Communication

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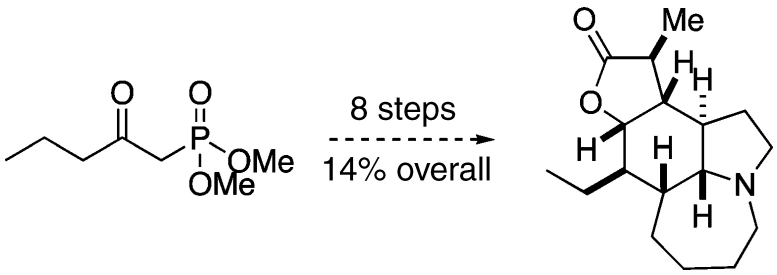
J. Am. Chem. Soc., **2005**, 127 (45), 15712-15713• DOI: 10.1021/ja055629m • Publication Date (Web): 22 October 2005



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Published on Web 10/22/2005

An Expeditious Total Synthesis of (±)-Stenine

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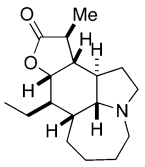
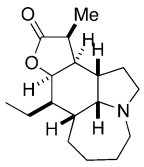
The development of rapid and efficient routes to complex natural product skeleta serves both target- and diversity-oriented synthetic chemistry. The *Stemona* alkaloids provide attractive targets for both kinds of research due to the diversity of structures found in this family of alkaloids and the range of biological activities associated with this class.[1] Stenine (**1**), in particular, has provided researchers with a synthetic challenge that has been met in the racemic manifold by Hart,[2] Padwa,[3] and, in a formal synthesis, this laboratory.[4] Enantioselective syntheses of this target were recorded nearly simultaneously by Wipf[5] and Morimoto.[6] The difficulty of this target, which features a central cyclohexane fused to three other rings and bearing a stereogenic center at every carbon, is evinced by the fact that these syntheses required 16−33 steps and provided the target in overall yields of 0.9−7.2%.

Our interest in this alkaloid and its congeners was recently reinforced by reports that neostenine, a stereoisomer of stenine, has antitussive activity comparable to that of codeine.[7] Clearly, the existing methodology available for the total synthesis of these compounds would not be sufficient for the procurement of sufficient quantities for detailed biological evaluation or the synthesis of analogues. In this paper, we describe a new approach to the synthesis of *Stemona* alkaloids that has strong potential for the practical solution of both of these issues.



