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A Short Total Synthesis of (±)-Aspidospermidine

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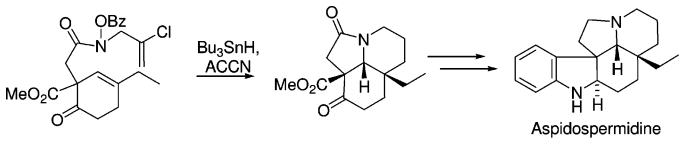
ABSTRACT

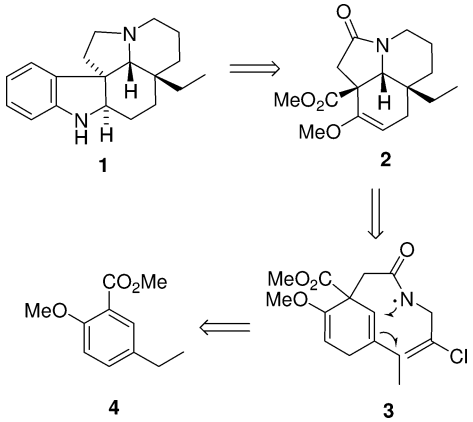


A cascade radical cyclization starting from an amidyl radical has been used for the construction of (±)-aspidospermidine. This approach has also been developed for the preparation of a tricycle whose framework is contained in the stemona alkaloids.

The Aspidosperma family of indole alkaloids has inspired many synthetic strategies for the construction of their pentacyclic framework, in particular the parent compound aspidospermidine **1**.[1] Our interest in the use of nitrogen-centered radicals[2] for the formation of various heterocycles led us to investigate such an approach in the synthesis of aspidospermidine. We have previously demonstrated the potential of cyclizations of amidyl radicals in the synthesis of (±)-13-deoxyserratine.[3]

Our proposed synthesis of aspidospermidine hinges on the 5-*exo*/6-*endo* cascade of radical cyclizations from amidyl radical **3** to provide the tricyclic system **2**, which would later be converted to aspidopermidine using the known Fischer indole synthesis. The presence of the chlorine atom on the alkene inhibits 5-*exo* closure in the second cyclization.[4] The required cyclohexadiene radical precursor could be prepared starting from an aromatic precursor **4** (Scheme 1).

Scheme 1. Approach to Aspidospermidine



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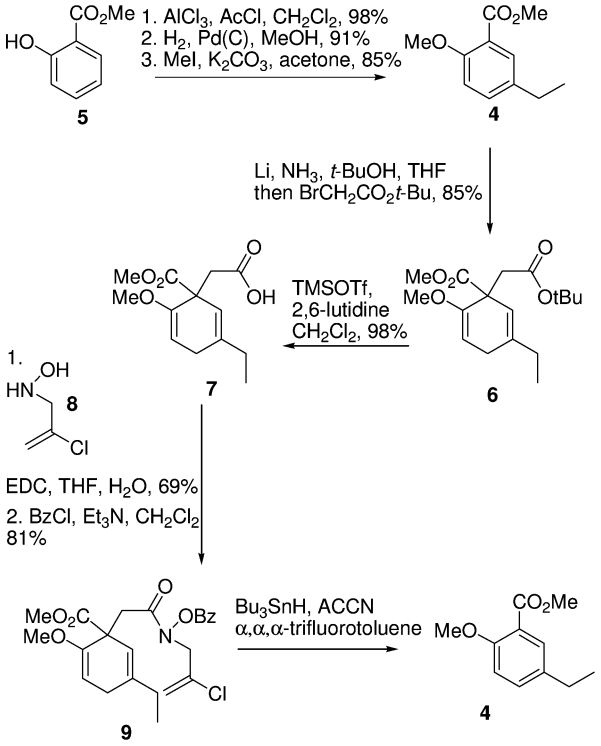
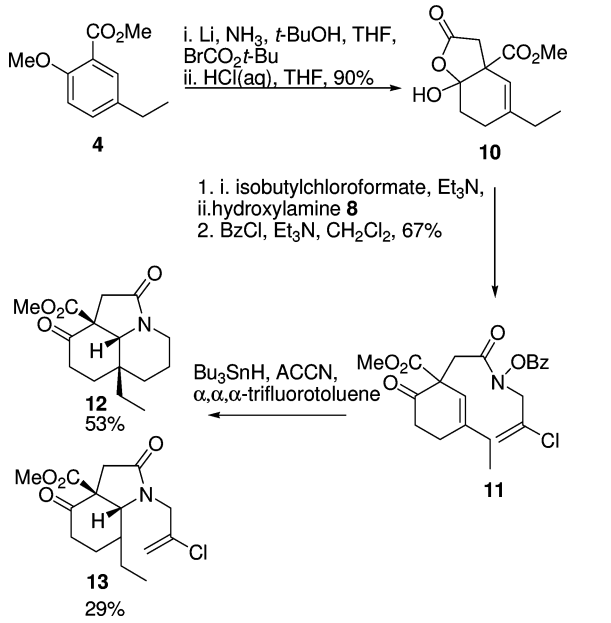
Scheme 2. Failed Ring Closure



