ORGANIC LETTERS

2002
Vol. 4, No. 9
1515−1517

Total Synthesis of (±)-Stenine Using the IMDAF Cycloaddition of a 2-Methylthio-5-amido-substituted Furan

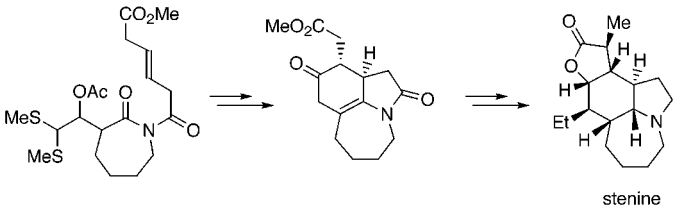
John D. Ginn and Albert Padwa*

Department of Chemistry, Emory University, Atlanta, Georgia 30322

chemap@emory.edu

Received February 19, 2002

ABSTRACT



The intramolecular [4 + 2]-cycloaddition of a 2-methylthio-5-amidofuran was used to create the azepinoindole skeleton present in the *Stemona* alkaloid stenine. The rearranged cycloadduct was converted to stenine (1) in 11 additional steps via a sequence that features a Crabtree catalyst directed hydrogenation (9→10), iodolactonization (2→11), and a Keck allylation (11→12).

The pyrrolo[1,2-*a*]azepine nucleus is a common structural motif shared by several of the stemona alkaloids, including stenine (**1**), whose hydroindole core skeleton contains six contiguous stereocenters.[1] Members of the stemona family are generally classified into six groups according to their structural features.[2] Many of these alkaloids possess diverse physiological properties[3] as well as structural complexity and, therefore, have attracted the interest of synthetic chemists.[4] Previous syntheses of stenine have focused on the initial construction of the hydroindole portion (BD rings), with closure to the seven-membered azepine ring being postponed until the end of the synthesis.[5] We envisioned an alternative approach, in which the azepine ring would be incorporated at any early point in the synthetic sequence and then used as a template for setting the required stereochemistry. Scheme 1 depicts the basic features of our strategy directed toward stenine. Our synthesis relies on an intramolecular Diels−Alder reaction of a 2-amido-5-alkylthio-substituted furan (IMDAF) to create the azepinoindole skeleton.[6] This is followed by a series of reductions to set the syn−anti stereochemical relationship at the incipient ring fusion sites present in stenine. In this letter, we describe a highly efficient synthesis of (±)-stenine using this cycloaddition strategy that we hope to extend to other members of the stemona family.

The required 2-methylthio-5-amidofuran (**4**) necessary for the intramolecular [4 + 2]-cycloaddition reaction was

(1) Pilli, R. A.; Ferreira de Oliveira, M. C. *Nat. Prod. Rep.* **2000**, *17*, 117.

(2) Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. *Tetrahedron* **2002**, *58*, 61.

(3) Sakata, K.; Aoki, K.; Chang, C. F.; Sakurai, A.; Tamura, S.; Murakoshi, S. *Agric. Biol. Chem.* **1978**, *42*, 457. Tereda, M.; Sano, M.; Ishii, A. I.; Kino, H.; Fukushima, S.; Noro, T. *J. Pharm. Soc. Jpn.* **1982**, *79*, 93. Shinozaki, H.; Ishida, M. *Brain Res.* **1985**, *334*, 33.

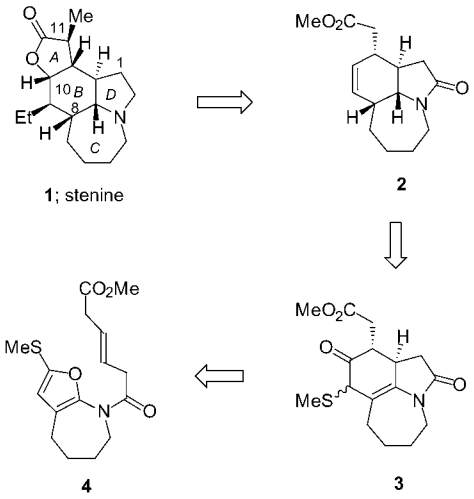
(4) For approaches to some of the Stemona alkaloids, see: Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923. Williams, D. R.; Reddy, J. P.; Amato, G. S. *Tetrahedron Lett.* **1994**, *35*, 6417. Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295. Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990. Kende, A. S.; Smalley, T. L.; Huang, H. *J. Am. Chem. Soc.* **1999**, *121*, 7431. Kende, A. S.; Martin Hernando, J. I.; Milbank, J. B. J. *Org. Lett.* **2001**, *3*, 2505.