*Stenine (**1**)*

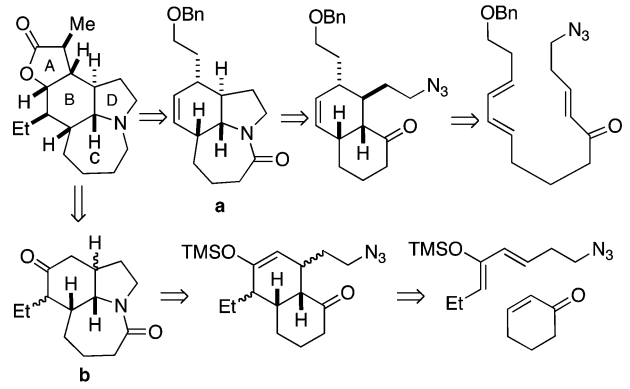


*Neostenine (**2**)*

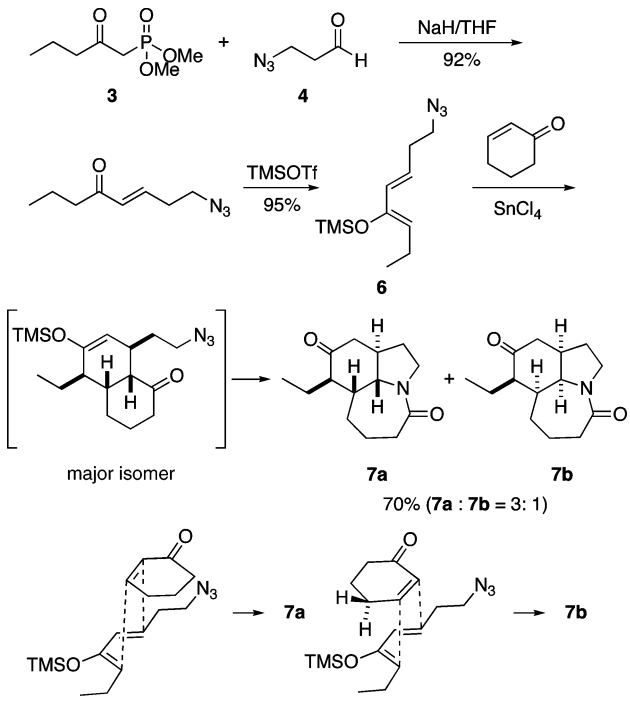
Our original approach to stenine was based on the premise that the BCD ring system could be obtained through an intramolecular Schmidt reaction on a ketone that would itself arise from an intramolecular Diels−Alder reaction of the triene shown in Scheme 1. We quickly learned that both the Diels−Alder and Schmidt reactions could be carried out in the same pot upon treatment with a Lewis acid, but that the reaction was poorly regio- and stereoselective. Thus, compound **a** was only available in 43% yield at best. Other issues were the number of steps needed to provide the "starting" triene (about 12) and the utilization of Hart's iodolactonization/radical allylation sequence to install the ethyl group. This sequence has the virtues of stereocontrol and relative efficiency, but nonetheless requires three steps for the removal of the terminal methylene carbon to afford the requisite ethyl substituent.

Subsequently, we have investigated domino reactions that combine an *intermolecular* Diels−Alder reaction with a Schmidt reaction.[8] This sequence is featured in an alternative retrosynthetic analysis shown at the bottom of Scheme 1. Application of a different Diels−Alder disconnection to that used previously and subsequent Schmidt reaction would afford a ketone **b** that would only require butyrolactone attachment. This route would involve a much more

Scheme 1



Scheme 2



facile preparation of the diene component and the direct, early incorporation of the ethyl group. On the other hand, the stereochemical outcome of the sequence was uncertain; the expected *endo*-selectivity would afford an intermediate corresponding to the *epi*-ethyl version of neostenine **2**, whereas an *exo*-Diels−Alder would lead to natural stenine stereochemistry. In this paper, we show that both outcomes can be effected through choice of Lewis acid and present a very short (nine-step) synthesis of (±)-stenine.

The known[9] Horner−Wadsworth−Emmons reagent **3** was prepared in 99% yield from commercially available dimethyl methylphosphonate and butyryl chloride (Scheme 2). Olefination

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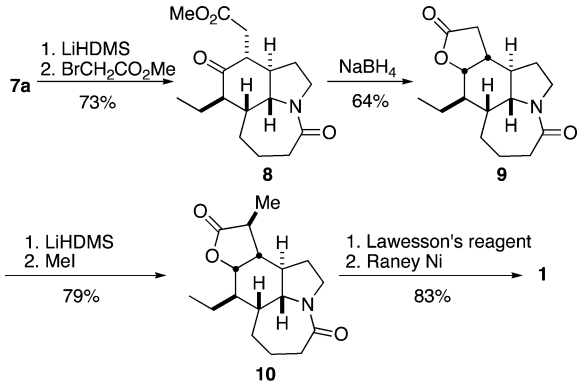
Scheme 3

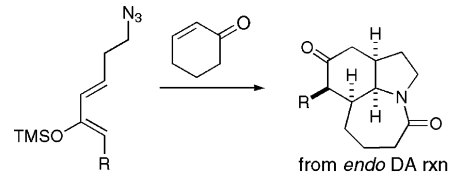


of aldehyde **4** (itself known[10] and made in a single step from acrylaldehyde and hydrazoic acid) afforded an enone that was readily converted to the corresponding trimethylsilyloxy diene. Treatment of the latter with cyclohexenone and $SnCl_4$ afforded a ca. 3:1 ratio of Diels−Alder/Schmidt adducts **7a** and **7b**, with the former compound—from an *exo*-selective Diels−Alder step—predominating. Presumably, *exo*-selectivity predominates because the *endo* alternative encounters significant steric encumbrance between one of the γ protons with the incoming nucleophilic silyl enol ether.[11] This stereostructure was supported by NOE studies, an X-ray structure of a later intermediate, and by the eventual conversion of **7a** to stenine.