Scheme 3. Construction of the Key Tricyclic Intermediate

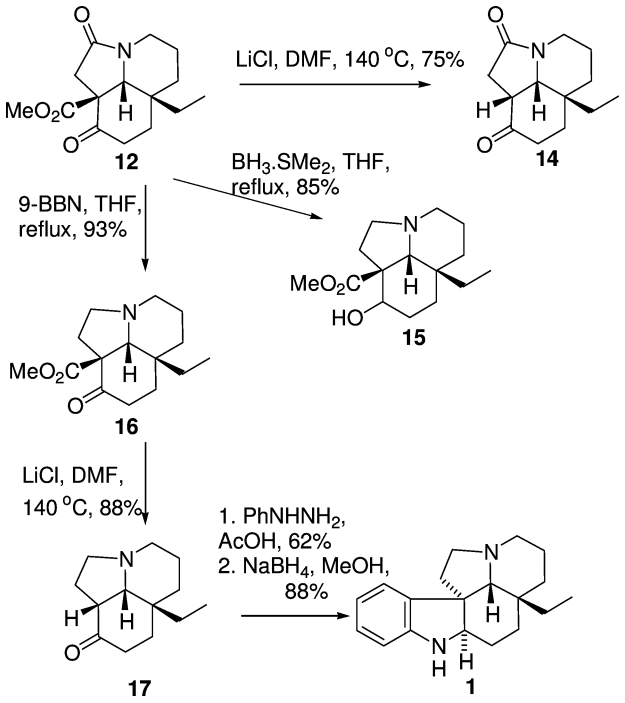


The desired presursor for the amidyl radical cyclization was synthesized as shown in Scheme 2. Birch reduction and alkylation of the ester **4** with *tert*-butyl bromoacetate formed cyclohexadiene **6**. Numerous conditions for the cleavage of the *tert*-butyl ester also resulted in cyclization onto the enol ether. TMSOTf and 2,6-lutidine cleanly provided the required acid **7**, which was coupled to the hydroxylamine with EDC. The starting material for the formation of the amidyl radical, the benzoate ester **9**, was formed on treatment with benzoyl chloride. However, when **9** was treated with tributyltin hydride and 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) in refluxing α,α,α-trifluorotoluene, no amidyl radical cyclization took place; aromatization occurred instead to give intermediate **4**. Thus, in one clean sweep, the side chain we had painstakingly attached was cut off and we were returned to our starting point.