(5) For total syntheses of stenine, see: Chen, C. Y.; Hart, D. J. *J. Org. Chem.* **1990**, *55*, 6236. Chen, C. Y.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 3840. Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106. Morimoto, Y.; Iwahashi, M.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 904.

(6) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1998**, *63*, 3986. Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304. Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595. Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716.

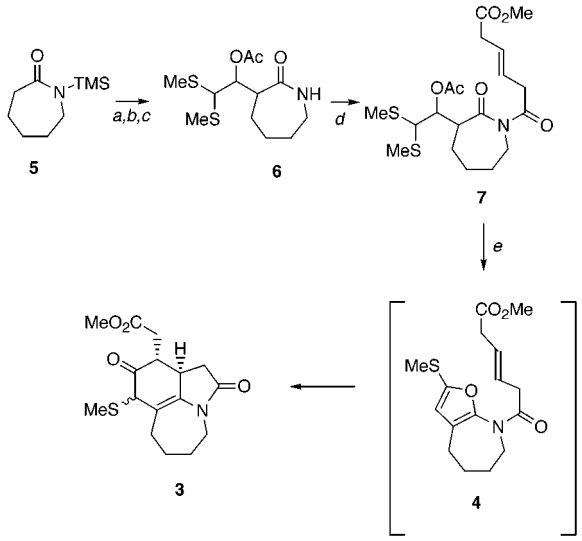
10.1021/ol025746b CCC: $22.00
Published on Web 03/28/2002

Scheme 1



prepared by a dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)[7] induced cyclization of imido dithioacetal **7** (Scheme 2).[8] The synthesis of **7** involved a mixed aldol

Scheme 2[a]

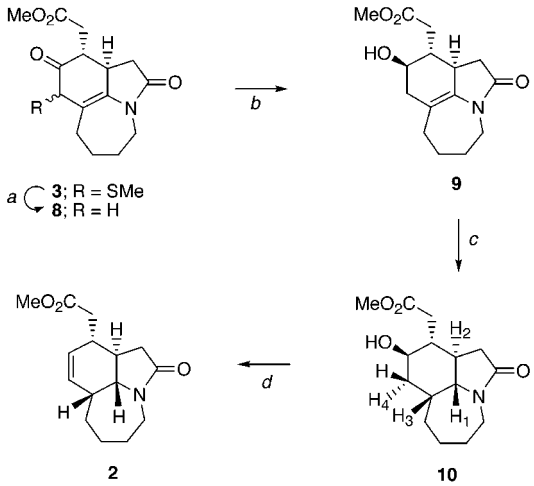


[a] Reagents: (a) LDA; (b) $(MeS)_2CHCHO$; (c) Ac_2O; (d) $MeO_2CCH_2CH{=}CHCH_2COCl$; (e) DMTSF, NEt_3.

reaction of *N*-trimethylsilyl ϵ-caprolactam (**5**) with bis-(methylsulfanylacetaldehyde)[9] followed by quenching with acetic anhydride to give amide **6** in 80% yield. The resulting lactam was acylated with *trans*-5-chlorocarbonyl-pent-3-enoic acid methyl ester[10] in the presence of 4 Å powdered molecular sieves as a neutral scavenger to furnish imide **7** in 85% yield as a 4:1 mixture of diastereomers. Methylsulfenylation of one of the methylthio groups of **7** with DMTSF induces a thionium-promoted cyclization, and the resulting dihydrofuran readily loses acetic acid to furnish the desired furan.[11] Interestingly, amidofuran **4** could not be isolated under the conditions of its formation, as it rapidly rearranged at room temperature to afford azepinoindole **3** in 80% yield as a 1:1 mixture of diastereomers. Conformational effects imposed by the placement of a carbonyl group within the tether, combined with a rotational bias about the C(2)−N bond, apparently enhances the rate of the IMDAF reaction of **4** so that it occurs readily at 25 °C.[12]

