Total Synthesis of (±)-Aspidospermidine

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(±)-Aspidospermidine (**1**) has been synthesized from readily available methyl 3-ethyl-2-oxocylopentanecarboxylate (**17**) in 5.9% yield over 13 steps. The key step of the synthesis is an intramolecular cascade reaction that simultaneously forms the B, C, and D rings of **1**. A high-yielding method of closing the remaining E ring is also described.

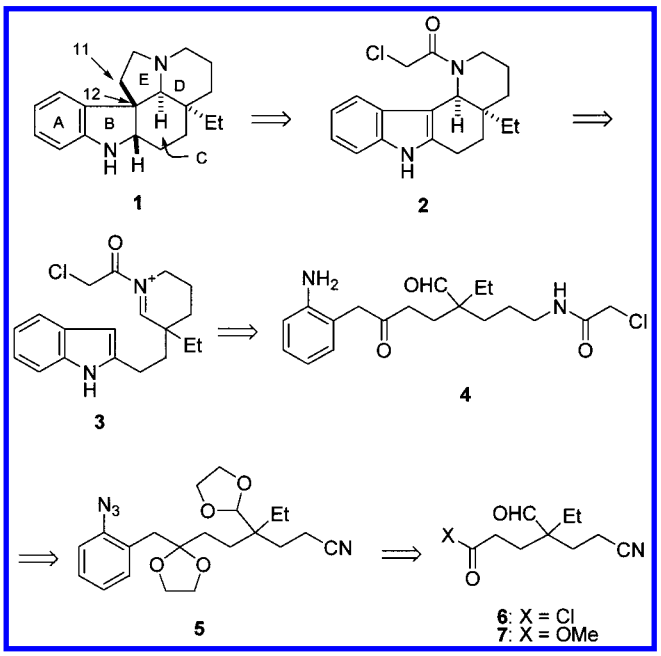
A considerable amount research has been devoted to the synthesis of aspidospermidine[1,2] (**1**), the parent compound of the *Aspidosperma* alkaloids,[3] which comprise a large family of diverse structures. Current interest in the synthesis of these alkaloids partially results from the pharmacological activity exhibited by a few of its members.[4] Although **1** is not of pharmacological interest, its lack of functionality makes it an attractive target for the development of new synthetic pathways to these compounds.

The core structure of the *Aspidosperma* alkaloids is typified by the [6.5.6.6.5] ABCDE ring system. Herein we report a novel intramolecular cascade reaction in which monocyclic precursor **4** undergoes a tricyclization to form the B, C, and D rings. Furthermore, a facile method of closing the E ring in high yield, which has thus far been a major hindrance in the efficient realization of this pentacyclic ring system, is discussed.[5]

Our retrosynthesis of **1**, shown in Scheme 1, begins with the displacement of an acyl halide by the three position of the indole (**2**), closing the E ring, followed by reduction of the amide and indolenine. The cornerstone of the new synthesis was to be a cascade reaction wherein compound **4** would undergo two cyclization reactions, resulting in an acylimmonium ion and an indole (**3**). The indole should undergo a Mannich-like ring closure, forming **2**. Cascade precursor **4** could be derived from the hypothetical precursor **5** by simultaneous reduction of the azide and nitrile functions, followed by hydrolysis of the acetals. We hoped to prepare **5** by coupling a suitable organometallic derivative of *o*-azidotoluene with acyl halide **6**, which could arise from two Michael reactions of butanal with methyl acrylate and acrylonitrile.

The synthesis of **7** has actually been reported, albeit in low yield (ca. 14%).[6] To improve the accessibility of this compound, attempts were made to prepare **7** from both **8**[7] and **9**[8] by Michael addition of the corresponding pyrrolidine enamines[9] with acrylonitrile or methyl acrylate, respectively. However, refluxing either enamine with excess Michael acceptor in a variety of solvents for extended periods of time failed to produce **7**, typically resulting in a return of starting material with a 30−40% loss to decomposition. Since enamine alkylations of similarly substituted enamines with more electrophilic reagents such as allyl bromide are known,[10] we rationalized that in the case of **9**, addition of a Lewis acid might sufficiently increase the electrophilicity of methyl acrylate to overcome the steric hindrance imposed by the trisubstituted enamine. Indeed, the incorporation of BF_3·Et_2O into the reaction mixture provided **7** in 44% yield from **9**. Because of problems encountered later in this synthetic route, further optimization of this reaction was not explored.

Scheme 1



(1) For leading references, see: (a) d′Angelo, J.; Desmale D. *J. Org. Chem.* **1994**, *59*, 2292. (b) Urrutia, A.; Rodríguez, J. G. *Tetrahedron* **1999**, *55*, 11095. (c) Forns, P.; Diez, A.; Rubiralta, M. *J. Org. Chem.* **1996**, *61*, 7882.

