A Combined Intramolecular Diels-Alder/Intramolecular Schmidt Reaction Process: A Formal Synthesis of (±)-Stenine[**]

Jennifer E. Golden and Jeffrey Aubé*

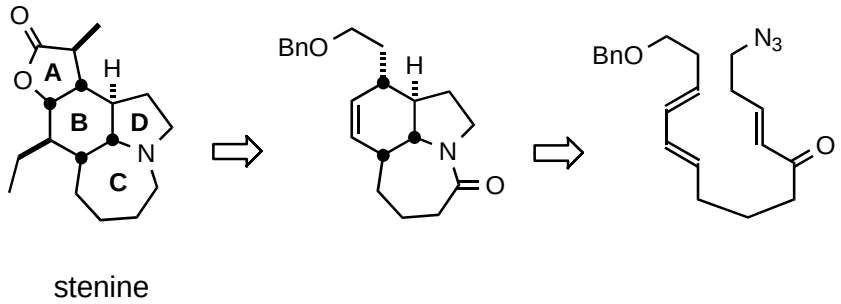
[*] Prof. Dr. J. Aubé
University of Kansas
Department of Medicinal Chemistry
Malott Hall
1251 Wescoe Hall Dr., Room 4070
Lawrence, KS 66045-2506
Fax: (785)864-5326
Email: jaube@ku.edu

Dr. J. E. Golden
Stanford University
Department of Chemistry
Stanford, CA 94305

[**] Financial support was provided by the National Institutes of Health (Grant GM-49093). J. Golden gratefully acknowledges the Madison A. and Lila Self Fellowship Program for its support. The authors also thank Dr. David Vander Velde for NMR assistance and Dr. Doug Powell for crystallographic data.

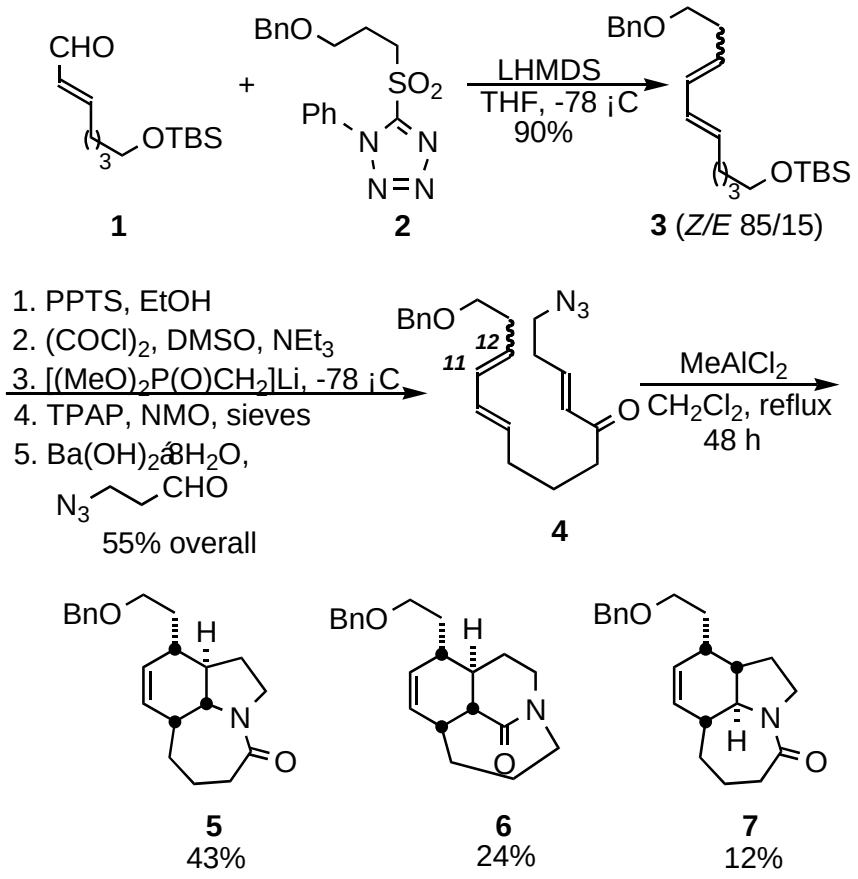
One hallmark of an attractive synthetic strategy is the efficient assembly of advanced intermediates. One way of achieving this goal has been the development of cascade reactions.[1] An objective of this laboratory has been to advance the utility of the intramolecular Schmidt reaction of azides and ketones in total synthesis.[2] Herein, we describe the combination of an intramolecular Schmidt reaction with an intramolecular Diels-Alder process – two efficient reactions that benefit from Lewis acid promotion. The specific context of this work is the formal total synthesis of stenine, shown retrosynthetically in Scheme 1.

