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An Approach to the Synthesis of Stenine

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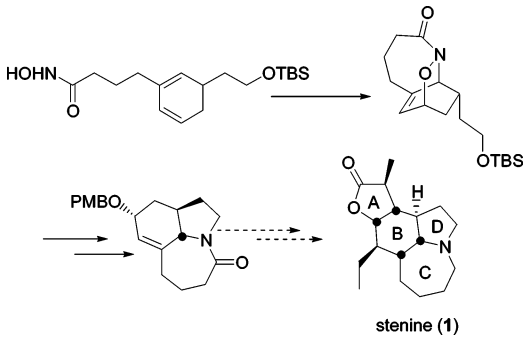
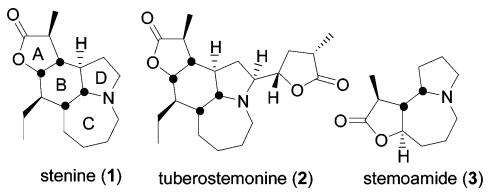
ABSTRACT



A type 2 *N*-acylnitroso intramolecular Diels–Alder reaction followed by reductive N–O bond cleavage formed the B and C rings of the *Stemona* alkaloid stenine. Further elaboration provided the functionalized tricyclic core.

Extracts from the roots of stemonaceous plants (*Stemona* and *Croomia*) have been used in China and Japan for centuries as respiratory treatments for humans and as anthelmintics for domestic animals.[1] These extracts were found to contain a wealth of complex alkaloids including stenine (**1**), tuberostemonine (**2**), and stemoamide (**3**).[2] These



Stemona alkaloids provide attractive targets for total synthesis due to their intriguing structures and the range of associated biological activities.[3] Stenine (**1**) has stood out as a particularly challenging target to synthetic chemists.[4] This challenge has been answered in racemic form by Hart, Padwa, and Aubé.[5] To date, only Wipf and Morimoto have reported enantioselective syntheses of this target.[6] The difficulties of this target lie in its fully substituted central cyclohexane ring,

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(3) Some examples are: (a) Booker-Milburn, K. I.; Hirst, P.; Charmant, J. P. H.; Taylor, L. H. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1642. (b) Williams, D. R.; Shamim, K.; Reddy, J. P.; Amato, G. S.; Shaw, S. M. *Org. Lett.* **2003**, *5*, 3361. (c) Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848. (d) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295. (e) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299. (f) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923.

(4) Uyeo, S.; Irie, H.; Harada, H. *Chem. Pharm. Bull.* **1967**, *15*, 768.

(5) (a) Chen, C.-Y.; Hart, D. J. *J. Org. Chem.* **1990**, *55*, 6236. (b) Chen, C.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 3840. (c) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515. (d) Padwa, A.; Ginn, J. D. *J. Org. Chem.* **2005**, *70*, 5197. (e) Golden, J. E.; Aubé, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4316. (f) Zeng, Y.; Aubé, J. *J. Am. Chem. Soc.* **2002**, *127*, 15712.

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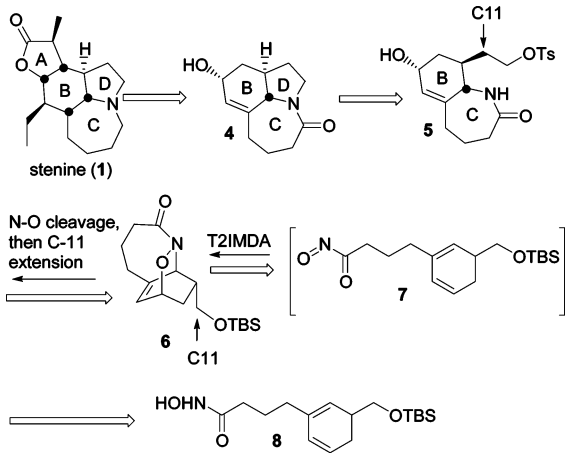
tricyclic core with an additional fused lactone ring, and seven contiguous stereogenic centers.

