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First Asymmetric Total Synthesis of (+)-Sparteine

Brenton T. Smith, John A. Wendt,† and Jeffrey Aubé*

The University of Kansas, Department of Medicinal Chemistry, Malott Hall,
1251 Wescoe Hall Drive, Room 4070, Lawrence, Kansas 66045-7582

jaube@ku.edu

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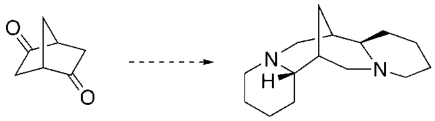
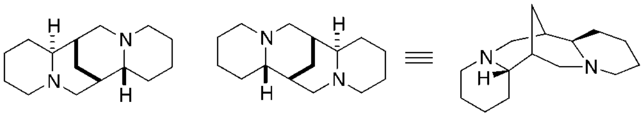
ABSTRACT



(+)-Sparteine

The total synthesis of (+)-sparteine was accomplished from 2,5-norbornadione in 15 steps and 15.7% overall yield. The key steps were two ring-expansion reactions, one involving an intramolecular Schmidt reaction and one using a novel variant of the photo-Beckmann rearrangement.

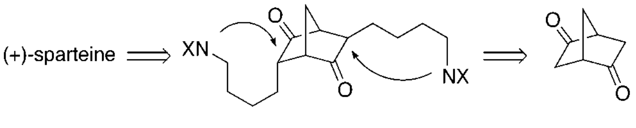
The lupidine alkaloid (−)-sparteine is used as a cardiovascular agent[1] and has found widespread use in recent years as a chiral ligand for asymmetric deprotonations, oxidations, conjugate addition, and other asymmetric reactions.[2] (−)-Sparteine, as isolated from certain papilionaceous plants such as Scotch broom, is commercially available. Its enantiomer, (+)-sparteine, is also naturally occurring but not easily obtained from natural sources. Although it can be prepared from (−)-lupanine,[3] no asymmetric total synthesis[4] of (+)-sparteine exists (or of its (−)-enantiomer, for that matter), which limits the use of this chiral ligand.



(-)-Sparteine (+)-Sparteine

Herein, we describe a total asymmetric synthesis of sparteine that can deliver either enantiomer of this alkaloid in pure form.[5] Our basic plan and the principal challenges of this synthesis are shown in Scheme 1. We envisioned making the tetracyclic structure of the target using sequential nitrogen ring-expansion reactions on a bicyclic substrate that

Scheme 1



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[†] Current address: Pharmacia Corp., 4901 Searle Parkway, Skokie, IL 60077.

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(3) Ebner, T.; Eichelbaum, M.; Fischer, P.; Meese, C. O. *Arch. Pharm. (Weinheim)* **1989**, *322*, 399−403.

(4) Racemic total syntheses of sparteine: (a) Leonard, N. J.; Beyler, R. E. *J. Am. Chem. Soc.* **1948**, *70*, 2298−2299. (b) Anet, E. L. F. J.; Hughes, G. K.; Ritchie, E. *Aust. J. Sci. Res.* **1950**, *3A*, 635−641. (c) Anet, E.; Hughes, G. K.; Ritchie, E. *Nature* **1950**, *165*, 35−36. (d) Van Tamelen, E. E.; Foltz, R. L. *J. Am. Chem. Soc.* **1960**, *82*, 2400. (e) Van Tamelen, E. E.; Foltz, R. L. *J. Am. Chem. Soc.* **1969**, *91*, 7372−7377. (f) Bohlmann, F.; Müller, H.-J.; Schumann, D. *CB* **1973**, *106*, 3026−3034. (g) Binning, F. *Arzneim.-Forsch.* **1974**, *24*, 752−753. (h) Oinuma, H.; Dan, S.; Kakisawa, H. *J. Chem. Soc., Chem. Commun.* **1983**, 654−655. (i) Takatsu, N.; Noguchi, M.; Ohmiya, S.; Otomasu, H. *Chem. Pharm. Bull.* **1987**, *35*, 4990−4992. (j) Wanner, M. J.; Koomen, G. J. *J. Indian Chem. Soc.* **1997**, *74*, 891−895.