Scheme 1



Stenine and related alkaloids[3-11] have drawn considerable attention from synthetic chemists due in part to the historical use of root extracts of *stemonaceous* plants in Japanese and Chinese folk medicine.[6] Efforts in this area have already culminated in four total syntheses of stenine by teams led by Hart,[7] Wipf,[8] Morimoto,[9] and most recently, Padwa.[10] The first three of these syntheses feature the stepwise construction of the ABD ring substructure followed by final C-ring formation. Additionally, routes developed by Hart and Morimoto utilize a Diels-Alder reaction as the key step, and both subsequently implement a Curtius rearrangement to install a nitrogen atom adjacent to the carbonyl group. While the present work was in progress, Jung and coworkers[11] published a partial synthesis using a Diels-Alder reaction similar to that shown in Scheme 1, followed by a four-step Beckmann rearrangement/*N*-alkylation sequence to form the BCD skeleton. *We now report an approach in which the formation of all three rings of a key intermediate and four of the stereocenters were formed in a single chemical step beginning with acyclic precursor* ***4*** (Scheme 2).

Scheme 2

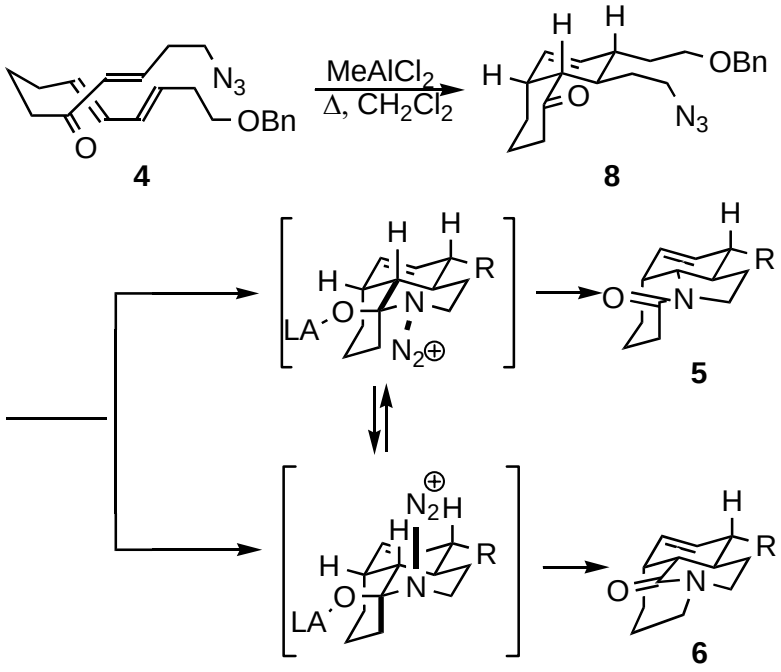


The cascade reaction substrate **4** was prepared using standard methodology (Scheme 2). Diene **3** was generated in 90% yield from a modified Julia coupling[12] between aldehyde **1** and sulfone **2**, affording an inseparable 85:15 mixture of isomers at the new double bond.[13] Removal of the silyl group, followed by Swern oxidation, gave an aldehyde that was treated with the lithium anion of dimethyl methylphosphonate. This provided a β-hydroxyphosphonate that was subsequently oxidized with TPAP/NMO. The resulting β-ketophosphonate was subjected to a Horner-Wadsworth-Emmons reaction[14] with 2-azidoethanal[15] to afford triene **4** in 55% yield from **3**.