A common feature among many members of the *Stemona* alkaloid class is the 7-membered azepane C ring. We have recently found that azepanes can be accessed with control of stereochemistry by a procedure utilizing a type 2 intramolecular Diels−Alder (T2IMDA) cyclization of a C-2 tethered diene joined to an acylnitroso dienophile. This reaction gives rise to oxazinolactams.[7] These cycloadducts can be further elaborated by reductive cleavage of the N−O bond to give azocin-2-ones. The T2IMDA method for azepane construction could provide a general method for the synthesis of *Stemona* alkaloids and their analogues. In this Letter, we apply this strategy to the tricyclic BCD core of stenine and lay the foundation for its total synthesis.

Our retrosynthetic analysis of stenine begins with the removal of the lactone A ring and ethyl group on the B ring to give the BCD core **4** (Scheme 1). On the basis of previous

Scheme 1



work[5,6] it was anticipated that both the A ring and the ethyl group could be introduced at a late stage of the sequence. Disconnection of the D ring of the tricyclic core **4** at the C−N bond reveals the fused BC ring system **5**. Further disconnection to **6** by an adjustment at C11 and N−O bond closure reveals the oxazinolactam. Compound **6** was expected to be the product of a T2IMDA cyclization of acyclnitroso **7**. Acyclnitroso **7** was anticipated to be accessible from hydroxamic acid **8**. The single stereocenter in **8** was expected to control the π-facial selectivity of the cycloaddition and ultimately all stereocenters in the molecule.

The synthesis of Diels−Alder cycloaddition precursor **8** began with 5-hydroxymethylcyclohex-2-enone **9**, which was obtained in three steps from commercially available tri-

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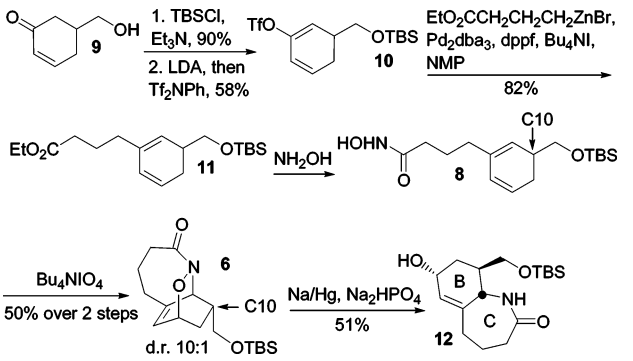
Scheme 2



methoxybenzoic acid (Scheme 2).[8] The alcohol was protected as the TBS ether. The ketone was treated with LDA and then Tf_2NPh to give triflate **10** in 58% yield. A Negishi coupling was used to install the side chain at C-2 of the cyclohexadiene ring.[9] Diene **11** was converted to the corresponding hydroxamic acid **8** by treatment with $NH_2OH{\cdot}HCl$ and KOH. Oxidation of **8** by Bu_4NIO_4 at 0 °C generated an acylnitroso species that underwent in situ cycloadditon. The reaction is the first example of a cyclic diene as a participant in the acylnitroso T2IMDA. The product, a 10:1 mixture of diastereomers at C10, was isolated in 50% yield for the two steps. Variation of temperature and solvent resulted in a negligible effect on diastereoselectivity of the cycloaddition. The two cycloadducts were found to be physically inseperable. The mixture of diastereomers was treated by Na/Hg in the presence of Na_2HPO_4 to afford two separable products in 51% yield. The structure of the desired major diastereomer **12** was confirmed by X-ray crystallography.