Presumably, this is the result of abstraction of a doubly allylic hydrogen by a tributyltin radical or by radicals derived from the initiation.[5] To eliminate the possibility of this occurring, the methyl enol ether was deprotected prior to the radical step. By treating the crude Birch reduction product with aqueous hydrochloric acid in THF, deprotection of both the *tert*-butyl ester and methyl enol ether groups gave the desired acid, which existed in the lactolized form **10**. This was converted to the new benzoate ester radical precursor **11** (Scheme 3).

Pleasingly, the amidyl radical formed on treatment of **11** with tributyltin hydride and ACCN underwent 5-*exo* cyclization in useful yield. The major product of the reaction was the tricycle **12**, where desired 6-*endo* cyclization had followed. The minor product (29%) was the monocyclized

Scheme 4. Final Steps to Aspidospermidine



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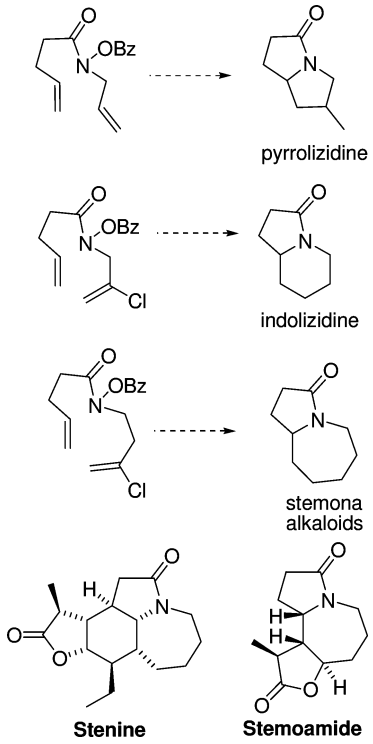
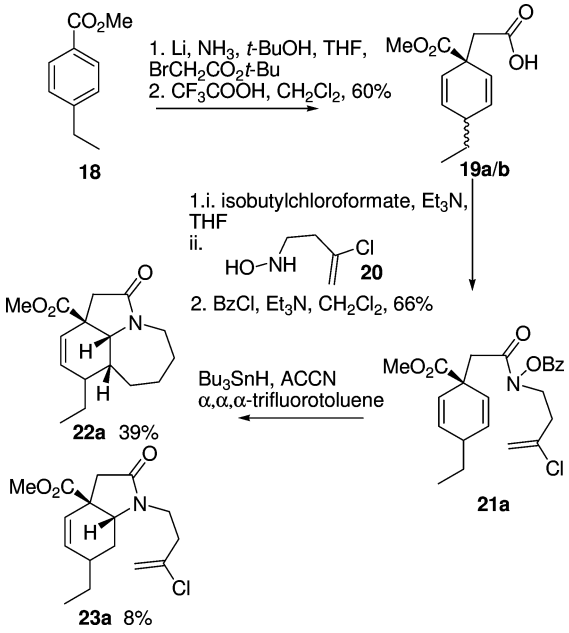
(5) For precedence of this fragmentation, see inter alia: (a) Jackson, L. V.; Walton, J. C. *Chem. Commun.* **2000**, 3273. (b) Jackson, L. V.; Walton, J. C. *Tetrahedron Lett.* **1999**, *40*, 7019. (c) Baguley, P. A.; Jackson, L. V.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 304. (d) Studer, A.; Amrein, S. *Angew. Chem., Int. Ed* **2000**, *39*, 3080. (d) Amrein, S.; Studer, A. *Helv. Chim. Acta* **2002**, *85*, 3559.

Scheme 5. General Route to Pyrrolizidine, Indolizidine, and Stemona Skeletons



Scheme 6. Approach to the Stemona Structure



derivative **13**. It is interesting to note that in the absence of the chlorine, the isomer with the pyrrolizidine structure was obtained by two consecutive 5-*exo* ring closures in 46% yield. The chlorine substituent was therefore necessary for regiocontrol.