Treatment of **4** with $MeAlCl_2$ in refluxing methylene chloride afforded tricyclic lactams **5**, **6**, and **7** in 79% overall yield and a ratio of 3.6:2:1, respectively. As expected (see below), the major diastereomer, **5**, had the stereochemistry required for the stenine synthesis. The structures of lactams **5** and **7** were confirmed by X-ray crystallography of the corresponding debenzylated derivatives. We assign the unusual bridged lactam structure to compound **6** based on ^{13}C chemical shift data (the carbonyl carbon appears at 188 ppm vs. 171-175 ppm for compounds **5** and **7**) and a $\nu_{C=O}$ value of 1690 cm^{-1} (cf. 1625-1600 cm^{-1} for **5** and **7**). These data are consistent with considerable loss of conjugation between the nitrogen lone pair and the carbonyl compound in the twisted amide linkage and are in agreement with similar bridged lactams.[16] Additionally, its stereostructure is consistent with 2D-NMR spectroscopic analysis.

Both **5** and **6** are proposed to result from a single Diels-Alder adduct **8**, *via* an *endo*-transition state (Scheme 3).[17] The azide can then add to the Lewis-acid-coordinated ketone. Assuming anti-periplanar C→N bond migration,[18] an intermediate containing an equatorial N_2^+ *en route* to lactam would afford lactam **5**, whereas an axially oriented leaving group would give bridged compound **6**. Bridged lactam formation has not been previously observed in an intramolecular Schmidt reaction, although an analogous case was recently observed in a ketal-mediated example. Lactam **7** results from an *exo*-transition state in the Diels-Alder cyclization, followed by the D-ring-forming/C-ring-expansion process.

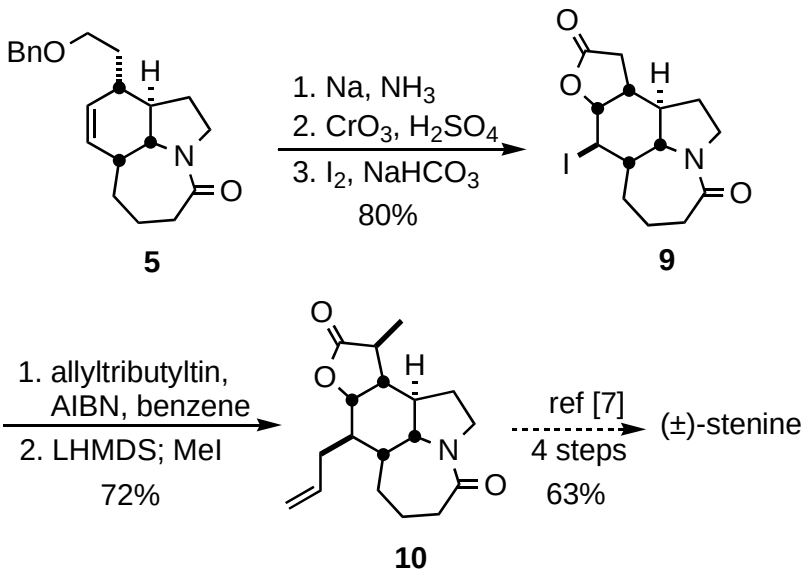
Scheme 3



It has proved possible to affect modest changes in product distribution through modifications of Lewis acid and reaction conditions, but the overall yield of 43% for **5** is both reproducible and represents the most favorable results to date. In the context of an inseparable 85:15 mixture of 11,12-double bond stereoisomers of **4**, this yield corresponds to an overall conversion of the reactive *trans-trans* triene isomer to **5** of 51%.

The formal synthesis was finished as shown in Scheme 4. Removal of the benzyl ether from **5**, oxidation of the resulting alcohol and iodolactonization gave butyrolactone **9** in 80% yield from **5**. Keck allylation[19] followed by methylation[20] of the lactone proceeded stereoselectively to provide Hart intermediate **10** in 72% yield over two steps. All spectroscopic and physical data of compound **10** was in agreement with Hart's published data.[7]

Scheme 4



In summary, we have completed a formal synthesis of (±)-stenine using a domino Diels-Alder/Schmidt reaction strategy. Our route affords advanced intermediate **10** in 12 steps and in 12% overall yield from **1**. We are currently investigating the further streamlining of this overall approach and its application to other *stemona* alkaloids. [21]

Supporting Information. Experimental procedures and characterization data for new compounds.