(2) The numbering scheme is that of Biekmann, K.; Spiteller-Friedmann, M.; Spiteller, G. *J. Am. Chem. Soc.* **1963**, *85*, 631.

(3) Cordell, G. A. In *The Alkaloids*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic Press: New York, 1979; Vol. 17, pp 199−384. Saxton, J. E. *Nat. Prod. Rep.* **1993**, *10*, 349−395; **1994**, *11*, 493.

(4) Antitumor Bisindole Alkaloids from *Carentheus roseus*. In *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press: San Diego, 1990; Vol. 37.

(5) For leading references, see: Padwa, A.; Price, A. T. *J. Org. Chem.* **1998**, *63*, 556.

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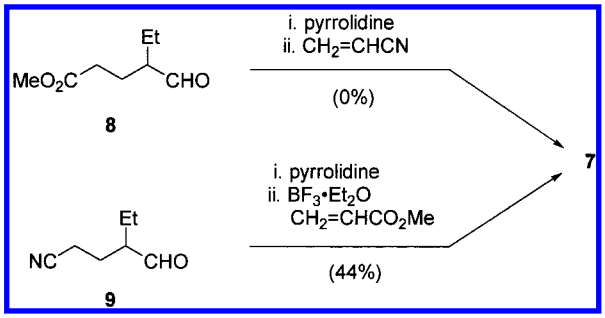


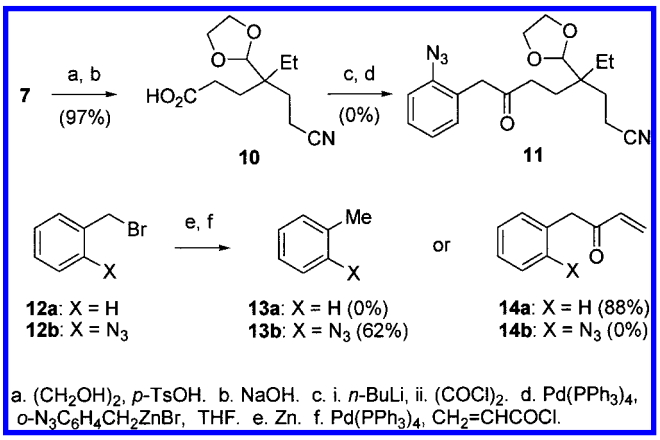
As shown in Scheme 2, protection of the aldehyde as the dioxolane and subsequent ester hydrolysis provided acid **10** in quantitative yield. Acid **10** was converted into the corresponding acyl chloride, which was treated with *o*-azidobenzylzinc bromide in the presence of palladium according to the method of Negishi et al.[11] However, all attempts to link these two segments met with failure. In hope of remedying this problem, a brief model study was performed. Acryloyl chloride was treated with the bromozinc derivatives, derived from reaction of benzyl bromide (**12a**) and *o*-azidobenzyl bromide (**12b**) with zinc, in the presence of tetrakis(triphenylphosphine)palladium. In the case of benzyl bromide, the coupling proceeds smoothly at −78 °C to provide the desired enone **14a** in 88% yield. Unfortunately, the introduction of nitrogen-containing functionalities at the *ortho* position inhibits the coupling reaction. In the case of *o*-azidobenzyl bromide (**12b**) the only product obtained is *o*-azidotoluene (**13b**).[12] This indicates that the organozinc species formed but was not reactive in the acylation reaction. An attempt to prepare the organozinc derivative from *o*-nitrobenzyl bromide gave only decomposition products, whereas *o*-phthalamidobenzyl bromide[13] was unreactive when treated with zinc. Because of this failure, we looked to alternate methods for generating **4**.

Our second synthetic route (Scheme 3) takes advantage of the strategic placement of carbonyl functionality, which allows access to **4** via oxidative cleavage of a properly substituted cyclopentene (**15**). This cyclopentene could be generated by reduction of **16**, followed by chloroacylation. We envisioned **16** arising from alkylation and cyanoethylation of the readily available β-ketoester **17**.[14]

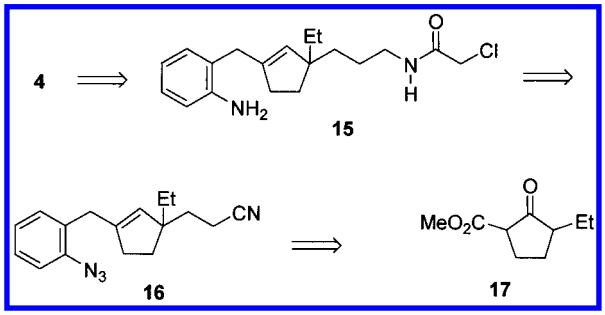
Alkylation of **17** with *o*-azidobenzyl bromide proceeds in superb yield if one uses Cs_2CO_3 in lieu of K_2CO_3 as the base. Initial attempts at cyanoethylation of **18** utilizing standard Michael addition conditions gave only moderate yields (40−55%) of the desired Michael adduct **19**, often returning starting material as well as numerous side products. Optimization of this reaction revealed that treatment of **18** with Cs_2CO_3 in *t*-BuOH proceeds so cleanly that it can be taken on to the hydrolysis/decarboxylation step without purification to provide **20** in 77% yield for the two steps (Scheme 4).