Removal of the methylthio group was easily accomplished by treating **3** with Raney Ni in ethanol, which afforded azepinoindole **8** as a single diastereomer in 92% isolated yield. Subsequent reduction of the keto group under Luche conditions[13] provided alcohol **9** in 77% isolated yield as a single diastereomer (Scheme 3). The next step involved a

Scheme 3[a]



[a] Reagents: (a) Raney-Ni, EtOH; (b) $NaBH_4$, $CeCl_3$, MeOH; (c) Crabtree's catalyst, H_2, CH_2Cl_2; (d) MsCl, NEt_3, DBU, D.

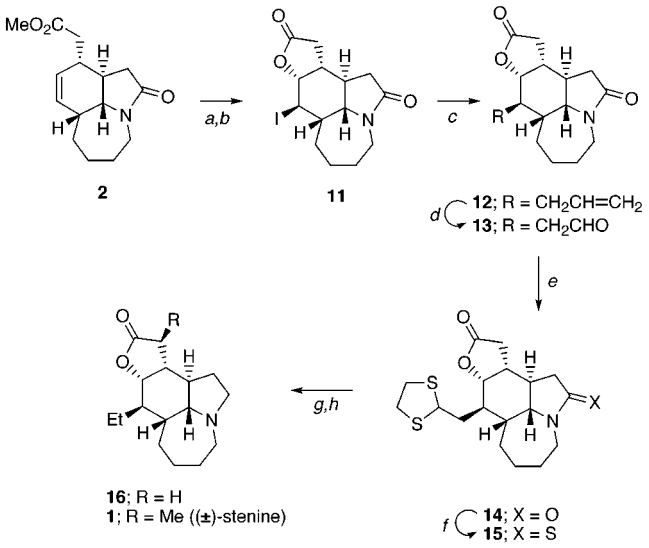
controlled hydrogenation of the enamide π-bond. Hindered, substituted double-bonds are often difficult to hydrogenate, requiring forcing conditions, and frequently lead to a mixture of isomers.[14] Indeed, the hydrogenation of **9** under heterogeneous conditions using several palladium or rhodium catalysts resulted in a mixture of products. Excellent stereochemical control could be obtained, however, by hydrogenation of **9** with the catalyst system $[Ir(cod)pyr(PCy_3)]PF_6/CH_2Cl_2$ described by Crabtree and co-workers.[15] The addition of hydrogen is directed by the presence of the C_{10} hydroxyl

(7) Kim, J.; Pau, J.; Caserio, M. *J. Org. Chem.* **1979**, *44*, 1544. Trost, B.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529. Trost, B.; Sato, T. *J. Am. Chem. Soc.* **1985**, *107*, 719.
(8) Padwa, A.; Ginn, J. D.; McClure, M. S. *Org. Lett.* **1999**, *1*, 1559.
(9) Nakane, M.; Hutchinson, C. *J. Org. Chem.* **1978**, *43*, 3922.
(10) DiMaio, J.; Gibbs, B.; Lefebvre, J.; Konishi, Y.; Munn, D.; Yue, S. *J. Med. Chem.* **1992**, *35*, 3331.
(11) For a related furan synthesis utilizing cuprous ions to remove the sulfide group of a thioacetal, see: Cohen, T.; Herman, G.; Falck, J. R.; Mura, A. J., Jr. *J. Org. Chem.* **1975**, *40*, 812.
(12) Bur, S. K.; Lynch, S. M.; Padwa, A. *Org. Lett.* **2002**, *4*, 473.
(13) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(14) Nell, P. G. *Synlett* **2001**, 160.
(15) Crabtree, R. H.; Felkin, H.; Fellebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183.