The completion of the synthesis is shown in Scheme 3. All of the additional stereocenters were generated by highly selective substrate-directed reactions: an axially directed alkylation and reduction afforded compounds **8** and **9** (an X-ray of this compound was performed to verify the structure; see Supporting Information), respectively. The completion of the synthesis followed known procedures. Thus, alkylation proceeded smoothly to give the known lactam **10**. Conversion of **10** to stenine required selective lactam carbonyl reduction, which was accomplished as previously reported.[2,3,5] The spectra of the natural product thus prepared fully matched those literature values. Overall, the total synthesis was accomplished in only eight steps from known **3** (or nine steps from commercially available reagents) and 14% overall yield.

The value of this general strategy to the synthesis of neostenine and other congeners would be enhanced by access to the *endo*-Diels−Alder adduct **7b** or its synthetic equivalent. In preliminary work, we have shown that this can be accomplished in two ways (Scheme 4). In one experiment, we reacted **6** with $BF_3{\bullet}OEt_2$, which afforded exclusively *endo* material in modest yield. Alternatively, we have previously shown that a diene lacking the terminal ethyl group gave better yields of a moderately *endo*-selective reaction.[8]

Scheme 4



diene	Lewis acid	product(s)	yield (endo/exo ratio)
6 (R = Et)	$BF_3{\bullet}OEt_2$	**7b**	30% (endo only)
11 (R = H)	$SnCl_4$	**12a,b**	82% (3.4 : 1)

This work demonstrates the utility of the Diels−Alder/Schmidt reaction sequence for complex synthesis. The brevity of the route, in particular, the four-step preparation of tricyclic compounds **7a** and **7b**, suggests that it will be amenable to an analogue program based on total synthesis. Experiments in this direction are underway.

Acknowledgment. We thank the National Institute of General Medical Sciences (GM-49093) for financial support, David Vander Velde and Sarah Neuenswander for NMR help, Ben Neuenswander for HPLC-MS, and Douglas Powell for X-ray crystallography.

Supporting Information Available: Experimental details and characterization data for new compounds, including the X-ray structure of **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) The *Stemona* alkaloids have been associated with insecticidal, anthelmintic, antitussive, and various neurochemical effects, although mechanisms have rarely been identified. For reviews, see: (a) Edwards, O. E. *Alkaloids (Academic Press)* **1967**, *9*, 545−551. (b) Götz, M.; Strunz, G. M. In *Alkaloids*; Wiesner, K., Ed.; Butterworth: London, 1973; Vol. 9, pp 143−160. (c) Xu, R.-S. *Stud. Nat. Prod. Chem.* **2000**, *21*, 729−772. (d) Pilli, R. A.; Ferreira de Oliveira, M. d. C. *Nat. Prod. Rep.* **2000**, *17*, 117−127.
(2) (a) Chen, C.-Y.; Hart, D. J. *J. Org. Chem.* **1990**, *55*, 6236−6240. (b) Chen, C.-Y.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 3840−3849.
(3) (a) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515−1517. (b) Padwa, A.; Ginn, J. D. *J. Org. Chem.* **2005**, *70*, 5197−5206.
(4) (a) Golden, J. E.; Aubé, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4316−4318. For a similar approach, see: (b) Jung, S. H.; Lee, J. E.; Joo, H. J.; Kim, S. H.; Koh, H. Y. *Bull. Korean Chem. Soc.* **2000**, *21*, 159−160.
(5) (a) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106−11112. This group has also extended their general approach to encompass several more complex analogues of stenine as well: (b) Wipf, P.; Spencer, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 225−235.
(6) (a) Morimoto, Y.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 5773−5776. (b) Morimoto, Y.; Iwahashi, M.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 904−906.
(7) Chung, H.-s.; Hon, P.-m.; Lin, G.; But, P. P.-h.; Dong, H. *Planta Med.* **2003**, *69*, 914−920.
(8) Zeng, Y.; Reddy, D. S.; Hirt, E.; Aubé, J. *Org. Lett.* **2004**, *6*, 4993−4995.
(9) Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387−6393.
(10) Ma, Y. *Heteroatom Chem.* **2002**, *13*, 307−309.
(11) Ge, M.; Stoltz, B. M.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1927−1929.

JA055629M