JOC*Article*

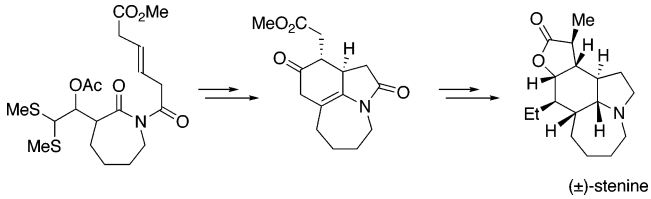
Studies on the Synthesis of (±)-Stenine: A Combined Intramolecular [4 + 2]-Cycloaddition/Rearrangement Cascade

Albert Padwa* and John D. Ginn

Department of Chemistry, Emory University, Atlanta, Georgia 30322

chemap@emory.edu

Received March 14, 2005



Several cyclic 2-(methylthio)-5-amidofurans containing tethered unsaturation were prepared via the reaction of dimethyl(methylthio)sulfonium tetrafluoroborate (DMSTF) with β-alkoxy-γ-dithiane lactams. Thermolysis of these furans resulted in an intramolecular Diels−Alder reaction (IMDAF). The resulting oxa-bridge cycloadducts underwent a subsequent 1,2-methylthio shift to form tricyclic lactams in high yield. Furan **9**, annealed to an azepine ring, underwent the IMDAF reaction at or below room temperature. Conformational effects imposed by the placement of a carbonyl group within the tether, combined with a rotational bias about the C(2)−N bond, enhances the rate of the IMDAF reaction of the seven-ring system so that it occurs readily at 25 °C. The feasibility of using the cascade sequence in the context of a total synthesis of the *Stemona* alkaloid (±)-stenine was explored. The eventual synthesis of (±)-stenine was carried out by an intramolecular Diels−Alder reaction of a 2-amido-5-methylthio-substituted furan containing a *trans*-pent-3-enoic acid methyl ester side chain in order to create the desired azepinoindole skeleton. This was followed by a series of reductions to set the syn-anti stereochemical relationship at the incipient ring fusion sites present in stenine. All six stereocenters at the azepinoindole core were derived in high stereoselectivity from the functionality present in the rearranged cycloadduct **10**. Compound **10** was converted to stenine in 11 additional steps via a sequence that features a Crabtree's-catalyst directed hydrogenation, iodolactonization, and a Keck allylation.

In recent years, we have been investigating the intramolecular [4 + 2]-cycloaddition/rearrangement cascade of 2-amidofurans as a strategy for the synthesis of a variety of hexahydroindolinone alkaloids.[1−4] This approach, demonstrated by the thermolysis of thiofuran **1** to lactam **4**, proceeds by an initial Diels−Alder cycloaddition to first produce oxabicycle **2** as a transient species which undergoes a nitrogen-assisted ring opening to generate the zwitterionic intermediate **3** (Scheme 1).[5] A subsequent 1,2-methylthio shift provides the observed tricyclic lactam as a single diastereomer (**4b**) which, if allowed to stand over a period of time, undergoes epimerization to furnish a mixture of stereoisomers.[6] The stereochemistry of the resulting tricyclic lactam **4** is derived from an IMDAF cycloaddition[7] where the sidearm of the tethered alkenyl group is oriented *syn* (*exo*) with respect to the oxygen bridge. Products resulting from an *endo* sidearm transition state were neither detected nor

(1) (a) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304. (b) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1998**, *63*, 3986.

(2) (a) Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595. (b) Padwa, A.; Dimitroff, M.; Liu, B. *Org. Lett.* **2000**, *2*, 3233.

(3) (a) Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716. (b) Wang, Q.; Padwa, A. *Org. Lett.* **2004**, *6*, 2189.

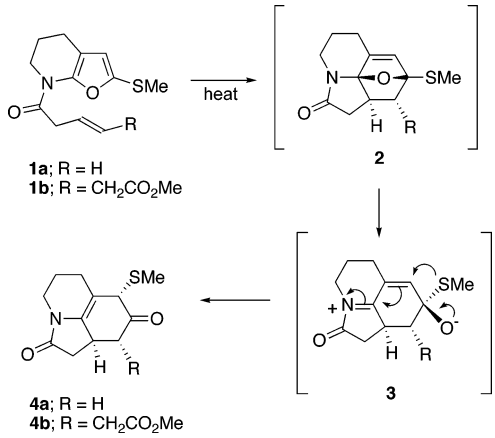
(4) (a) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088. (b) Padwa, A.; Brodney, M. A.; Satake, K.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 4617. (c) Lynch, S. M.; Bur, S. K.; Padwa, A. *Org. Lett.* **2002**, *4*, 4643. (d) Padwa, A.; Brodney, M. A.; Lynch, S. M.; Rashatasakhon, P.; Wang, Q.; Zhang, H. *J. Org. Chem.* **2004**, *69*, 3735.

(5) Padwa, A.; Ginn, J. D.; Bur, S. K.; Eidell, C. K.; Lynch, S. M. *J. Org. Chem.* **2002**, *67*, 3412.

(6) A somewhat related methylthio group migration was reported by Wu and co-workers in their studies of the intramolecular Diels−Alder reaction of a furan containing a tethered allenyl ether dienophile; see: (a) Wu, J.-H.; Shao, W. D.; Ying, F. H. *Tetrahedron Lett.* **1994**, *35*, 729. (b) Wu, H.-J.; Ying, F. H.; Shao, W. D. *J. Org. Chem.* **1995**, *60*, 6168. (c) Wu, H.-J.; Yen, C. H.; Chuang, C. T. *J. Org. Chem.* **1998**, *63*, 5064.

10.1021/jo050515e CCC: $30.25
Published on Web 05/18/2005

SCHEME 1

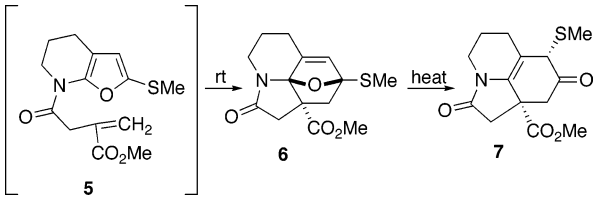


isolated. This result is not so surprising since, in these mobile cycloaddition equilibria, the *exo* adducts are expected to be thermodynamically more favored. This stereochemical result is also consistent with that reported by others for related furanyl systems possessing short tethers.[8,9] It should be noted that tricyclic lactam **4** possesses a configuration in which the methylthio group and the angular hydrogen are on the same face. This feature, combined with the exclusive formation of one diastereomer in the thermolysis of **1**, suggest a concerted 1,2-shift of the methylthio group. While a stepwise elimination−stereoselective addition of the methylthio substituent is possible, the lack of stereodirecting features within these systems is inconsistent with the observed degree of stereoselectivity.

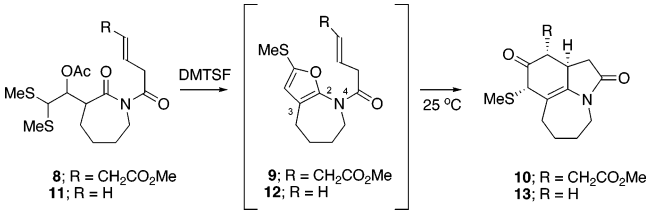
The formation of tricyclic lactam **4a** (or **4b**) required heating the 2-thio-substituted furan **1a** (or **1b**) at reflux in toluene. Amido(thiomethyl)furan **5**, on the other hand, was highly reactive providing oxabicycle **6** in 77% yield at room temperature. Heating a benzene solution of this cycloadduct at reflux afforded the tricyclic lactam **7** in 80% yield (Scheme 2). The facility of this [4 + 2]-cycloaddition is presumably related to HOMO−LUMO interactions where the presence of the electron-deficient carbomethoxy group in **5** diminishes the energy gap between the interacting MOs and facilitates the overall reaction.

During the course of our studies with these systems, we noted that the unactivated seven-ring furan homologue of **1** (i.e., **9**) also underwent the cycloaddition/rearrangement cascade but, most surprisingly, at tem-

SCHEME 2



SCHEME 3



peratures as low as 10 °C. We were not able to isolate or even detect 2-thiomethylamido-furan **9** under the conditions used for its formation (vide infra) as it rapidly furnished the tricyclic lactam **10** in 87% yield at or below room temperature. A similar rate difference between the six and seven ring annealed furans was also noticed when the unsubstituted ϵ-lactam **11** was treated with DMTSF which gave rise to tricyclic lactam **13** in 85% yield at 25 °C (Scheme 3).[10] In contrast, the cyclization/rearrangement cascade for the six-membered ring-fused thiofuran **1a** (or **1b**) required heating at 110 °C in order to form the tricyclic lactam **4a** (or **4b**) (see Scheme 1). That none of the intermediate oxabicycles could be observed in the course of these reactions suggests that the cycloaddition step is rate determining.