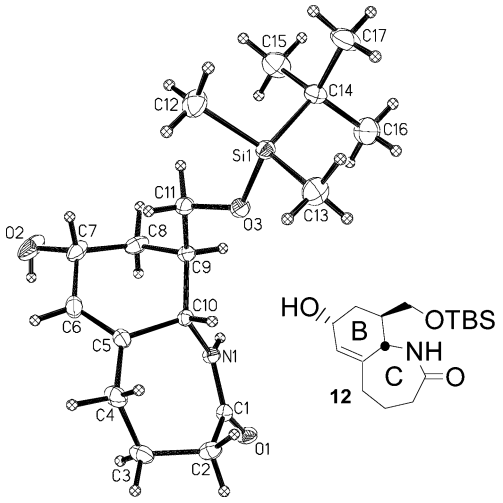
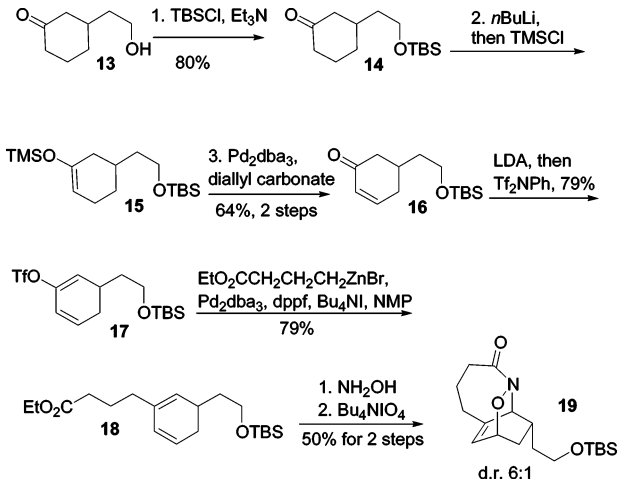


Figure 1. ORTEP plot of compound **12**.

Our next set of experiments focused on completion of the tricyclic core. However, attempts to homologate the molecule at C11 failed. It was concluded that it would be wise to

incorporate the two-carbon chain earlier in the synthesis. The synthetic plan was revised to utilize known alcohol **13** as the starting material.[10] Alcohol **13** was protected as the TBS ether to give intermediate **14** (Scheme 3). Ketone **14** was

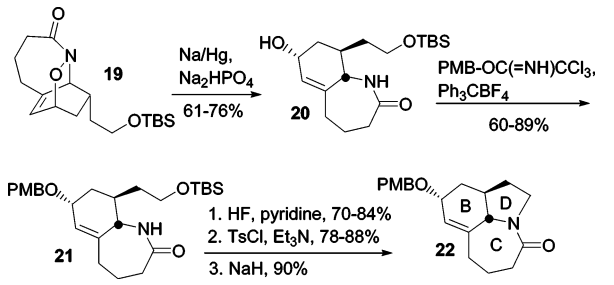
Scheme 3



kinetically deprotonated, and the resulting enolate was trapped as TMS enol ether **15**. Ether **15** was then oxidized to enone **16** by using a Pd-mediated oxidation with diallyl carbonate. Enone **16** was treated first with LDA and then with Tf_2NPh to give triflate **17** in 79% yield. Triflate **17** was treated with 4-ethoxy-4-oxobutylzinc bromide in the presence of $Pd_2(dba)_3$, dppf, NMP, and Bu_4NI to afford diene **18** in 76% yield. Diene **18** was converted to the corresponding hydroxamic acid by treatment with $NH_2OH{\cdot}HCl$ and KOH. Without further purification, oxidation and cycloaddition of the hydroxamic acid produced a 6:1 ratio of diastereomers in 50% overall yield for the two steps.

The diastereomers were not separable, Treatment with Na/Hg in the presence of Na_2HPO_4 afforded alcohol **20** and its diastereomer in 61−76% combined yield (Scheme 4). The desired major diastereomer could be purified by recrystallization at this stage. Protection of alcohol **20** as the PMB

Scheme 4



ether was catalyzed by Ph_3CBF_4 to afford ether **21** in 60−89% yield. Removal of TBS by HF and pyridine, followed by tosylation and base-mediated cyclization, resulted in the key tricyclic product **22**.

In summary, the synthesis of the pivotal BCD ring system of stenine has been achieved by an acylnitroso T2IMDA cyclization. The key cycloadditions proceeded with good selectivity in both instances to control stereochemistry of the precursor to the azepane C ring in the natural product. The tricyclic BCD core is set up for further elaboration toward the total synthesis. In this approach, the stereocenter in **13** sets subsequent asymmetric carbons. A large-scale synthesis of enantioenriched **13** has been carried out by using an enantioselective Michael addition.[11] Enantioenriched **13** is currently being used for the enantioselective synthesis of (−)-stenine. Future effort will be aimed at the completion of the synthesis, as well as the exploration of applications to other *Stemona* alkaloids.

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

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