Preliminary attempts were made to convert **20** directly to the alkene. However, steric hindrance about the ketone prevented the formation of the tosylhydrazone, the vinyl phosphate, and the vinyl triflate. Circumvention of this problem necessitated reduction of the ketone and subsequent elimination of the alcohol. Ketone **20** reduced cleanly in the presence of $CeCl_3$, but the subsequent dehydration proved to be difficult. Treatment with either thionyl chloride or phosphorus oxychloride in the presence of various bases resulted in poor yields (25−30%), with most of the material being lost to decomposition. Additionally, sulfonation reactions were slow and poor yielding, often giving many products, and although the trifluoroacetate could be formed cleanly, all elimination attempts resulted in either hydrolysis or no reaction. Ultimately, the use of PCl_5 was found to provide a 4:1 mixture of inseparable olefin isomers **16** and **21** in 63% yield.

Scheme 2



Scheme 3



With **16** in hand, simultaneous hydride reduction of the azide and cyano groups provided diamine **22**, and chloroacylation of the primary amine proceeded readily to give **15**. Although attempts to access **4** directly from **15** resulted solely in decomposition, after protection of the aniline nitrogen as the *tert*-butyl carbamate (**23**), ozonolysis successfully cleaved the alkene to provide **24** in modest yield. Efforts were made to accomplish oxidative cleavage by dihydroxylation and oxidative cleavage of the syn diols. However, subjecting **23** to various dihydroxylation conditions resulted in either return of starting material or slow decomposition. These results were not unexpected because of the steric hindrance about the alkene. Alternatively, it was thought that epoxidation and formation of the trans diol could give access to **24** upon treatment with $Pb(OAc)_4$. Although epoxidation proceeded readily, the compound suffered rearrangement to what appeared to be a quinoline upon acidification.

As a result of the difficulty in purifying **24** it was typically carried on to the cascade reaction crude. Treatment of **24** with a 1:1 CH_2Cl_2/TFA solution provides **2** in

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(13) Chakravarty, A. K.; Dastidas, P. P. G.; Pakreshi, S. C. *Tetrahedron* **1982**, *38*, 1797.

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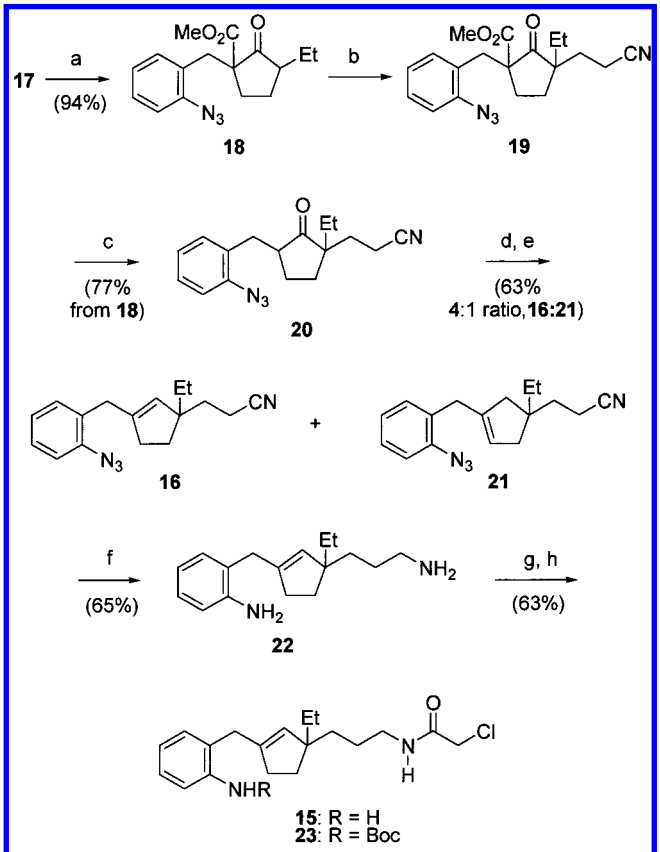
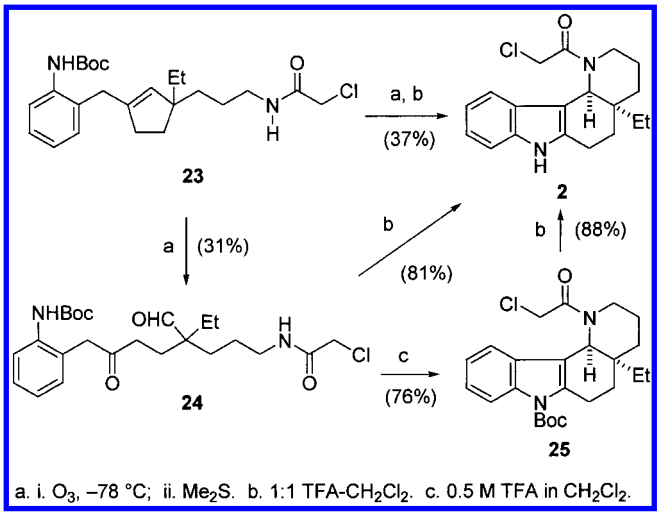
Scheme 4