Because there was no clear precedent regarding whether the origin of the observed rate differences between the six- and seven-membered ring systems resided in either ground-state conformational effects or relative strain within the transition states, we opted to investigate the ground-state conformations of furans **1a** and **12** as well as the transition states through which these reactants must pass to obtain the corresponding oxabicycles. The results of our calculations[11−13] show that the six-membered ring annealed to the furan in **1a** adopts a half-chair conformation in which the C(3)−C(2)−N−C(4) dihedral angle is 156.0°. The seven-membered ring annealed to the furan in **12** adopts a low-energy conformation that imparts a 119.7° angle, but a simple ring flip provides another conformation in which the angle increases to 132.7°. The rapid interconversion between these two conformers of furan **12** (a calculated 2.2 kcal/mol energy difference) allows **12** to adopt a reactive conformation more easily than furan **1a**. The observed difference in reactivity between the six and seven-

(7) For examples of intramolecular Diels−Alder reaction of furans (IMDAF) that contain heteroatoms attached directly to the furan ring; see: (a) Padwa, A.; Kappe, C. O.; Cochran, J. E.; Snyder, J. P. *J. Org. Chem.* **1997**, *62*, 2786. (b) Gewald, K. *Chem. Ber.* **1966**, *99*, 1002. (c) Boyd, G. V.; Heatherington, K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2523. (d) Nixon, W. J.; Garland, J. T.; DeWitt-Blanton, C., Jr. *Synthesis* **1980**, 56. (e) Aran, V. J.; Soto, J. L. *Synthesis* **1982**, 513. (f) Semmelhack, M. F.; Park, J, *Organometallics* **1986**, *5*, 2550. (g) Chatani, N.; Hanafusa, T. *J. Org. Chem.* **1987**, *52*, 4408. (h) Cutler, S. J.; El-Kabbani, F. M.; Keane, C.; Fisher-Shore, S. L.; DeWitt-Blanton, C., Jr. *Heterocycles* **1990**, *31*, 651. (i) Vaidya, N. A.; Nixon, W. J.; Fatmi, A. A.; DeWitt-Blanton, C. *J. Org. Chem.* **1982**, *47*, 2483. (j) Schlessinger, R. H.; Bergstrom, C. P. *Tetrahedron Lett.* **1996**, *37*, 2133. (k) Schlessinger, R. H.; Wu, X.-H.; Pettus, T. R. R. *Synlett* **1995**, 536. (l) Schlessinger, R. H.; Pettus, T. R. R.; Springer, J. P.; Hoogsteen, K. *J. Org. Chem.* **1994**, *59*, 3246. (m) Schlessinger, R. H.; Bergstrom, C. P. *J. Org. Chem.* **1995**, *60*, 16.

(8) (a) Woo, S.; Keay, B. A. *Tetrahedron: Asymmetry* **1994**, *5*, 1411. (b) Rogers, C.; Keay, B. A. *Tetrahedron Lett.* **1991**, *32*, 6477. (c) Rogers, C.; Keay, B. A. *Synlett,* **1991**, 353. (d) Rogers, C.; Keay, B. A. *Can. J. Chem.* **1992**, *70*, 2929.

(9) (a) De Clercq, P. J.; Van Royen, L. A. *Synth. Commun.* **1979**, *9*, 771. (b) Van Royen, L. A.; Mijngher, R.; De Clercq, P. J. *Bull. Soc. Chim. Belg.* **1984**, *93*, 1019. (c) Fischer, K.; Hünig, S. *J. Org. Chem.* **1987**, *52*, 564.

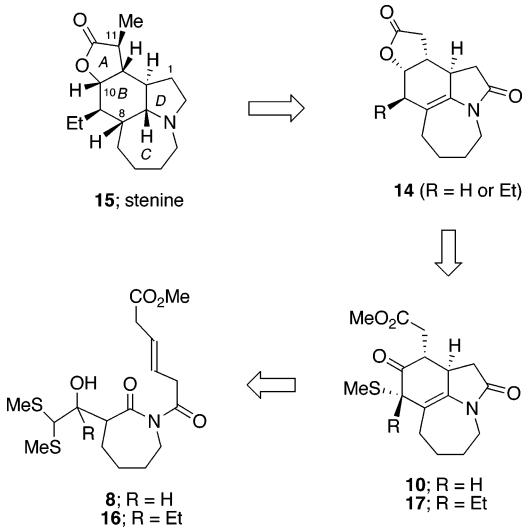
(10) Bur, S. K.; Lynch, S. M.; Padwa, A. *Org. Lett.* **2002**, *4,* 473.

(11) Ground-state conformations were explored by optimizing structures using the B3LYP/3-21G* model[12,13] as implemented by Gaussian 98. We thank Dr. Scott K. Bur for carrying out these calculations.

(12) For Becke's three-parameter exchange functional, see: Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(13) For the LYP correlation functional, see: Lee, C.; Yang, W.; Parr, R. *Phys. Rev. B* **1988**, *37*, 785.

SCHEME 4



membered ring systems correlates with a bias in the rotation about the C(2)−N bond which allows the 7-ring system to readily achieve the proper two-plane orientation approach needed for the Diels−Alder cycloaddition. Significant ring strain in the transition state with the six-membered ring system may also account for its higher activation energy.

Considering the facility with which lactam **8** is converted into tricyclic lactam **10** and to further demonstrate the viability of our sequential cycloaddition process as a practical strategy for the synthesis of complex heterocycles, we have explored the feasibility of using this key reaction in the context of a total synthesis of the *Stemona* alkaloid (±)-stenine (**15**). Scheme 4 depicts the basic features of our strategy directed toward this compound. Alkaloids from *Stemona* plants have been used in Chinese and Japanese folk medicine as cough-relief agents and insecticides.[14] The alkaloids of this family, having relatively complex polycyclic structures, have been classified into six groups according to their structural features.[15] The pyrrolo[1,2-*a*]azepine nucleus is a common structural motif shared by several of the *Stemona* alkaloids, including stenine (**15**), whose hydroindole core skeleton contains six contiguous stereocenters.[16] Several groups have completed the synthesis of simple as well as more complex members of the *Stemona* group.[17] The novel polycyclic architecture of stenine has attracted synthetic efforts by several research groups.[18−22] Hart and Chen reported a total synthesis of racemic stenine in 1990.[18] Enantioselective syntheses of (−)-stenine were later independently described by Wipf[19] and Morimoto.[20] These three early syntheses of stenine feature the stepwise construction of the hydroindole portion (BD rings), with closure to the seven-membered azepine ring being postponed until the end of the synthesis. More recently, Aubé and Golden completed a formal synthesis of (±)-stenine by making use of a clever domino Diels−Alder/Schmidt reaction strategy.[21] We envisioned an alternative approach to stenine, in which the azepine ring would be incorporated at an early point in the synthetic sequence and then used as a template for setting the required stereochemistry.[22] Our synthesis relies on an intramolecular Diels−Alder reaction of a 2-amido-5-methylthio substituted furan derived from lactam **8** (or **16**) to create the azepinoindole skeleton (see Scheme 4). This would be followed by a series of reductions to set the syn-anti stereochemical relationship at the incipient ring fusion sites present in stenine.

First-Generation Approach

We approached the synthesis of stenine in two different ways using the dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) induced cyclization−cycloaddition cascade as the key reaction step for both undertakings.[23] The overall approach was devised on the assumption that it should be possible to induce cyclization of the amide carbonyl group onto the resulting thionium ion formed from the DMTSF reaction of the dithioacetal. It is known that treatment of thioketals with DMTSF[24] causes the carbon−sulfur bond to become labile upon methylthiolation.[25] The resulting (methylthio)sulfonium ion easily dissociates to produce a thionium ion and methyl disulfide.[26] Once the dihydrofuran ring has been forged, elimination of water (or acetic acid) should proceed readily to furnish the desired 2-(methylthio)amidofuran necessary for the Diels−Alder cycloaddition.

In the first plan, the synthesis of ϵ-lactam **16** (ethyl group already in place) was achieved by a mixed aldol reaction of *N*-trimethylsilyl ϵ-caprolactam **18** with 1,1-bis(methylsulfanyl)butan-2-one[27] followed by quenching with acid to give lactam **19** in 65% yield as a 5:1-mixture

(14) (a) Gotz, M.; Edwards, O. E. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. IX, pp 545−551. (b) Gotz, M.; Edwards, O. E. In *The Alkaloids*; Weisner, K., Ed.; Academic Press: London, 1973; Vol. IX, pp 143−160.

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

(16) (a) Pilli, R. A.; Ferreira de Olivera, M. C. *Nat. Prod. Rep.* **2000**, *17*, 117. (b) Lin, W.-H.; Ye, Y.; Xu, R.-S. *J. Nat. Prod.* **1992**, *55*, 571.

(17) (a) Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848. (b) Williams, D. R.; Fromhold, M. G.; Earley, J. D. *Org. Lett.* **2001**, *3*, 2721. (c) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990. (d) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295. (e) Sibi, M. P.; Subramanian, T. *Synlett* **2004**, 1211. (f) Lindsay, K. B.; Pyne, S. G. *Synlett* **2004**, 779. (g) Brüggemann, M.; McDonald, A. I.; Overman, L. E.; Rosen, M. D.; Schwink, L,; Scott, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 15284. (h) Rigby, J. H.; Laurent, S.; Cavezza, A. M. J.; Heeg, M. J. *J. Org. Chem.* **1998**, *63*, 5587. (i) Hinman, M. M.; Heathcock, C. H. *J. Org. Chem.* **2001**, *66*, 7751. (j) Xiang, L.; Kozikowski, A. P. *Synlett* **1990**, 279.

(18) (a) Chen, C. Y.; Hart, D. J. *J. Org. Chem.* **1990**, *55*, 6236. (b) Chen, C. Y.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 3840.

(19) (a) Goldstein, D. M.; Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1995**, *117*, 11106. (b) Wipf, P.; Kim, Y. *Tetrahedorn Lett.* **1992**, *33*, 5477. (c) Wipf, P.; Goldstein, D. M. *Tetrahedron Lett.* **1996**, *37*, 739.

(20) (a) Morimoto, Y.; Iwahashi, M.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 904. (b) Morimoto, M.; Iwahashi, M. *Synlett* **1995**, 1221. (c) Morimoto, Y.; Iwahashi, M.; Kinoshita, T.; Nishida, K. *Chem. Eur. J.* **2001**, *7*, 4107.

(21) Golden, J. E.; Aubé, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4316.

(22) For a preliminary report of our work, see: Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515.

(23) Padwa, A.; Ginn, J. D.; McClure, M. S. *Org. Lett.* **1999**, *1*, 1559.

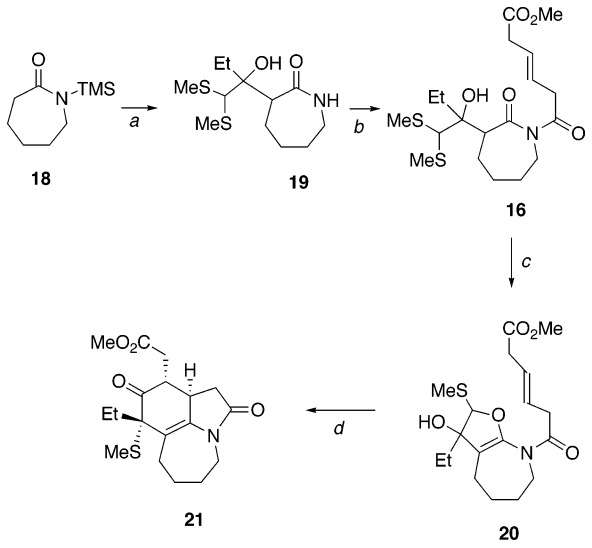
(24) (a) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529. (b) Trost, B. M.; Sato, T. *J. Am. Chem. Soc.* **1985**, *107*, 719. Commercially available from Aldrich Chemical Co.