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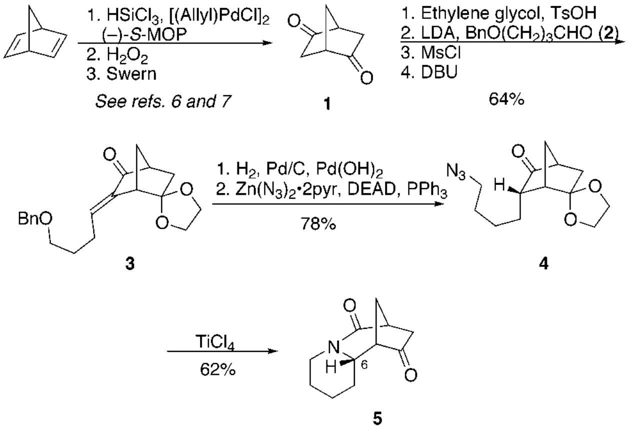
would ultimately be derived from the C_2-symmetrical, chiral ketone **1**. Reduction of the resulting bislactam would lead to sparteine. Note that the stereochemistry of sparteine requires that one of the two appendages containing an ultimately reactive nitrogen moiety be placed onto this ketone in an *endo* position and the other in an *exo* orientation.

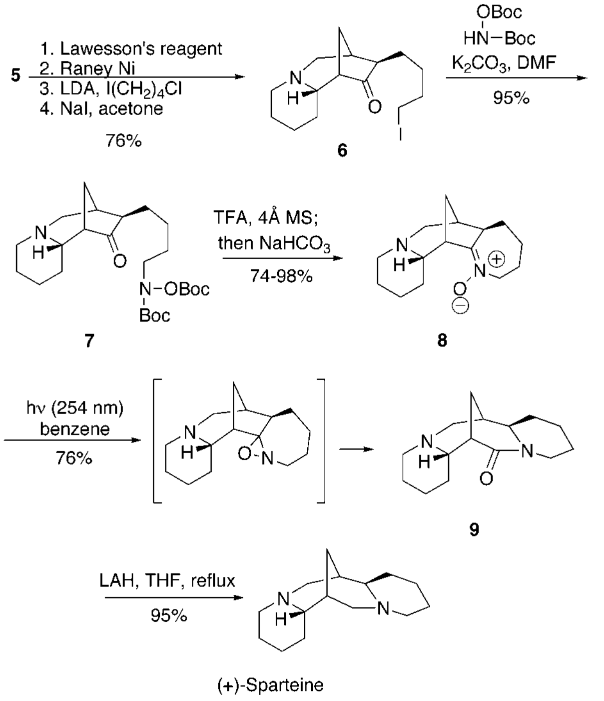
Norbornadiene was subjected to chiral (bis)hydrosilation ($HSiCl_3$, (−)-*S*-MOP, allylpalladium chloride dimer; then H_2O_2, KI, $KHCO_3$), which was previously shown to provide the diol[6] corresponding to (+)-**1** with high enantio- and regioselectivity (Scheme 2). Swern oxidation gave diketone (+)-**1**,[7] which could be brought to effective enantiomeric purity by simple recrystallization from ether/hexane ($[\alpha]_D$ −4.5 (*c* 2.7, EtOH), mp 141.5−142 °C). Our attempts to alkylate enolates derived from **1** directly failed due to apparent decomposition. However, monoketalization followed by an aldol reaction with aldehyde **2**[8] gave enone **3** following elimination. At this point, treatment with H_2 and Pd/C both removed the benzylic ether and reduced the α,*β*-unsaturated olefin. Hydrogenation from the less hindered *exo* face established the desired *endo* orientation of this side chain. A modified Mitsunobu azidation[9] afforded **4**, which was treated with excess $TiCl_4$ to smoothly effect an intramolecular Schmidt reaction,[10] which was accompanied by deketalization and resulted in **5**.