group delivering the desired syn−anti stereochemistry at the ring fusion sites.[16] The relevant coupling constants in the NMR spectrum of **10** (J_{12} = 10.2 Hz, J_{13} = 5.5 Hz) were fully consistent with its assignment and comparable in value to those found in related ring systems.[17] Final confirmation of the stereochemistry comes from a single-crystal X-ray analysis of **10**. This result demonstrates that rapid access to the stereochemically correct azepinoindole moiety of stenine (and related stemona alkaloids) can be achieved via a Crabtree catalyst directed hydrogenation reaction. Regiocontrolled dehydration of alcohol **10** to alkene **2** sets the stage for the formation of the butyrolactone ring. Before the planned iodolactonization of the γ,δ-unsaturated ester,[5] alcohol **10** was converted to the corresponding mesylate and this was followed by treatment with DBU in refluxing toluene to effect elimination providing **2** in 64% yield. The requirement of forcing conditions for elimination is undoubtedly related to the need of the system to adopt an antiperiplanar relationship of the mesylate and H_4 proton (see **10**). This can only be achieved by populating the more strained boat conformation, thereby diminishing the rate of elimination.

The conversion of **2** to stenine (**1**) was accomplished using the sequence of reactions outlined in Scheme 4. Thus, hydrolysis of the methyl ester with LiOH followed by treatment with iodine gave iodolactone **11** in 60% yield.[5] Subsequent Keck allylation with allyltributyl-stannane[18] using the Hart/Wipf protocol[5] furnished **12** in 62% yield and with excellent diastereoselectivity. Johnson−Lemieux oxidation[19] of the allyl group afforded the expected aldehyde **13**, which was treated with 1,2-ethanedithiol and $BF_3{\cdot}Et_2O$ to give **14** in 48% yield for both steps. Conversion of the amide to the corresponding thioamide with Lawesson's reagent[20] provided **15** in 73% yield. Desulfurization with Raney nickel furnished **16** in 93% yield. Methylation of the lactone enolate derived by treating **16** with LDA followed by reaction with methyl iodide afforded racemic stenine (**1**) in an overall yield of 2.1% for the 16-step sequence starting from ϵ-caprolactam. Confirmation of the structure was obtained by comparison of the spectral data with an authentic sample provided by Professor Wipf.

Scheme 4[a]



[a] Reagents: (a) LiOH, H_2O; (b) I_2, MeCN; (c) $CH_2{=}CHCH_2SnBu_3$, AIBN; (d) OsO_4, $NaIO_4$; (e) $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$; (f) Lawesson's reagent; (g) Raney-Ni (h) LDA, HMPA, MeI.

In summary, this approach to stenine demonstrates the utility of the intramolecular [4 + 2]-cycloaddition of 2-alkylthio-5-amidofurans for preparing stereochemically complex perhydroindole ring systems. All six stereocenters at the azepinoindole core can be derived in high stereoselectivity from the functionality present in the rearranged cycloadduct **3**. Further application of this methodology toward the construction of more complex stemona alkaloids is currently in progress in our laboratory and will be reported at a later date.

Acknowledgment. This research was supported by the National Institutes of Health (GM59384 and GM60003). We thank our colleague, Dr. Kenneth Hardcastle, for his assistance with the X-ray crystallographic studies together with Grants NSF CHE-9974864 and NIH S10-RR13673. We thank Professors David Hart and Peter Wipf for providing spectral data for stenine as well as an authentic sample.

Supporting Information Available: Complete description of the synthesis and characterization of all compounds prepared in this study together with an Ortep drawing for compound **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL025746B

(16) For the preferred addition of hydrogen from one face of a homoallylic alcohol, see: Crabtree, R. H.; Davis, M. W. *Organometallics* **1983**, *2*, 681. Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072.

(17) Rigby, J. H.; Laurent, S.; Cavezza, A.; Heeg, M. J. *J. Org. Chem.* **1998**, *63*, 5587.

(18) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829.

(19) Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(20) Scheibye, S.; Pedersen, B. S.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.