(25) (a) Kice, J. L.; Favstritsky, N. A. *J. Am. Chem. Soc.* **1969**, *91*, 1751. (b) Smallcombe, S. H.; Caserio, M. C. *J. Am. Chem. Soc.* **1971**, *93*, 5826. (c) Kim, J. K.; Pau, J. K.; Caserio, M. C. *J. Org. Chem.* **1979**, *44*, 1544.

(26) (a) Braish, T. F.; Saddler, J. C.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 3647. (b) Gracia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 3939.

(27) Solladié, G.; Boeffel, D.; Maignan, J. *Tetrahedron* **1996**, *52*, 2065.

SCHEME 5[a]

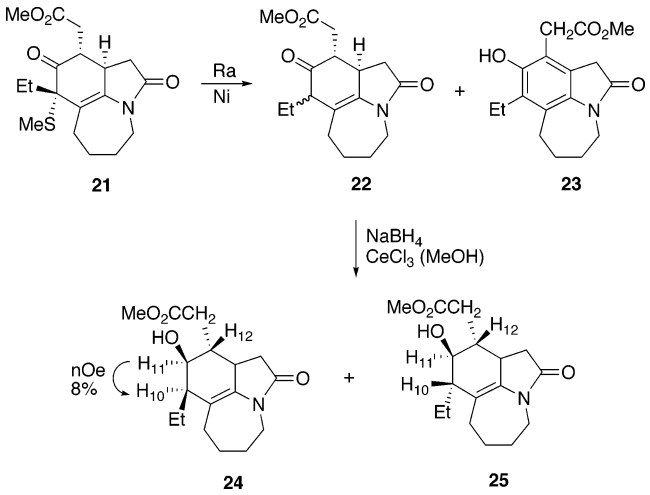


[a] Reagents: (a) LDA, $(MeS)_2CHCOEt$, H^+; (b) $MeO_2CCH_2CH{=}CHCH_2COCl$; (c) DMTSF, NEt_3; (d) *p*-toulenesulfonic acid, THF, 25 °C.

of diastereomers (Scheme 5). Acylation of **19** with *trans*-5-chlorocarbonyl-pent-3-enoic acid methyl ester[28] in the presence of 4 Å powdered molecular sieves as a neutral scavenger furnished the key imide **16** necessary for the critical cyclization step. We were pleased to find that when **16** was treated with DMTSF, dihydrofuran **20** was isolated in 67% yield as a mixture of diastereomers. This mixture of alcohols was treated with *p*-toluenesulfonic acid at 25 °C in THF to furnish azepinoindole **21** in 72% isolated yield as a single diastereomer. Under the acidic conditions used for the dehydration of **20**, the thiofuran intermediate was not detected as it underwent a rapid IMDAF/methylthio rearrangement cascade to give **21** in 72% yield. The stereochemical assignment of **21** was made on the basis of analogy with related systems where X-ray data had been obtained.

With a feasible route to the tricyclic core of the *Stemona* family in hand, we explored the possibility of forming lactone **14** (R = C_2H_5; Scheme 4) by selective reduction of the keto carbonyl group in **21** followed by a subsequent lactonization reaction. Unfortunately, all of our attempts to selectively reduce the keto carbonyl group present in **21** were unsuccessful. In each case examined, either the keto carbonyl group failed to be reduced or else over-reduction of the enamido and ester groups occurred. This may be a consequence of the steric environment around the keto center which is adjacent to both tertiary and quaternary sites. To create a more favorable steric environment for reduction, we decided to first remove the thiomethyl functionality by reduction with Raney-nickel. This resulted in an inseparable 3:1 mixture of diastereomers of **22** in 37% yield together with 12% of phenol **23**. While the diastereomers of **22** could not be totally separated, their relative stereochemistry was established by a subsequent Luche reduction[29] which furnished alcohols **24** (39%) and **25** (13%), respectively (Scheme 6).

SCHEME 6



The relative stereochemistry of each diastereomer was established by nOe difference experiments. Irradiation of H_{11} in **24** showed an 8% enhancement for the signal of H_{10} as might be expected of vicinal protons in a *cis*-configuration.[30]

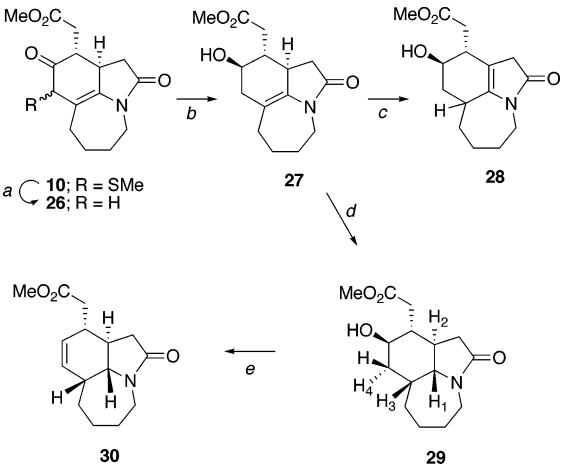
Second-Generation Approach

Since all of our efforts to improve the diastereoselectivity associated with the Raney-nickel reduction of **21** failed, we were forced to examine a slightly longer, but ultimately practical alternative strategy toward stenine. As was mentioned earlier, the DMTSF-induced reaction of imide **8** proceeded readily at 25 °C and furnished the rearranged tricyclic lactam **10** in 87% yield. Removal of the methylthio group was easily accomplished by treating **10** with Raney Ni in ethanol, which afforded azepinoindole **26** as a single diastereomer in 95% isolated yield. Subsequent reduction of the keto group under Luche conditions[29] provided alcohol **27** in 77% isolated yield as a single diastereomer (Scheme 7). Interestingly, when **27** was treated with mild acid it underwent a clean double bond isomerization to give the isomeric enamide **28** in 70% yield and whose structure is related to the fused tricyclic azepinoindole core found in didehydrotuberostemonine.[16]

The next step in the synthesis involved a controlled hydrogenation of the enamido π-bond. Hindered, substituted double bonds are often difficult to hydrogenate, requiring forcing conditions, and frequently lead to a mixture of isomers.[31] Indeed, the hydrogenation of **27** under heterogeneous conditions using several palladium or rhodium catalysts resulted in a mixture of products. Homo-allylic alcohols have been demonstrated to direct the hydrogenation of olefins when cationic iridium or rhodium catalysts are used.[32] Excellent stereochemical control could be obtained by hydrogenation of **27** with the catalyst system $[Ir(cod)pyr(Pcy_3)]PF_6/CH_2Cl_2$ de-

(28) DiMaio, J.; Gibbs, B.; Lefebvre, J.; Konishi, Y.; Munn, D.; Yue, S. *J. Med. Chem.* **1992**, *35*, 3331.
(29) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(30) Noggle, J. H.; Schirmer, R. E. *The Nuclear Overhauser Effect*; Academic Press: New York, 1971.
(31) Nell, P. G. *Synlett* **2001**, 160.
(32) For the preferred addition of hydrogen from one face of a homoallylic alcohol, see: (a) Crabtree, R. H.; Davis, M. W. *Organometallics* **1983**, *2*, 681. (b) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072.

SCHEME 7[a]

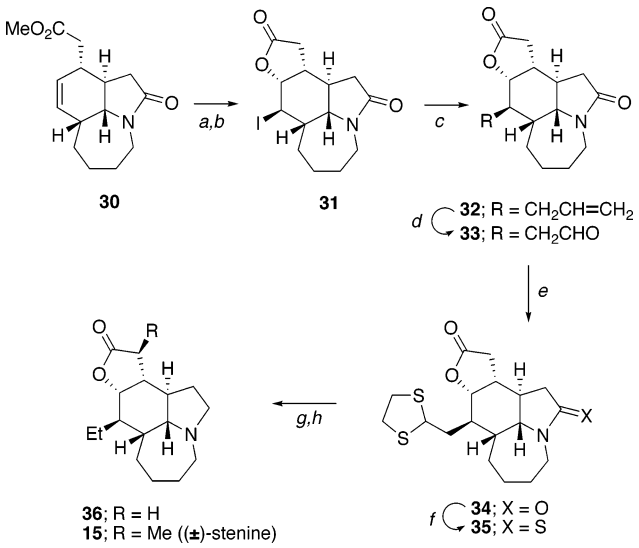


[a] Reagents: (a) Raney-Ni, EtOH; (b) $NaBH_4$, $CeCl_3$, MeOH; (c) 2 N HCl; (d) Crabtree's catalyst, H_2, CH_2Cl_2; (e) MsCl, NEt_3, DBU, heat.

scribed by Crabtree and co-workers[33] to give **29** in 80% yield. The addition of hydrogen is directed by the presence of the C_{10} hydroxyl group delivering the desired syn-anti stereochemistry at the ring fusion sites.[32] The relevant coupling constants in the NMR spectrum of **29** (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 systems.[17h] Final confirmation of the stereochemistry comes from a single-crystal X-ray analysis of **29**. This result demonstrates that rapid access to the stereochemically correct azepinoindole moiety of stenine (and related *Stemona* alkaloids) can be achieved via a Crabtree's-catalyst directed hydrogenation reaction. Before the planned iodolactonization of the γ,δ-unsaturated ester, alcohol **29** was converted to the corresponding mesylate and this was followed by treatment with DBU in refluxing toluene to effect elimination providing **30** 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 **29**). This can only be achieved by populating the more strained boat conformation, thereby diminishing the rate of elimination.