REFERENCES

[1] For reviews of domino processes in organic synthesis, see: a) L. F. Tietze, U. Beifuss, *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131-163; b) R. A. Bunce, *Tetrahedron* **1995**, *51*, 13103-13159; c) K. Neuschuetz, J. Velker, R. Neier, *Synthesis* **1998**, 227-255; d) P. J. Parsons, C. S. Penkett, A. Shell, J. *Chem. Rev; Washington, D. C.)* **1996**, *96*, 195-206; e) H. Waldmann, *Org. Synth. Highlights II* **1995**, 193-202; f) L. F. Tietze, *Chem. Rev.*

(Washington, D. C.) **1996**, *96*, 115-136; g) L. F. Tietze, A. Modi, *Medicinal Res. Reviews* **2000**, *20*, 304-322.

[2] a) J. Aubé, G. L. Milligan, *J. Am. Chem. Soc.* **1991**, *113*, 8965-8966; b) J. Aubé, P. S. Rafferty, G. L. Milligan, *Heterocycles* **1993**, *35*, 1141-1147; c) G. L. Milligan, C. J. Mossman, J. Aubé, *J. Am. Chem. Soc.* **1995**, *117*, 10449-10459; d) R. Iyengar, K. Schildknegt, J. Aubé, *Org. Lett.* **2000**, *2*, 1625-1627.

[3] For approaches to croomine, see: a) S. F. Martin, K. J. Barr, *J. Am. Chem. Soc.* **1996**, *118*, 3299-3300; b) S. F. Martin, K. J. Barr, D. W. Smith, S. K. Bur, *J. Am. Chem. Soc.* **1999**, *121*, 6990-6997; c) D. R. Williams, D. L. Brown, J. W. Benbow, *J. Am. Chem. Soc.* **1989**, *111*, 1923-1925.

[4] For approaches to stemoamide, see: a) P. A. Jacobi, K. Lee, *J. Am. Chem. Soc.* **1997**, *119*, 3409-3410; b) P. A. Jacobi, K. Lee, *J. Am. Chem. Soc.* **2000**, *122*, 4295-4303; c) A. S. Kende, J. I. Martin Hernando, J. B. J. Milbank, *Org. Lett.* **2001**, *3*, 2505-2508; d) A. Kinoshita, M. Mori, *J. Org. Chem.* **1996**, *61*, 8356-8357; e) A. Kinoshita, M. Mori, *Heterocycles* **1997**, *46*, 287-299; f) Y. Kohno, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2063-2070; g) D. R. Williams, J. P. Reddy, G. S. Amato, *Tetrahedron Lett.* **1994**, *35*, 6417-6420.

[5] For approaches to other *stemona* alkaloids, see: a) D. R. Williams, M. G. Fromhold, J. D. Earley, *Org. Lett.* **2001**, *3*, 2721-2724; b) J. H. Rigby, S. Laurent, A. Cavezza, M. J. Heeg, *J. Org. Chem.* **1998**, *63*, 5587-5591; c) C. H. Heathcock, M. M. Hinman, *J. Org. Chem.* **2001**, *66*, 7751-7756; d) L. Xiang, A. P. Kozikowski, *Synlett* **1990**, 279-281.

[6] a) M. Gotz, O. E. Edwards, In *Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. IX, pp 545-551; b) M. Gotz, G. M. Strunz, In *Alkaloids*; Weisner,

K., Ed.: London, 1973; Vol. IX, pp 143-160; c) For a review of *stemona* alkaloids, see: R. A. Pilli, M. d. C. Ferreira De Oliveira, *Nat. Prod. Rep.* **2000**, *17*, 117-127.