Scheme 2



Although the direct alkylation of keto lactam **5** was inefficient (10−19%), the corresponding amine reacted smoothly with base and 1,4-iodochlorobutane to give **6** in 76% overall yield for four steps (Scheme 3). This time, simple *exo* alkylation gave the chloride as a single stereoisomer. Obtained from a Finklestein reaction, the iodide could be converted to the corresponding azide with ease. However, we were not able to effect another intramolecular Schmidt reaction on this compound (or *many* closely related analogues!) under a wide range of conditions known to promote this process.[10] We hypothesize that the inactivity of these compounds was due to preferential Lewis or protic acid coordination to the amine nitrogen or lactam carbonyl instead of the ketone needed for successful reaction with the weakly nucleophilic azide.[11] We therefore turned our attention to nitrogen nucleophiles that should not require promotion by Lewis acid catalysts, eventually rescuing this route with a novel variant of the photo-Beckmann rearrangment.[12]

Scheme 3



The literature holds only a few examples of the photochemical rearrangement of nitrones embedded into a multicyclic structure and fewer still that proceed in acceptable chemical yields.[13] In the present case, displacement of the iodide with BocNHOBoc followed by deprotection of the hydroxylamine gave nitrone **8** by intramolecular condensation. Photolysis in benzene at 254 nm afforded smooth

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(5) Early studies related to this synthesis have appeared: Wendt, J. A.; Aubé, J. *Tetrahedron Lett.* **1996**, *37*, 1531−1534.

(6) Hayashi, T. *Acta Chem. Scand.* **1996**, *50*, 259−266.

(7) Weissfloch, A.; Azerad, R. *Bioorg. Med. Chem.* **1994**, *2*, 493−500.

(8) This aldehyde was prepared from butanediol in 90% overall yield by monobenzylation followed by TEMPO oxidation.

(9) Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130−132.

(10) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449−10459.

(11) Some circumstantial evidence in support of this view includes the following two observations: (1) IR spectroscopy of the keto lactam **5** shows that the lactam carbonyl is readily coordinated by Lewis acids (the $\nu_{C=O}$ shifts by ca. −20 cm^{-1} in the presence of $TiCl_4$), but there is no evidence for coordination of the ketone carbonyl in even a very large excess of Lewis acid (>20 equiv). (2) Even simple acid-promoted reactions such as dimethyl ketal formation of compounds such as **5** have proven difficult.

(12) (a) Suginome, H.; Furukawa, K.; Orito, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 917−921. (b) Suginome, H.; Furukawa, K.; Orito, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1004−1005. (c) Suginome, H.; Kaji, M.; Yamada, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 321−326. (d) Suginome, H. *Kagaku No Ryoiki* **1976**, *30*, 578−591.

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rearrangement to the lactam in 76% yield. Removal of the lactam carbonyl with LAH afforded (+)-sparteine in essentially quantitative yield. The specific rotation of the synthetic material was $[\alpha]_D$ +21.3 (*c* 1.7, EtOH) as compared to $[\alpha]_D$ −20.7 (*c* 1.8, EtOH) measured for levrorotatory material purchased from Aldrich. The enantiomeric purity of the synthetic material was confirmed by chiral GC.

In summary, we were able to complete the first asymmetric total synthesis of (+)-sparteine using two different kinds of nitrogen ring-expansion reactions. We are currently working toward streamlining this route and attaining a truly practical synthesis of this rare material.

Acknowledgment. This work was supported by the NIH (GM-49093). We also thank Dr. Craig Mossman for suggesting that we make sparteine in the first place.

Supporting Information Available: Experimental details for new compounds, copies of ^{1}H and ^{13}C NMR spectra, and chiral GC analyses of **1** and (+)-sparteine. This material is available free of charge via the Internet at http://pubs.acs.org.

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