The conversion of tricyclic lactam **30** to (±)-stenine **15** was accomplished using the sequence of reactions outlined in Scheme 8. Thus, hydrolysis of the methyl ester in **30** with LiOH followed by treatment with iodine gave iodolactone **31** in 60% yield.[18,19] Subsequent Keck allylation with allyltributylstannane[34] using the Hart/Wipf protocol[18,19] furnished **32** in 62% yield and with excellent diastereoselectivity. Johnson−Lemieux oxidation[35] of the allyl group afforded the expected aldehyde **33**, which was treated with 1,2-ethanedithiol and $BF_3{\cdot}Et_2O$ to give **34** in 50% yield for both steps. Conversion of the amide to the corresponding thioamide with Lawesson's reagent[36] provided **35** in 77% yield. Desulfurization with Raney

SCHEME 8[a]



[a] Reagents: (a) LiOH, H_2O; (b) I, MeCN; (c) $CH_2{=}CHCH_2SnBu_3$, AlBN, (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.

nickel furnished **36** in 93% yield. Methylation of the lactone enolate derived by treating **36** with LDA followed by reaction with methyl iodide afforded racemic stenine (**15**) in 2.1% overall yield for the 16-step sequence starting from ϵ-caprolactam. Confirmation of the structure was obtained by comparison of the spectral data with that of an authentic sample provided by Professor Wipf.

In conclusion, this cascade approach to the *Stemona* alkaloid stenine demonstrates the utility of the intramolecular [4 + 2]-cycloaddition of 2-alkylthio-5-amidofurans for preparing stereochemically complex perhydroindole ring systems. All six centers at the azepinoindole core can be derived in high stereoselectivity from the functionality present in the rearranged cycloadduct **10**. We are currently refining this strategy and further applying the methodology toward other *Stemona* alkaloids.

Experimental Section

Acetic Acid 2,2-Bis(methylsulfanyl)-1-(2-oxopiperidin-3-yl) Ethyl Ester. To 5.0 mL (36 mmol) diisopropylamine in THF (100 mL) cooled to 0 °C was added *n*-butyllithium (24 mL of a 1.5 M solution in hexane). The mixture was stirred at 0 °C for 30 min, and then 6.1 g (36 mmol) of 1-trimethylsilanylpiperidin-2-one[37] dissolved in THF (50 mL) was added. The reaction mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of 5.0 g (37 mmol) of 2,2-bis(methylsulfanyl)acetaldehyde[38] dissolved in THF (50 mL) was added over a 3 h period. After the addition was complete, 5.0 mL (53 mmol) of acetic anhydride was added, and the mixture was slowly warmed to room temperature and stirred for 12 h. The solution was poured into a saturated aqueous $NaHCO_3$ solution and the organic phase was separated. The aqueous phase was washed with ethyl acetate, and the organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash silica gel chromatography (5% EtOAc/hexane) to provide 6.9 g (70%) of the titled compound as a 1:1-mixture of diastereomers: IR (neat), 1742, 1661, and 1231 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$)

(33) Crabtree, R. H.; Felkin, H.; Fillebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183.
(34) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829.
(35) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
(36) Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223.
(37) Hua, D. H.; Miao, S. W.; Bharathi, S. N. Katsuhira, T.; Bravo, A. A. *J. Org. Chem.* **1990**, *55*, 3682.
(38) Nakane, M.; Hutchinson, C. *J. Org. Chem.* **1978**, *43*, 3922.

(diastereomer A δ 1.62 (m, 1H), 1.73 (m, 1H), 1.92 (m, 2H), 2.08 (s, 3H), 2.10 (s, 3H), 2.18 (s, 3H), 3.09 (ddd, 1H, J = 10.8, 6.0, and 2.4 Hz), 3.25 (m, 2H), 4.58 (d, 1H, J = 10 Hz), 5.19 (dd, 1H, J = 10 and 2.4 Hz), and 6.13 (s, 1H); (diastereomer B δ 1.71 (m, 2H), 1.96 (m, 2H), 2.08 (s, 3H), 2.16 (s, 3H), 2.18 (s, 3H), 3.05 (m, 1H), 3.29 (m, 2H), 4.06 (d, 1H, J = 7.6 Hz), and 5.69 (dd, 1H, J = 7.6 and 4.8 Hz), and 5.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (diastereomer A δ 12.9, 13.6, 21.3, 22.3, 25.2, 42.3, 42.8, 56.9, 74.3, 170.7, and 171.0; (diastereomer B δ 13.4, 14.2, 21.0, 21.7, 22.0, 31.2, 43.2, 57.2, 72.3, 169.9, and 171.7; HRMS calcd for $C_{11}H_{19}NO_3S_2$ 277.0806, found 277.0804.

Acetic Acid 1-(1-But-3-enoyl-2-oxopiperidin-3-yl)-2,2-bis(methylsulfanyl) Ethyl Ester. To a 2.1 g (7.6 mmol) sample of the above lactam dissolved in CH_2Cl_2 (40 mL) was added 7.6 g of oven-dried 4 Å powdered molecular sieves followed by 1.3 g (13 mmol) of but-3-enoyl chloride.[39]The reaction mixture was stirred at 25 °C for 15 h and then filtered through a silica gel column and washed with Et_2O. The organic phase was washed with a saturated aqueous $NaHCO_3$ solution and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the crude mixture was subjected to flash silica gel chromatography (4% EtOAc/hexane) to give 2.5 g (94%) of the titled compound as a yellow oil which contained a 1:1 mixture of diastereomers that were separated by HPLC (reversed phase 1:1 MeOH/H_2O) for analytical characterization: IR (neat) 3076, 3012, 2917, 2857, 1751, 1689, 1640, 1425, and 1238 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (diastereomer A) 1.68−1.85 (m, 2H), 1.92−1.98 (m, 1H), 2.03−2.10 (m, 1H), 2.08 (s, 3H), 2.15 (s, 3H), 2.20 (s, 3H), 3.23−3.30 (m, 1H), 3.66 (dd, 2H, J = 6.8 and 0.8 Hz), 3.72−3.77 (m, 2H), 3.90 (d, 1H, J = 8.0 Hz), 5.10−5.16 (m, 2H), 5.70 (dd, 1H, J = 8.0 and 4.2 Hz), and 5.94−6.04 (m, 1H)); (diastereomer B) δ 1.60−1.80 (m, 2H), 1.94−2.07 (m, 2H), 2.11 (s, 3H), 2.21 (s, 3H), 2.14 (s, 3H), 3.15 (m, 1H), 3.57−3.64 (m, 1H), 3.66−3.69 (m, 2H), 3.82−3.89 (m, 1H), 4.22 (d, 1H, J = 9.6 Hz), 5.11−5.17 (m, 2H), 5.40 (dd, 1H, J = 9.6 and 3.2 Hz), and 5.97−6.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (diastereomer A) δ 13.2, 14.0, 21.0, 21.7, 43.6, 44.2, 46.0, 56.8, 72.1, 118.4, 131.4, 169.8, 173.7, and 174.8; (diastereomer B) δ 12.9, 13.6, 21.2, 21.9, 23.7, 43.9, 44.3, 46.3, 56.4, 73.6, 118.3, 131.6, 170.3, 172.4, and 175.1; HRMS calcd for $C_{15}H_{23}NO_4S_2$ 345.1068, found 345.1064.

Acetic Acid 1-[1-(3-Methylbut-3-enoyl)-2-oxopiperidin-3-yl]-2,2-bis-6-[3-(1-acetoxy-2,2-bis(methylsulfanyl)ethyl)-2-oxopiperidin-1-yl]-6-oxohex-3-enoic Acid Methyl Ester. To a 0.2 g (0.7 mmol) sample of acetic acid 2,2-bis(methylsulfanyl)-1-(2-oxopiperidin-3-yl) ethyl ester in CH_2Cl_2 (3.5 mL) were added 0.8 g of oven dried 4 Å powdered molecular sieves and 0.2 g (1.1 mmol) of 5-chlorocarbonyl-pent-3-enoic acid methyl ester.[28] The mixture was stirred at room temperature for 15 h, and this was followed by filtration through a plug of silica with Et_2O. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (3% EtOAc/hexane) to give 0.3 g (96%) of the titled compound as a yellow that consisted of a 1:1 mixture of diastereomers: IR (neat) 2950, 2918, 1738, 1688, 1434, 1392, 1370, 1290, 1224, and 1156 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60−1.85 (m, 5H), 1.91−2.02 (m, 3H), 2.07 (s, 3H), 2.11 (s, 3H), 2.11 (s, 3H), 2.14 (s, 3H), 2.14 (s, 3H), 2.19 (s, 3H), 3.09−3.10 (m, 4H), 3.11−3.19 (m, 1H), 3.22−3.34 (m, 1H), 3.56−3.68 (m, 5H), 3.67 (s, 3H), 3.67 (s, 3H), 3.71−3.77 (m, 2H), 3.82−3.88 (m, 1H), 3.89 (d, 1H, J = 8.0 Hz), 4.21 (d, 1H, J = 9.2 Hz), 5.40 (dd, 1H, J = 9.2 and 3.2 Hz), 5.61−5.70 (m, 3H), and 5.73−5.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 13.2, 13.6, 14.0, 21.0, 21.2, 21.6, 21.9, 23.7, 38.0, 43.0, 43.1, 43.5, 44.0, 46.0, 46.3, 52.0, 56.5, 56.8, 72.1, 73.5, 125.5, 125.6, 127.1, 127.3, 169.8, 170.3, 172.3, 172.3, 172.4, 174.8, and 175.0; HRMS calcd for $C_{18}H_{27}NO_6S_2$ 417.1280, found 417.1276.