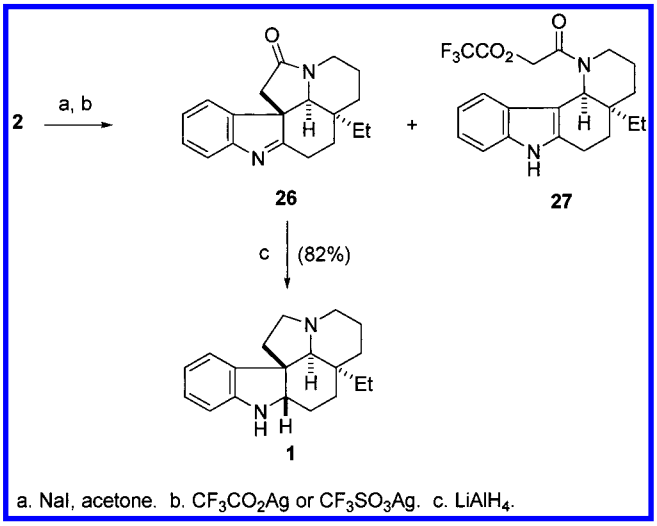
Scheme 5



53% yield from **23**.[15] To demonstrate the utility of this cascade reaction, compound **24** was painstakingly purified and subjected to identical reaction conditions. These conditions gave the deprotected tetracyclic indole derivative **2** in 81% yield. Under less acidic conditions, the Boc-protected indole **25** is produced in 76% yield (Scheme 5).

Having achieved three out of the four cyclizations, we next sought to close the E ring. Literature precedence showed that the formation of the $C_{11}-C_{12}$ bond late in the synthesis can be difficult. Until recently, use of intramolecular S_N2 displacement to form the pyrollidine ring resulted in low yields, especially in the case of haloacetamides.[16,17] This is, in part, due to steric impedance about the pseudopentacoordinate transition state. Magnus et al.[17] had attempted the same ring closure with both **2** and the bromide analogue under a variety of conditions but were unsuccessful. Additionally they tried to close the E ring by replacing the haloacetamide with a 2-bromoethyl group but were again unsuccessful. To circumvent this problem they resorted to closing the E ring with a Pummerer reaction, which added several steps to their overall synthesis. More recently Rubiralta et al. have successfully closed the pyrollidine ring system in high yield via base-mediated displacement using the 2-alkylsulfonylethyl derivative.[18]

Scheme 6



We chose to pursue the closure of the E ring via the haloacetamide, as we felt that it would require less protecting-group manipulation and would better protect the primary amine. Because the acyl iodide should be significantly more reactive than its chloro and bromo analogues, it was synthesized and treated with silver trifluoroacetate (Scheme 6). Under these conditions, indolenine **26** was isolated in 43% yield, along with a nearly equal amount of an unstable side product in which chloride appears to have been replaced by trifluoroacetate. Use of silver triflate eliminates this side product and provides **26** in 86% yield, based on chloride **2**. Reduction of both the amide and the indolenine provides aspidospermidine (**1**) in 82% yield.

In conclusion, the syntheses of aspidospermidine proceeds in 5.9% yield over 13 steps. This synthetic strategy should prove useful for the construction of other members of the *Aspidosperma* family because the piece-wise construction of the cascade precursor allows for incorporation of varied functionality. Furthermore, the discovery of a facile method of closing the E ring may allow for the implementation of synthetic routes that may have been otherwise discounted.

(15) The isolated yield of **25** is lower than the yield of the ozonolysis/cascade because material must be sacrificed to obtain clean material.

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

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