[7] a) C.Y. Chen, D. J. Hart, *J. Org. Chem.* **1990**, *55*, 6236-6240; b) D. J. Hart, C.Y. Chen, *J. Org. Chem.* **1993**, *58*, 3840-3849.

[8] a) P. Wipf, Y. Kim, D. M. Goldstein, *J. Am. Chem. Soc.* **1995**, *117*, 11106-11112; b) P. Wipf, Y. Kim, *Tetrahedron Lett.* **1992**, *33*, 5477-5480; c) P. Wipf, D. M. Goldstein, *Tetrahedron Lett.* **1996**, *37*, 739-742.

[9] a) Y. Morimoto, M. Iwahashi, K. Nishida, Y. Hayashi, H. Shirahama, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 904-906; b) Y. Morimoto, M. Iwahashi, *Synlett* **1995**, 1221-1222; c) Y. Morimoto, M. Iwahashi, T. Kinoshita, K. Nishida, *Chem. Euro. J.* **2001**, *7*, 4107-4116.

[10] J. D. Ginn, A. Padwa, *Org. Lett.* **2002**, *4*, 1515-1517.

[11] S. H. Jung, J. E. Lee, H. J. Joo, S. H. Kim, H. Y. Koh, *Bull. Korean Chem. Soc.* **2000**, *21*, 159-160.

[12] a) P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, 26-28; b) P. J. Kocienski, A. Bell, P. R. Blakemore, *Synlett* **2000**, 365-366.

[13] Aldehyde **1** was prepared in 94% overall yield from 1,5-pentanediol via the following route: (a) NaH, TBSCl, THF; (b) oxalyl chloride, DMSO, NEt_3; (c) Ph_3PCHCO_2Et, CH_2Cl_2, reflux 16 h; (d) DIBAL-H, Et_2O, 2h; (e) oxalyl chloride, DMSO, NEt_3. Sulfone **2** was synthesized from 1,3-propanediol in 84% overall yield via the following sequence: (a) NaH, BnBr, DMF, 24h; (b) CBr_4, PPh_3, CH_2Cl_2; (c) 1-phenyl-1*H*-tetrazole-5-thiol, NaH, DMF; (d) *m*-CPBA, $NaHCO_3$, CH_2Cl_2.

[14] I. Paterson, K. S. Yeung, J. B. Smaill, *Synlett* **1993**, 774-776.

[15] J. H. Boyer, *J. Am. Chem. Soc.* **1951**, *73*, 5248-5252.

[16] a) A. Greenberg, In *Structure and Reactivity*; J. F. Liebman, A. Greenberg, Eds.; VCH: New York, 1988; pp 139-178; b) A. Greenberg, D. T. Moore, T. D. DuBois, *J. Am. Chem. Soc.* **1996**, *118*, 8658-8668; c) A. Greenberg, C. A. Venanzi, *J. Am. Chem. Soc.* **1993**, *115*, 6951-6957; d) K. J. Shea, T. G. Lease, J. W. Ziller, *J. Am. Chem. Soc.* **1990**, *112*, 8627-8629.

[17] For a discussion of preferential boat-like transition states in this type of Diels-Alder reaction, see: J. W. Coe, W. R. Roush, *J. Org. Chem.* **1989**, *54*, 915-930.

[18] Y. Kishi, R. M. Goodman, *J. Am. Chem. Soc.***1998**, *120*, 9392-9393, and references therein.

[19] J. B. Yates, G. E. Keck, *J. Am. Chem. Soc.* **1982**, *104*, 5829-5830.

[20] M. W. Rathke, *J. Am. Chem. Soc.* **1970**, *92*, 3222-3223.

[21] CCDC files 185839 (compound **5**) and 185840 (compound **7**) contain the crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Statement for Table of Contents

A formal synthesis of (±)–stenine was accomplished using a domino intramolecular Diels-Alder/intramolecular Schmidt reaction process as the key step. This protocol, which utilized an azido triene precursor, provided an advanced tricyclic intermediate in which four stereocenters and three rings were established in a single step.

Graphics for Table of Contents here

Keywords

Azide, lactam, Diels-Alder, stenine, ring expansion.