***N*-(2-Methylsulfanyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyridin-7-yl)-6-oxohex-3-enoic 1-Acid Methyl Ester (1b).** To a 0.9 g (2.2 mmol) sample of the above in CH_3CN (11 mL) at −40 °C was added 0.45 g (2.2 mmol) of DMTSF. The reaction mixture was stirred at −40 °C for 3 h, and then 1.5 mL (11 mmol) of NEt_3 was added. The mixture was diluted with ether and then poured into a saturated aqueous $NaHCO_3$ solution. The organic phase was separated, and the aqueous phase was washed with ether. The combined organic layer was dried over anhydrous K_2CO_3, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (5% EtOAc/hexane) to give 0.4 g (62%) of **1b** as a yellow oil: IR (neat) 1735, 1668, 1622, 1512, 1237, and 1165 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85−1.93 (m, 2H), 2.38 (s, 3H), 2.45 (t, 2H, J = 6.6 Hz), 3.01 (d, 2H, J = 6.6 Hz), 3.68 (d, 2H, J = 6.3 Hz), 3.68 (s, 3H), 3.80−3.84 (m, 2H), 5.66−5.85 (m, 2H), and 6.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 20.6, 23.2, 38.1, 39.8, 43.2, 52.0, 105.4, 117.8, 125.6, 127.3, 141.2, 146.2, 169.0, and 172.3; HRMS calcd for $C_{15}H_{19}NO_4S$ 309.1035, found 309.1037.

(7-Methylsulfanyl-2,8-dioxo-1,2,5,6,7,8,9,9a-octahydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-9-yl)acetic Acid Methyl Ester (4b). A solution of 0.2 g (0. 68 mmol) of **1b** in toluene (7 mL) was heated at reflux for 4 h. The reaction mixture was cooled to rt, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (4% EtOAc/hexane) to give 0.18 g (86%) of **4b** which was first obtained as a single diastereomer (pale yellow oil) but rapidly epimerized to a 3:1-mixture upon purification: IR (neat) 1738, 1674, 1513, 1282, 1205, and 1162 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76−1.90 (m, 3H), 1.94−2.02 (m, 1H), 2.01 (s, 3H, minor), 2.04 (s, 3H, major), 2.24−2.34 (m, 2H), 2.36−2.43 (m, 1H), 2.54 (dd, 1H, J = 16.4 and 8.8 Hz, major), 2.63 (dd, 1H, J = 17.0 and 9.4 Hz, minor), 2.72−2.88 (m, 2H), 3.14−3.21 (m, 1H, minor), 3.28−3.38 (m, 1H, major), 3.53 (s, 1H), 3.56−3.65 (m, 1H), 3.64 (s, 3H, major), and 3.65 (s, 3H, minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 15.6, 20.8, 21.0, 22.5, 23.4, 31.5, 34.5, 34.6, 35.8, 38.6, 38.9, 44.1, 49.5, 51.9, 52.0, 52.7, 52.8, 54.0, 54.0, 102.8, 103.7, 137.1, 139.4, 172.1, 172.2, 172.6, 172.7, 201.2, and 201.9; HRMS calcd for $C_{15}H_{19}NO_4S$ 309.1035, found 309.1032.

2-(2-[3-(1-Acetoxy-2,2-bis(methylsulfanyl)ethyl)-2-oxopiperidin-1-yl]-2-oxoethyl)acrylic Acid Methyl Ester. To a 0.5 g (1.8 mmol) sample of acetic acid 2,2-bis(methylsulfanyl)-1-(2-oxopiperidin-3-yl) ethyl ester in CH_2Cl_2 (10 mL) was added 1.8 g of oven-dried powdered 4 Å molecular sieves and 0.44 g (2.7 mmol) of 3-methoxycarbonyl-but-3-enoyl chloride.[40] The mixture was stirred at room temperature for 15 h, followed by filtration through a plug of silica with ether. The filtrate was washed with a saturated aqueous $NaHCO_3$ solution and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (5% EtOAc/hexane) to give 0.6 g (90%) of the titled compound as a pale oil which consisted of a 1:1 mixture of diastereomers: IR (neat) 1744, 1699, 1371, and 1149 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63−1.83 (m, 4H), 1.92−2.00 (m, 2H), 2.08 (s, 3H), 2.11 (s, 3H), 2.11 (s, 3H), 2.14 (s, 3H), 2.14 (s, 3H), 2.19 (s, 3H), 2.16−2.22 (m, 1H), 2.33−2.89 (m, 1H), 2.55−3.62 (m, 1H), 3.62−3.78 (m, 4H), 3.73 (s, 6H), 3.85−3.88 (m, 6H), 4.22 (d, 1H, J = 9.6 Hz), 5.39 (dd, 1H, J = 9.6 and 3.2 Hz), 5.69 (m, 2H), 5.70 (dd, 1H, J = 8.4 and 4.0 Hz), and 5.26 (dd, 2H, J = 3.2 and 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 13.1, 13.5, 13.9, 20.9, 21.0, 21.1, 21.6, 21.8, 23.7, 43.4, 43.5, 43.7, 44.1, 46.0, 46.3, 52.2, 56.5, 56.7, 72.0, 73.6, 127.9, 128.0, 135.1, 135.2, 167.1, 169.8, 170.3, 172.5, 173.7, 174.0, and 174.2. Anal. Calcd for $C_{17}H_{25}NO_6S_2$: C, 50.60; H, 6.24; N, 3.47. Found: C, 50.33; H, 6.19; N, 3.56.

Acetic Acid 2,2-Bis(methylsulfanyl)-1-(2-oxoazepan-3-yl) Ethyl Ester. To 5.3 mL (38 mmol) of diisopropylamine in

(39) Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006.

(40) Achiwa, K.; Chaloner, P.; Parker, D. *J. Organomet. Chem.* **1981**, *218*, 249.

THF (100 mL) at 0 °C was added 30 mL of a 1.25 M solution of *n*-butyllithium in hexane (38 mmol). The mixture was stirred at 0 °C for 30 min. To this solution was added 8.0 g (38 mmol) of 1-trimethylsilanylazepan-2-one[37] dissolved in THF (50 mL). The reaction mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of 5.2 g (38 mmol) of 2,2-bis(methylsulfanyl)acetaldehyde dissolved in THF (50 mL) was added dropwise. After the addition of the aldehyde was complete, 5.2 mL (55 mmol) of acetic anhydride was added, and the mixture was slowly warmed to rt and stirred for 12 h. The solution was poured into a saturated aqueous solution of $NaHCO_3$, and the organic phase was separated. The aqueous phase was washed with EtOAc and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography (3% EtOAc/hexane) to provide 8.8 g (80%) of the titled compound as a yellow oil consisting of a 4:1 mixture of diastereomers: IR (neat) 1743, 1666, 1434, and 1236 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (major) δ 1.42−1.83 (m, 5H), 1.96−2.08 (m, 1H), 2.21 (s, 6H), 2.15 (s, 3H), 3.10−3.35 (m, 3H), 4.39 (d, 1H, J = 10.4 Hz), 5.32 (dd, 1H, J = 10.0 and 7.2 Hz), and 5.84 (t, 1H, J = 8.0 Hz); (minor) δ 1.36−1.48 (m, 2H), 1.53−1.64 (m, 1H), 1.67−1.71 (m, 1H), 1.79−1.84 (m, 1H), 1.98−2.03 (m, 1H), 2.12 (s, 3H), 2.17 (s, 3H), 2.18 (s, 3H), 3.15−3.21 (m, 2H), 3.32−3.40 (m, 1H), 4.20 (d, 1H, J = 3.2 Hz), 5.65 (dd, 1H, J = 9.2 and 2.8 Hz), and 6.04 (t, 1H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (major) δ 12.8, 14.5, 21.3, 27.0, 29.2, 29.3, 42.4, 45.5, 56.5, 73.7, 171.1, and 176.4; (minor) δ 14.8, 15.4, 21.0, 25.9, 29.3, 29.4, 42.2, 45.5, 57.2, 73.6, 170.6, and 177.4. Anal. Calcd for $C_{12}H_{21}NO_3S_2$: C, 49.46; H, 7.26; N, 4.81. Found: C, 49.31; H, 7.22; N, 4.73.

6-[3-(1-Acetoxy-2,2-bis(methylsulfanyl)ethyl)-2-oxoazepan-1-yl]-6-oxohex-3-enoic Acid Methyl Ester (8). To a 5.4 g (18 mmol) sample of the above lactam in CH_2Cl_2 (100 mL) was added 18 g of oven-dried 4 Å powdered molecular sieves and 4.7 g (16 mmol) of 5-chlorocarbonylpent-3-enoic acid methyl ester.[28] The mixture was stirred at 25 °C for 15 h and was then filtered through a plug of silica with ether. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (5% EtOAc/hexane) to give 6.7 g (85%) of **8** as a yellow oil consisting of a 4:1 mixture of diastereomers. A sample of the major diastereomer was separated by flash silica gel chromatography: IR (neat) 1741, 1694, 1369, and 1142 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38−1.69 (m, 2H), 1.76−1.94 (m, 3H), 2.11 (s, 3H), 2.12 (s, 3H), 2.14 (s, 3H), 3.17−3.09 (m, 2H), 3.11−3.24 (m, 1H), 3.42−3.48 (m, 1H), 3.53−3.61 (m, 1H), 3.66 (s, 3H), 4.17 (d, 1H, J = 6.9 Hz), 4.66−4.72 (m, 1H), 5.36 (dd, 1H, J = 6.9 and 6.0 Hz), and 5.58−5.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 14.6, 21.2, 27.2, 27.6, 38.0, 42.5, 43.1, 48.3, 52.0, 56.5, 73.8, 125.5, 127.5, 170.8, 172.3, and 174.5. Anal. Calcd for $C_{19}H_{29}NO_6S_2$: C, 52.88; H, 6.77; N, 3.25. Found: C, 52.69; H, 6.63; N, 3.08.

