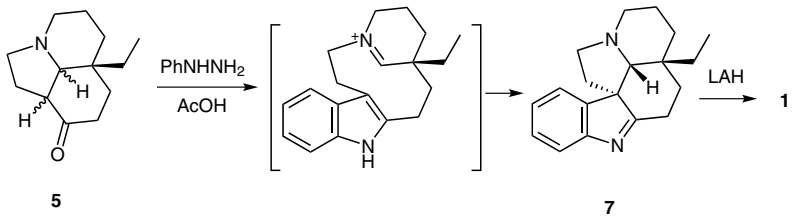
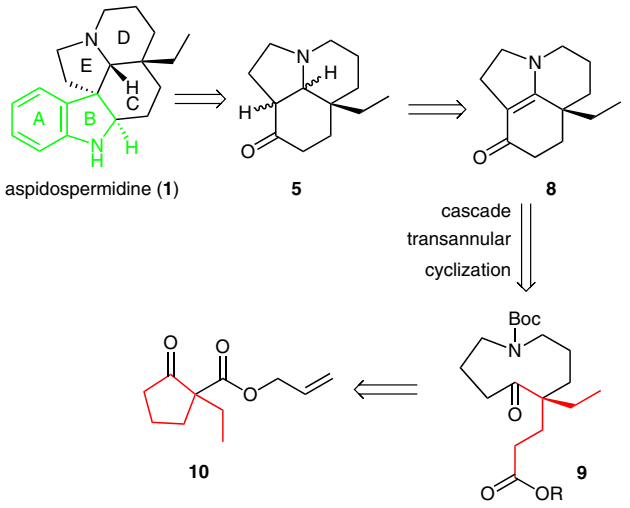


Figure 1 Natural products, intermediate ketone **5a**, and tetracyclic unnatural alkaloid **6**



Scheme 1

SYNLETT 2013, 24, 1303–1306
Advanced online publication: 08.05.2013
DOI: 10.1055/s-0033-1338447; Art ID: ST-2013-W0185-L