Tricycle **12** could be decarboxylated with lithium chloride in DMSO to give **14**, which has been previously converted into aspidospermidine[1a,q,w] in a sequence requiring protection of the ketone for reduction of the amide and then subsequent Fischer indole synthesis (Scheme 4). However, the ester in **12** provides hindrance to the ketone, and thus selective reduction of the lactam of **12** was envisaged.

Treatment with borane dimethyl sulfide complex gave only the desired alcohol **15**, the product of reduction of both lactam and ketone functionalities. The bulkier 9-BBN however provided selective reduction of the lactam.[6] Decarboxylation of the β-keto ester supplied the known tricycle **17**, which was converted to aspidosperidine via a Fischer indole synthesis with phenylhydrazine followed by sodium borohydride reduction.

With the amidyl radical cyclizations we have access to indolizidine and pyrrolizidine skeletons by a 5-*exo* cyclization followed by either a 5-*exo* or 6-*endo* cyclization. This second cyclization is directed 5-*exo* versus 6-*endo* by the presence or absence of the chlorine on the alkene. An extension of this work would be to investigate the analogous system involving 5-*exo* followed by 7-*endo* cyclization, which would generate the 5,7 system found in the *Stemona* alkaloids (Scheme 5).[7]

The precursor **21** for the amidyl radical cyclization was prepared in a similar way to the previous system **11** used in the synthesis of aspidospermidine. Birch reduction and alkylation of methyl *p*-ethylbenzoate followed by hydrolysis of the *tert*-butyl ester gave an equal mixture of two diastereomeric acids **19a/b**. These could be separated by crystallization of their benzylamine salts though the relative stereochemistry of each could not be determined by NOE studies. Coupling of one of these diastereomers with the hydroxylamine **20** and treatment with benzoyl chloride provided the radical precursor **21a**. Upon treatment of **21a** with tributyltin hydride and ACCN the major product **22** was obtained by 5-*exo* followed by 7-*endo* cyclization. Thus, three of the four rings of stenine could be assembled from methyl *p*-ethyl benzoate **18** in only four steps. Only one isomer is obtained in the cyclization and is very likely that indicated for **22a** in Scheme 6, according to molecular models, but this has not been totally ascertained yet.

(6) Collins, C. J.; Lanz, M.; Singaram, B. *Tetrahedron Lett.* **1999**, *40*, 3673.

(7) For previous syntheses of *Stemona* alkaloids, see: (a) Zeng, Y.; Aube, J. *J. Am. Chem. Soc.* **2005**, *127*, 15712. (b) Wipf, P.; Spencer, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 225. (c) Sibi, M. P.; Subramanian, T. *Synlett* **2004**, *7*, 1211. (d) Bruggemann, M.; McDonald, A. I.; Overman, L. E.; Rosen, M. D.; Schwink, L.; Scott, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 15284. (e) Williams, D. R.; Shamin, K.; Reddy, J. P. *Org. Lett.* **2003**, *5*, 3361. (f) Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848. (g) Golden, J. E.; Aube, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4316. (h) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515. (i) Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. J. *Tetrahedron* **2002**, *58*, 61. (j) Morimoto, Y.; Iwahashi, M.; Kinoshita, T. *Nishida, K. Chem. Eur. J.* **2001**, *7*, 4107. (k) Williams, D. R.; Fromhold, M. G.; Earley, J. D. *Org. Lett.* **2001**, *3*, 2721. (l) Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. J. *Org. Lett.* **2001**, *3*, 2505. (m) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295. (n) Pilli, R. A.; Ferreira de Oliveira, M. C. *Nat. Prod. Rep.* **2000**, *17*, 117 and references therein. (o) Kende, A. S.; Smalley, T. L.; Huang, H. *J. Am. Chem. Soc.* **1999**, *121*, 7431.

In summary, by a simple choice of precursor, all the possibilities indicated in Scheme 5 can be executed, thus opening a simple yet highly efficient strategy for the construction of numerous alkaloids possessing these ubiquitous skeletons.

Supporting Information Available: Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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