(8-Methylsulfanyl-2,9-dioxo-1,2,4,5,6,7,8,9,10,10a-decahydroazepino[3,2,1-*hi*]-indol-10-yl)acetic Acid Methyl Ester (10). To a 3.5 g (8.0 mmol) sample of imide **8** in CH_3CN (40 mL) at −40 °C was added 1.6 g (8.0 mmol) of DMTSF. The reaction mixture was stirred at −40 °C for 3 h, and then 5.6 mL (40 mmol) of triethylamine was added. The mixture was diluted with ether and poured into a saturated aqueous $NaHCO_3$ solution. The organic phase was separated, and the aqueous phase was washed with ether. The combined organic layer was dried over anhydrous K_2CO_3, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (4% EtOAc/hexane) to give 2.2 g (87%) of **10** which was first obtained as a single diastereomer (pale yellow oil) but rapidly epimerized to a 1:1 mixture upon purification: IR (neat) 1725, 1674, 1357, and 1206 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62−1.72 (m, 4H), 1.87−1.98 (m, 4H), 2.07 (s, 3H), 2.09 (s, 3H), 2.28−2.41 (m, 4H), 2.47−2.58 (m, 4H), 2.63−2.87 (m, 4H), 3.08−3.36 (m, 4H), 3.40 (s, 1H), 3.47 (d, 1H, J = 0.9 Hz), 3.65−3.68 (m, 1H), 3.69 (s, 3H), 3.71 (s, 3H), 3.78 (ddd, 1H, J = 9.3, 6.3, and 3.3 Hz), 4.06−4.12 (m, 1H), and 4.15−4.21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 16.1, 26.8, 27.0, 27.2, 27.7, 30.6, 31.3, 33.0, 34.9, 35.4, 36.3, 36.5, 41.7, 43.0, 43.1, 44.8, 48.8, 52.1, 52.2, 55.8, 57.2, 107.4, 110.1, 139.2, 141.0, 172.2, 172.3, 174.0, 174.5, 201.1, and 202.2. Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.55; N, 4.33. Found: C, 59.31; H, 6.42; N, 4.21.

6-{3-[1-(Bis(methylsulfanyl)methyl)-1-hydroxypropyl]-2-oxoazepan-1-yl}-6-oxohex-3-enoic Acid Methyl Ester (16). To an 8.0 g (28 mmol) sample of lactam **19** in CH_2Cl_2 (150 mL) were added 28 g of oven-dried 4 Å powdered molecular sieves and 7.0 g (40 mmol) of 5-chlorocarbonylpent-3-enoic acid methyl ester.[28] The reaction mixture was stirred at rt for 15 h, followed by filtration through a plug of silica with ether. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (5% EtOAc/hexane) to give 8.2 g (71%) of **16** as a yellow oil which contained a 15:1 mixture of diastereomers: IR (neat) 1730, 1656, 1437, and 1387 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (major) δ 0.92 (t, 3H, J = 7.6 Hz), 1.48−1.79 (m, 5H), 1.83−1.88 (m, 1H), 1.95−2.02 (m, 1H), 2.17 (q, 1H, J = 7.6 Hz), 2.20 (s, 3H), 2.29 (s, 3H), 3.08−3.12 (m, 2H), 3.26−3.34 (m, 1H), 3.42 (dd, 1H, J = 9.4 and 3.4 Hz), 3.54 (dd, 1H, J = 17.8 and 0.8 Hz), 3.67 (s, 3H), 3.77 (ddd, 1H, J = 17.8, 6.6, and 0.8 Hz), 4.07 (d, 1H, J = 0.8 Hz), 4.29 (s, 1H), 4.68 (dt, 1H, J = 15.2 and 4.4 Hz), and 5.63−5.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (major) δ 8.9, 17.8, 18.0, 25.5, 26.6, 27.0, 28.2, 37.9, 42.2, 43.4, 48.8, 52.0, 65.8, 81.4, 125.7, 127.2, 172.3, 174.7, and 180.7; HRMS calcd for $C_{19}H_{29}NO_4S_2$ [M − H_2O] 399.1538, found 399.1546.

***N*-(3-Ethyl-3-hydroxy-2-methylsulfanyl-2,3,4,5,6,7-hexahydrofuro[2,3-*b*]azepin-8-yl)-6-oxohex-3-enoic Acid Methyl Ester (20).** To an 8.2 g (20 mmol) sample of **16** in CH_3CN (100 mL) at −40 °C was added 3.9 g (20 mmol) of DMTSF. The reaction mixture was stirred at −40 °C for 3 h, and then 14 mL (100 mmol) of NEt_3 was added. The mixture was diluted with ether and poured into a saturated aqueous $NaHCO_3$ solution. The organic phase was separated, and the aqueous phase was washed with ether. The combined organic layer was dried over anhydrous K_2CO_3 and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (5% EtOAc/hexane) to give 4.8 g (67%) of **20** which was first obtained as a single diastereomer (pale yellow oil) but rapidly epimerized to a 1:1 mixture upon purification: IR (neat) 1735, 1670, 1438, 1386, 1329, and 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, J = 7.2 Hz), 1.50−1.81 (m, 6H), 2.06 (t, 2H, J = 6.0 Hz), 2.26 (s, 3H), 3.08−3.14 (m, 4H), 3.35−3.45 (m, 2H), 3.67 (s, 3H), 3.68 (d, 1H, J = 1.6 Hz), 3.81−3.87 (m, 1H), 5.65−5.73 (m, 1H), and 5.76−5.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.7, 14.2, 21.3, 25.5, 29.8, 30.4, 37.2, 38.8, 46.2, 52.1, 85.0, 94.3, 107.9, 125.9, 127.4, 149.7, 170.7, and 172.7; HRMS calcd for $C_{18}H_{27}NO_5SLi$ [M + Li] 376.1770, found 376.1767.

(8-Ethyl-8-methylsulfanyl-2,9-dioxo-1,2,4,5,6,7,8,9,10,-10*a*-decahydroazepino-[3,2,1-*hi*]indol-10-yl)acetic Acid Methyl Ester (21). To a 1.0 g (2.7 mmol) sample of **20** in THF (27 mL) cooled to 0 °C was added 0.05 g (0.3 mmol) of *p*-toluenesulfonic acid. The mixture was stirred at rt for 2 h and then poured into a saturated aqueous solution of $NaHCO_3$ and extracted with ether. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (4% EtOAc/hexane) to give 0.7 g (72%) of **21** as a clear oil: IR (neat) 1720, 1668, 1360, 1254, and 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, 3H, J = 7.6 Hz), 1.79−1.89 (m, 4H), 1.89 (s, 3H), 1.95−1.99 (m, 1H), 2.04−2.13 (m, 1H), 2.32−2.48 (m, 4H), 2.61 (dd, 1H, J = 16.2 and 9.0 Hz), 2.75−2.87 (m, 2H), 2.93−3.01 (m, 1H), 3.47−3.61 (m, 1H), 3.71 (s, 3H), and 3.98−4.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

10.1, 13.2, 24.8, 26.4, 26.9, 28.8, 32.8, 36.1, 37.3, 42.0, 50.2, 61.8, 112.5, 142.5, 172.5, 174.1, and 204.9; HRMS calcd for $C_{18}H_{25}NO_4S$ 351.1504, found 351.1408.

(8-Ethyl-2,9-dioxo-1,2,4,5,6,7,8,9,10,10a-decahydroazepino[3,2,1-*hi*]indol-10-yl)acetic Acid Methyl Ester (22). To a 0.1 g (0.3 mmol) sample of **21** in ethanol (2.8 mL) was added an excess of W-2 Raney nickel. The mixture was stirred at room temperature for 2 h and then filtered through a plug of silica with ethanol. The solvent was removed under reduced pressur,e and the residue was purified by flash silica gel chromatography (5% EtOAc/hexane) to give 0.03 g (37%) of **22** as a yellow oil consisting of a 3:1 mixture of inseparable diastereomers: IR (neat) 1724, 1681, 1454, 1364, 1325, and 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.75 (t, 3H, J = 7.2 Hz, minor), 0.89 (t, 3H, J = 7.6 Hz, major), 1.56−1.79 (m, 3H), 1.85−1.97 (m, 2H), 2.00−2.15 (m, 2H), 2.21−2.39 (m, 3H), 2.43 (d, 1H, J = 4.8 Hz, major), 2.51−2.62 (m, 1H), 2.67 (dd, 1H, J = 16.8 and 6.8 Hz), 2.74−2.92 (m, 2H), 3.11−3.18 (m, 1H), 3.67 (s, 3H, minor), 3.68 (s, 3H, major), 4.19−4.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major) 10.4, 22.8, 26.9, 27.3, 31.1, 31.9, 36.2, 37.6, 43.0, 49.6, 52.1, 54.3, 112.9, 138.6, 172.5, 174.0, and 210.0; δ (minor) 11.4, 16.1, 27.1, 27.4, 30.4, 31.4, 36.8, 41.7, 43.1, 46.6, 55.8, 114.9, 138.6, 172.4, 174.0, and 209.8; HRMS calcd for $C_{17}H_{23}NO_4Li$ $[M + Li]^+$ 312.1787, found 312.1786.

(8-Ethyl-9-hydroxy-2-oxo-1,2,4,5,6,7-hexahydroazepino-[3,2,1-*hi*]indol-10-yl)acetic Acid Methyl Ester (23). In addition to the above compound, 0.01 g (12%) of phenol **23** was isolated as white solid: mp 140−142 °C; IR (film) 1727, 1686, 1614, 1449, 1341, 1213, and 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, 3H, J = 7.6 Hz), 1.96−2.04 (m, 4H), 2.41 (q, 2H, J = 7.6 H), 2.93−2.96 (m, 2H), 3.42 (s, 2H), 3.58 (s, 2H), 2.74 (s, 3H), 3.94−3.97 (m, 2H), and 6.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 19.9, 24.3, 25.9, 26.2, 34.7, 35.6, 40.1, 53.1, 115.6, 122.1, 124.5, 130.8 138.1, 148.5, 174.1, and 175.1. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.67; H, 7.00; N, 4.57.