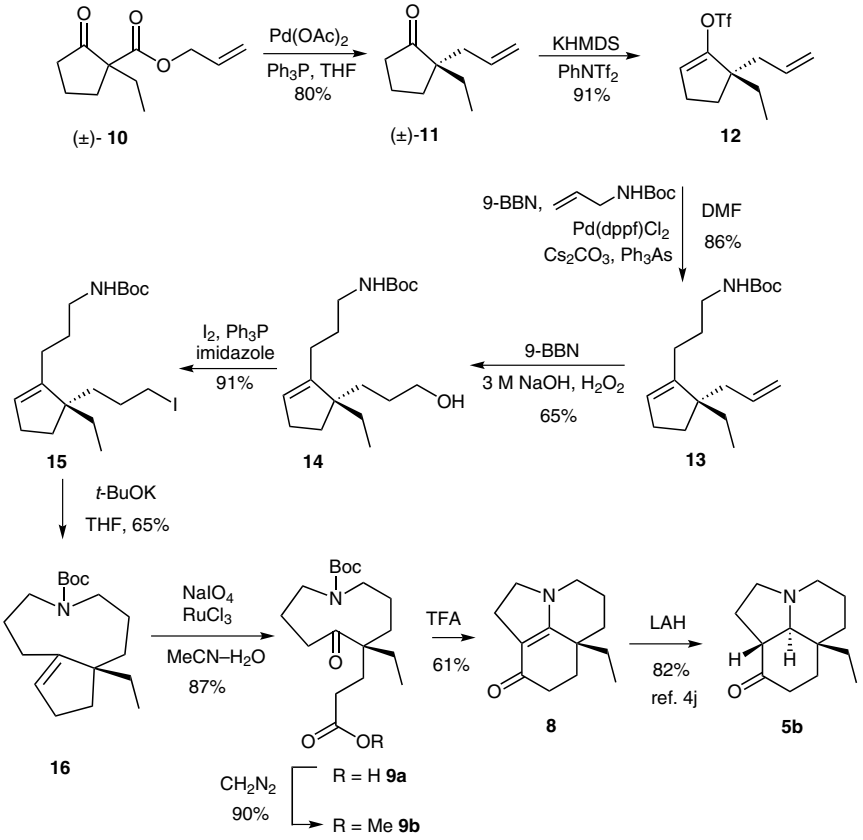


Scheme 2 Retrosynthetic analysis of aspidopsermidine

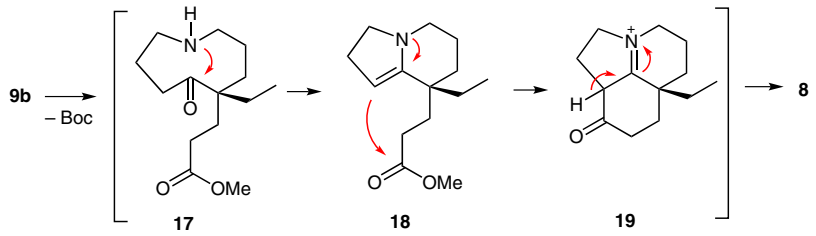
In the context of our ongoing synthetic endeavor on the complex polycyclic *Lycopodium* alkaloids,[6] we first observed an unusual intramolecular cascade cyclization while attempting to initiate a plausibly biomimetic cyclization approaching to lycojapodine A.[6a] Thus obtained product **6** is unique in the tetracyclic skeleton in which the left moiety of fused tricyclic vinylogous amide is similar to ketone **5**. Based on this observation, we conceived that our cascade cyclization would be synthetically useful and planed to showcase its utilities in the synthesis of *Aspidosperma* alkaloids.

As discussed above, we elected to intercept Stork's intermediate **5a** (or its diastereomeric equivalent **5**) to constitute a formal synthesis of **1**. Thus, our retrosynthesis of **5**, shown in Scheme 2, begins with the reduction of the internal double bond of a tricyclic vinylogous amide **8**, which in turn would be accessed from a key reaction of cascade transannular cyclization of functionalized nine-membered ring **9**. The challenging all-carbon quaternary stereocenter of the nine-membered ring **9** could be installed through an enantioselective decarboxylative alkylation reaction of β-keto ester **10**, a powerful methodology developed by the Stoltz group recently.[7]

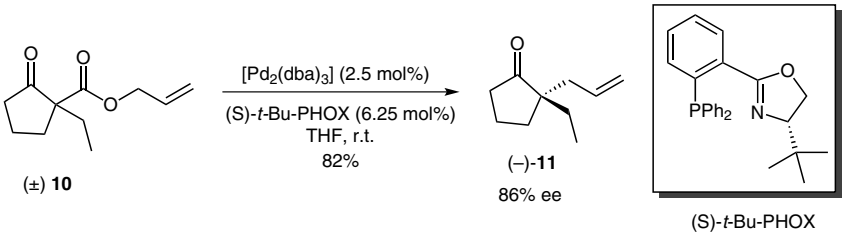
Our synthesis commenced with β-keto ester **10**, shown in Scheme 3, which could be easily prepared in multigram quantities in three steps from cheap adipic acid (see Supporting Information). At the outset, we took on the racemic β-keto ester **10** to test the decarboxylative alkylation reaction under the conditions of $Pd(OAc)_2/Ph_3P$, and the transformation proceeded nicely to provide α-quaternary cyclopentanone **11** in racemic form. Using this racemic cyclopentanone as a linchpin, elongation of a nitrogen-containing side chain on **11** was expected. To this end, we first converted the ketone into its vinyl triflate **12** with standard procedures in high yield, and then a highly effective Suzuki–Miyaura cross-coupling[8] between this vinyl triflate **12** and allylic carbamate derivative was enlisted to yield diene **13**. Selective hydroboration of the allylic position of **13** delivered the primary alcohol **14** uneventfully. Iodination of the alcohol **14** followed by the treatment of