(**8-Ethyl-9-hydroxy-2-oxo-1,2,4,5,6,7,8,9,10,10a-decahydroazepino[3,2,1-*hi*]indol-10-yl)acetic Acid Methyl Ester (24).** To a 0.1 g (0.4 mmol) sample of **22** in methanol (2 mL) cooled to 0 °C was added 0.16 g (0.4 mmol) of $CeCl_3 \cdot 7H_2O$. To this mixture was added 0.02 g (0.5 mmol) of $NaBH_4$ in three portions. The reaction mixture was stirred at 0 °C for 3 h followed by the addition of 1 mL of H_2O. The mixture was concentrated under reduced pressure, diluted with H_2O, and extracted with EtOAc. The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to provide a 3:1 mixture of diastereomers **24** and **25**. The residue was purified by flash silica gel chromato-graphy (5% EtOAc/hexane). The major fraction isolated from the column contained 0.045 g (39%) of **24** as a pale yellow oil: IR (neat) 1735, 1672, 1439, 1357, and 1209 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.2 Hz), 1.36−1.47 (m, 1H), 1.67−1.88 (m, 1H), 1.91 (d, 1H, J = 6.0 Hz), 1.91−2.09 (m, 2H), 2.10−2.18 (m, 1H), 2.18 (dd, 1H, J = 15.6 and 10.8 Hz), 2.30−2.47 (m, 3H), 2.60 (dd, 1H, J = 15.6 and 9.0 Hz), 2.75−2.83 (m, 1H), 3.15−3.22 (m, 1H), 3.68 (s, 3H), 3.99−4.05 (m, 1H), and 4.06−4.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 20.9, 26.3, 26.9, 28.4, 35.4, 35.8, 36.2 41.4, 41.6, 47.8, 52.0, 68.1, 114.6, 138.3, 173.5, and 174.4; HRMS calcd for $C_{17}H_{25}NO_4$ 307.1784, found 307.1779.

The minor faction isolated from the column contained 0.01 g (13%) of **25** as a pale yellow oil: IR (neat) 1736, 1673, 1405, and 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, 3H, J = 7.6 Hz), 1.48−1.72 (m, 4H), 1.83−1.89 (m, 2H), 2.10−2.28 (m, 4H), 2.33 (d, 1H, J = 7.2 Hz), 2.41−2.48 (m, 3H), 2.54 (dd, 1H, J = 16.0 and 7.2 Hz), 2.97−3.03 (m, 1H), 3.11−3.14 (m, 1H), 3.65−3.76 (m, 1H), 3.70 (s, 3H), and 4.18−4.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 22.3, 27.1, 27.6, 31.7, 35.3, 36.3, 39.0, 42.2, 42.8, 48.1, 52.2, 74.5, 117.1, 135.6, 174.5, and 174.5; HRMS calcd for $C_{17}H_{25}NO_4$ 307.1784, found 307.1773.

(2,9-Dioxo-1,2,4,5,6,7,8,9,10,10a-decahydroazepino[3,2,1-*hi*]indol-10-yl)acetic Acid Methyl Ester (26). To a 6.8 g (21 mmol) sample of tricyclic lactam **10** in ethanol (100 mL) was added an excess of W-2 Raney nickel. The mixture was stirred at 25 °C for 4 h and was then filtered through a plug of Celite with ethanol. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography (3% EtOAc/hexane) to give 5.6 g (95%) of **26** as a white solid: mp 67−68 °C; IR (KBr) 1721, 1682, 1397, and 1208 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.59−1.63 (m, 2H), 1.74−2.00 (m, 2H), 2.15−2.20 (m, 2H), 2.36 (dd, 1H, J = 16.3 and 9.0 Hz), 2.40 (dd, 1H, J = 16.8 and 4.2 Hz), 2.60 (dd, 1H, J = 16.3 and 7.2 Hz), 2.72 (dd, 1H, J = 16.8 and 7.2 Hz), 2.83−3.07 (m, 5H), 3.68 (s, 3H), and 4.21−4.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 31.6, 33.4, 36.0, 38.9, 44.3, 45.1, 49.3, 52.1, 108.8, 136.1, 172.4, 174.0, and 207.8. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.95; H, 6.91; N, 5.05. Found: C, 64.86; H, 6.84; N, 4.93.

(9-Hydroxy-2-oxo-1,2,4,5,6,7,8,9,10,10a-decahydroazepino[3,2,1-*hi*]-indol-10-yl) Acetic Acid Methyl Ester (27). To a 5.9 g (21 mmol) sample of **26** in methanol (100 mL) at 0 °C was added 8.7 g (23 mmol) of $CeCl_3 \cdot 7H_2O$. To this mixture was added 0.9 g (24 mmol) of $NaBH_4$ in three portions. The reaction mixture was stirred at 0 °C for 3 h and then 50 mL of H_2O was added. The mixture was concentrated under reduced pressure, diluted with H_2O, and extracted with EtOAc. The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (5% EtOAc/hexane) to give 4.5 g (77%) of **27** as a pale yellow oil: IR (neat) 1732, 1439, 1403, and 1365 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.49−1.54 (m, 2H), 1.84−1.88 (m, 2H), 1.92−2.00 (m, 1H), 2.09−2.24 (m, 4H), 2.38−2.60 (m, 6H), 2.83−2.89 (m, 1H), 3.62−3.68 (m, 1H), 3.68 (s, 3H), and 4.52−4.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 27.8, 33.5, 35.2, 36.0, 41.1, 41.6, 43.6, 43.7, 52.1, 71.0, 111.6, 135.3, 174.0, and 174.4. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.48; H, 7.58; N, 5.02. Found: C, 64.37; H, 7.61; N, 4.96.

(9-Hydroxy-2-oxo-1,2,4,5,6,7,7a,8,9,10-decahydroazepino-[3,2,1-*hi*]indol-10-yl)acetic Acid Methyl Ester (28). To a 2.5 g (9.4 mmol) sample of **27** in 50 mL of methanol at 0 °C was added a 2 N HCl solution, and the mixture was stirred for 3 h at rt and was then extracted with EtOAc. The combined organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (3% EtOAc/hexane) to give 1.9 g (70%) of **28** as a white solid: mp 129−131 °C; IR (film) 1734, 1682, 1658, 1438, 1241, and 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21−1.53 (m, 4H), 1.80−1.98 (m, 3H), 2.16 (ddd, 1H, J = 13.2, 6.2, and 3.4 Hz), 2.36−2.42 (m, 1H), 2.42−2.54 (m, 1H), 2.74−2.80 (m, 1H), 2.83−3.00 (m, 2H), 3.51−3.59 (m, 1H), 3.67 (s, 3H), and 4.28−4.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.9, 30.3, 35.2, 36.5, 36.5, 37.9, 40.1, 40.4, 41.8, 52.1, 71.5, 109.5, 142.9, 174.6, and 176.5. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.22; H, 7.51; N, 4.93.

(9-Hydroxy-2-oxo-dodecahydroazepino[3,2,1-*hi*]indol-10-yl)acetic Acid Methyl Ester (29). To an oven-dried, heavy-walled, high-pressure flask was added a solution of 0.5 g (1.8 mmol) of **27** dissolved in CH_2Cl_2 (50 mL). To this mixture was added 0.07 g (0.09 mmol) of Crabtree's catalyst.[32,33] The flask was evacuated, refilled with hydrogen three times, placed under an atmosphere of hydrogen (40 psi), and shaken for 10 h. The flask was evacuated, and the solvent was removed under reduced pressure. The residue was purified by recrystallization from acetone−hexane to give 0.4 g (80%) of **29** as a colorless solid: mp 142−144 °C; IR (film) 1730, 1674, 1363, 1261, and 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18−1.25 (m, 2H), 1.54−1.59 (m, 2H), 1.70−1.79 (m, 3H), 1.81−1.90 (m, 2H), 1.97 (ddd, 1H, J = 13.6, 4.4, and 2.4 Hz), 2.11 (dd, 1H, J = 15.0 and 12.2 Hz), 2.17−2.25 (m, 1H), 2.32 (td, 2H, J = 15.6 and 6.0 Hz), 2.45 (bs, 1H), 2.52−2.60 (m, 1H), 2.57 (dd, 2H, J

= 15.6 and 5.0 Hz), 3.38−3.45 (m, 1H), 3.40 (dd, 1H, J = 10.0 and 5.6 Hz), 3.66 (s, 3H), and 4.05−4.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8, 30.2, 31.4, 35.6, 35.9, 38.7, 40.4, 40.8, 41.2, 43.8, 52.1, 64.9, 71.3, 173.9, and 174.0. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 63.80; H, 8.14; N, 4.91.

(2-Oxo-1,2,4,5,6,7,7a,10,10a,10b-decahydroazepino[3,2,1-*hi*]indol-10-yl)acetic Acid Methyl Ester (30). To a 1.9 g (6.6 mmol) sample of **29** in CH_2Cl_2 (30 mL) at 0 °C was added 1.9 mL (13 mmol) of NEt_3 and 1.0 mL (13 mmol) of methanesulfonyl chloride. The mixture was stirred at 0 °C for 3 h and then poured into H_2O and extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give the titled compound as a thick oil which was immediately used in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22−1.29 (m, 2H), 1.35−1.40 (t, 1H, J = 7.2 Hz), 1.80−1.93 (m, 3H), 1.99−2.09 (m, 1H), 2.12−2.42 (m, 6H), 2.53−2.60 (m, 2H), 3.04 (s, 3H), 3.14−3.17 (m, 1H), 3.45 (dd, 1H, J = 10.5 and 5.7 Hz), 3.69 (s, 3H), 4.10−4.15 (m, 1H), and 4.55−4.63 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7, 30.1, 31.4, 34.8, 35.8, 37.8, 38.3, 38.9, 40.3, 40.7, 41.6, 52.2, 64.0, 80.4, 172.3, and 173.4.

To a sample of the above mesylate in toluene (30 mL) was added 4.9 mL (33 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The mixture was heated at reflux for 6 h and then cooled to 25 °C. The solution was poured into H_2O and extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (5% EtOAc/hexane) to give 1.1 g (64%) of **30** as a white solid: mp 97−99 °C; IR (film) 1736, 1690, 1358, 1193, and 1162 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21−1.38 (m, 3H), 1.61−1.95 (m, 4H), 2.10 (dd, 1H, J = 15.2 and 12.4 Hz), 2.23−2.44 (m, 4H), 2.50−2.58 (m, 2H), 3.54 (dd, 1H, J = 10.4 and 6.8 Hz), 3.66 (s, 3H), 4.10−4.15 (m, 1H), 5.53 (dt, 1H, J = 10.0 and 1.6 Hz), and 5.63 (ddd, 1H, J = 10.0, 4.8, and 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7, 30.1, 31.0, 35.9, 37.1, 38.6, 39.2, 41.1, 41.3, 51.9, 63.5 130.6, 130.9, 172.6, and 173.9. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.36; H, 8.09; N, 5.28.