Scheme 3 Synthesis of ketone **5b**



Scheme 4



Scheme 5

the iodide intermediate **15** with potassium *tert*-butoxide in THF, a cyclization occurred smoothly to close the nine-membered ring **16**. Eventually, the double bond of the cyclopentene ring inside of **16** was facilely cleaved by oxidation with $RuCl_3/NaIO_4$, furnishing two desired carbonyl functional groups for the next cascade reaction.[9] With the oxidative cleavage product **9a** in hand, we are poised for the pivotal cascade cyclization. First, we heated the acid compound **9a** at 100 °C in AcOH–H_2O (96:4) mixture;[10] a trace of cyclized vinylogous amide **8** could be isolated. In the case of methyl ester **9b** under the same conditions, 18% yield of the product was obtained. Then we took on the methyl ester **9b** as the substrate for the optimization of reaction conditions. It is soon to find that in the presence of pure AcOH heated at 110 °C, the yield can be enhanced to 32%. Using TFA as solvent instead of AcOH at lower temperature (90 °C), 61% yield of the product can be isolated. This cascade process toward tricyclic vinylogous amide **8** could be rationalized briefly as shown in Scheme 4.[11] Cleavage of the Boc gives a secondary amine **17** that attacks the ketone to form enamine **18**. The enamine **18** continues to proceed an intramolecular nucleophilic substitution to yield tricyclic system **19**, which is terminated by deprotonation. Vinylogous amide **8** was first reported by Banwell,[4j] and its internal double bond was reduced by the addition of lithium aluminium hydride to provide a tricyclic ketone **5b**. The stereochemistry of two methines of ketone **5b** was confirmed by the comparison with the data of Banwell. According to the Fischer indole reaction investigated by previous groups, **5b** could be led to aspidospermidine (vide ante).[12] During the performance of this work, the Stoltz group reported the enantioselective decarboxylative alkylation reaction of β-keto ester **10** (Scheme 5), an optical α-quaternary cyclopentanone (–)-**11** obtained in good yield and enantioselective excess.[7] Taken all together, in principle, here our route will constitute an enantioselective formal synthesis of **1**.

In conclusion, a formal synthesis of aspidospermidine is reported based on a novel synthesis of the pivotal tricyclic ketone in which a cascade transannular cyclization plays the key role; and decarboxylative alkylation reaction of β-keto ester to set up the quaternary stereocenter was efficiently adopted.

Synthesis of Vinylogous Amide 8

Methyl ester **9b** (28 mg, 0.0789 mmol) was dissolved in TFA (1.5 mL) and then placed in a 90 °C oil bath. The resulting deep orange reaction was stirred at 90 °C for 12 h. After the mixture was cooled to r.t., to the residue was added 6 N NaOH to reach pH >7 and diluted with $CHCl_3$ (3 mL), washed with brine, dried, and concentrated. The crude product was purified by flash column chromatography ($CHCl_3$–MeOH, 100:1) to provide 9.8 mg of tricyclic ketone **8** (61%) as dark yellow oil.

IR (KBr): ν_{max} = 3432, 2857, 1614, 1514, 1438, 1354, 1300, 1264, 1189, 923, 853, 702 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 3.60 (1 H, td, *J* = 10.8, 3.6 Hz), 3.30 (1 H, dd, *J* = 11.7, 6.0 Hz), 3.18 (1 H, q, *J* = 10.8 Hz), 2.80 (2 H, m), 2.63 (1 H, m), 2.44 (1 H, m), 2.27 (1 H, m), 1.60–2.00 (6 H, m), 1.54 (1 H, td, *J* = 13.2, 4.8 Hz), 1.13 (1 H, td, *J* = 13.8, 3.6 Hz), 0.89 (3 H, t, *J* = 7.8 Hz) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 190.4, 175.3, 107.8, 54.1, 47.3, 35.2, 33.8, 32.7, 28.8, 25.4, 24.2, 18.8, 8.1 ppm. HRMS (EI): *m/z* calcd for $C_{13}H_{19}NO$ $[M]^+$: 205.1467; found: 205.1469.

Acknowledgment

We thank the National Natural Science of China (No. 81102348, 21072200), Programs of 'One Hundred Talented People' and 'Western Light' Joint Scholar of Chinese Academy of Sciences for financial support.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) Similar to the description by Banwell,[4j] we also found the ensuing Fischer indolization process was capricious when carried out on a small scale.