Furo[2,3-*e*](8-iodo-2-oxo-1,2,4,5,6,7,7a,8,9,10,10a,10b-dodecahydroazepino-[3,2,1-*hi*]indol)-12-one (31). To a 0.3 g (1.0 mmol) sample of **30** in a 5:3 mixture of THF/MeOH (8 mL) at 0 °C was added an aqueous solution of LiOH (4.0 mL of a 1.0 M solution). The mixture was stirred at 0 °C for 3 h and was then acidified to pH 4 and concentrated under reduced pressure. The residue was diluted with H_2O and extracted with CH_2Cl_2, and the solvent was removed under reduced pressure. The residue was suspended in CH_3CN (10 mL) and cooled to 0 °C. To this mixture were added a 5% aqueous solution of $NaHCO_3$ (10 mL) and 0.8 g (3.0 mmol) of I_2. The mixture was stirred in the dark at 0 °C for 4 h and was poured into a 10% aqueous solution of $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by washing with cold $CHCl_3$ to give 0.2 g (60%) of **31** as a white solid: mp 155−156 °C; IR (film) 1762, 1674, 1418, 1173, and 1135 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.26−1.35 (m, 2H), 1.49−1.59 (m, 2H), 1.76−1.78 (m, 1H), 1.88−2.08 (m, 3H), 2.33−2.51 (m, 3H), 2.58−2.65 (m, 1H), 2.71−2.78 (m, 2H), 3.74 (dd, 1H, 11.2 and 8.0 Hz), 3.99 (dd, 1H, J = 10.0 and 7.6 Hz), 4.07−4.10 (m, 1H), and 4.93 (dd, 1H, J = 9.6 and 7.6 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 29.4, 30.0, 30.9, 32.7, 34.3, 36.5, 37.1, 38.4, 42.2, 49.6, 61.1, 83.3, 173.3, and 174.8. Anal. Calcd for $C_{14}H_{18}INO_3$: C, 44.82; H, 4.84; N, 3.73. Found: C, 44.62; H, 4.81; N, 3.65.

Furo[2,3-*e*](8-allyl-2-oxo-1,2,4,5,6,7,7a,8,9,10,10a,10b-dodecahydroazepino-[3,2,1-*hi*]indol)-12-one (32). To a 0.5 g (1.3 mmol) sample of **31** in benzene (15 mL) was added 0.8 mL (2.7 mmol) of allyltributyltin and 0.04 g (0.3 mmol) of 2,2′-azobis-isobutyronitrile (AIBN). The mixture was heated at reflux for 6 h during which time the solid slowly dissolved. The reaction mixture was cooled to 25 °C, and 0.4 mL (2.7 mmol) of DBU was added. The mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (4% EtOAc/hexane) to give 0.2 g (62%) of **32** as a white solid: mp 125−126 °C; IR (KBr) 1772, 1694, 1376, 1263, and 1175 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22−1.45 (m, 3H), 1.59−1.69 (m, 3H), 1.76−1.80 (m, 1H), 1.91−2.12 (m, 3H), 2.31 (dd, 1H, J = 17.8 and 9.0 Hz), 2.35−2.37 (m, 2H), 2.47−2.66 (m, 3H), 2.47−2.66 (m, 3H), 2.73−2.80 (m, 1H), 3.36 (dd, 1H, J = 10.8 and 7.6 Hz), 4.12−4.16 (m, 1H), 4.58 (dd, 1H, J = 10.8 and 8.6 Hz), 5.13−5.17 (m, 2H), and 5.79−5.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6, 29.7, 30.4, 33.6, 34.7, 36.9, 37.9, 37.9, 40.4, 42.0, 42.5, 61.4, 80.9, 118.8, 134.3, 173.7, and 176.1. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.45; H, 8.11; N, 4.78.

Furo[2,3-*e*](8-[1,3]dithiolan-2-ylmethyl-2-oxo-1,2,4,5,6,7,-7a,8,9,10,10a,10b-dodecahydroazepino[3,2,1-*hi*]indol)-12-one (34). To a 0.2 g (0.8 mmol) sample of **32** in a 1:1 mixture of THF:H_2O (8 mL) was added 0.04 g (0.2 mmol) of osmium tetroxide followed by 0.8 g (2.4 mmol) of sodium periodate. The reaction mixture was stirred for 30 min at room temperature and was poured into H_2O and extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and then filtered through a plug of Celite. The solvent was removed under reduced pressure to give 0.17 g of furo[2,3-*e*][2-oxo-8-(2-oxoethyl)-1,2,4,5,6,7,7a,-8,9,10,10a,10b-dodecahydroazepino-[3,2,1-*hi*]indol]-12-one (**33**) as a light yellow oil which was immediately used in the next step.

To a 0.15 g (0.6 mmol) sample of the above compound in CH_2Cl_2 (6 mL) cooled to −15 °C was added 0.06 mL (0.6 mmol) of 1,2-ethanedithiol followed by 0.08 mL (0.6 mmol) of boron trifluoride−etherate. The reaction mixture was stirred at −15 °C for 2 h and then poured into H_2O and extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (5% EtOAc/hexane) to give 0.095 g (50%) of **34** as a clear oil: IR (film) 1774, 1684, 1269, 1216, and 1165 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22−1.49 (m, 3H), 1.58−1.66 (m, 1H), 1.71−1.80 (m, 3H), 1.92−2.10 (m, 4H), 2.13−2.20 (m, 1H), 2.32 (dd, 1H, J = 17.4 and 9.2 Hz), 2.45−2.51 (m, 1H), 2.53 (dd, 1H, J = 15.0 and 6.6 Hz), 2.61 (p, 1H, J = 9.2 Hz), 2.74 (dd, 1H, J = 17.4 and 9.6 Hz), 3.19−3.29 (m, 4H), 3.45 (dd, 1H, J = 10.8 and 7.6 Hz), 4.11−4.15 (m, 1H), 4.57 (dd, 1H, J = 11.2 and 8.4 Hz), and 4.77 (dd, J = 9.6 and 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 30.0, 30.4, 33.8, 36.8, 37.8, 38.3, 38.4, 38.7, 42.1, 43.0, 43.4, 44.3, 55.0, 61.5, 83.5, 173.7, and 175.6. Anal. Calcd for $C_{18}H_{25}NO_3S_2$: C, 58.84; H, 6.86; N, 3.81. Found: C, 58.75; H, 6.71; N, 3.65.

Furo[2,3-*e*](8-[1,3]dithiolan-2-yl-methyl-2-thioxo-1,2,4,5,6,7,7a,8,9,10,10a,10b-dodecahydroazepino[3,2,1-*hi*]-indol)-12-one (35). To a 0.07 g (0.2 mmol) sample of **34** in CH_2Cl_2 was added 0.04 (0.1 mmol) of Lawesson's reagent. The mixture was stirred at 25 °C for 3 h and then filtered through a plug of silica gel with EtOAc. The solvent was removed under reduced pressure and the residue was purified by flash silica gel chromatography (3% EtOAc/hexane) to give 0.06 g (77%) of **35** as a clear oil: IR (film) 1773, 1479, 1310, 1215, and 1119 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22−1.53 (m, 3H), 1.63−1.99 (m, 6H), 2.03−2.17 (m, 2H), 2.31 (dd, 1H, J = 17.2 and 8.0 Hz), 2.59−2.77 (m, 3H), 2.79 (t, 1H, J = 12.6 Hz), 3.12−3.28 (m, 5H), 3.75 (dd, 1H, J = 11.6 and 7.6 Hz), 4.55 (dd, 1H, J = 10.0 and 8.0 Hz), 4.73 (dd, 1H, J = 9.6 and 5.6 Hz), and 4.74−4.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 28.8, 29.7, 33.3, 37.8, 38.3, 38.7, 39.2, 42.6, 43.3, 44.1, 47.3, 48.5, 51.8, 68.0, 83.2, 175.3, and 200.9. Anal. Calcd for $C_{18}H_{25}NO_2S_3$: C, 56.38; H, 6.58; N, 3.66. Found: C, 56.29; H, 6.51; N, 3.49.

Furo[2,3-*e*](8-ethyl-1,2,4,5,6,7,7a,8,9,10,10a,10b-dodecahydroazepino[3,2,1-*hi*]indol)-12-one (36). To a 0.01 g (0.026 mmol) sample of thioamide **35** in EtOH (0.5 mL) was added an excess of W-2 Raney nickel. The mixture was heated at reflux for 4 h and then cooled to room temperature and filtered through a plug of Celite with ethanol. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography on hexamethyldisilizane treated silica (20 wt %) (5% EtOAc/hexane) to give 0.007 g (93%) of **36** as a light yellow oil: IR (neat) 1775, 1458, 1379, 1329, and 1175 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.91 (t, 3H, J = 7.2 Hz), 1.21−1.67 (m, 9H), 1.88−2.05 (m, 4H), 2.17 (dd, 1H, J = 11.4 and 9.0 Hz), 2.24−2.30 (m, 2H), 2.42−2.48 (m, 2H), 2.71 (dd, 1H, J = 18.3 and 9.9 Hz), 2.85 (dt, 1H, J = 12.6 and 4.2 Hz), 3.13 (td, 1H, J = 9.0 and 4.2 Hz), and 4.57 (dd, 1H, J = 11.4 and 9.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.1, 22.7, 26.7, 27.6, 29.7, 30.1, 34.2, 39.4, 39.8, 43.1, 43.3, 53.6, 55.1, 68.3, 83.2, and 177.2. Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.95; H, 9.57; N, 5.32. Found: C, 72.83; H, 9.46; N, 5.22.

(±)-Stenine (15). To a solution containing 0.005 mL (0.04 mmol) of diisopropylamine in THF (0.1 mL) cooled to 0 °C was added *n*-butyllithium (0.02 mL of a 1.5 M solution in hexane). After being stirred for 1 h, the mixture was cooled to −78 °C, and a solution of 0.003 g (0.011 mmol) of **36** in THF (0.1 mL) was added dropwise. To this mixture was added 0.005 mL (0.003 mmol) of HMPA. The solution was stirred at −78 °C for 1 h followed by the addition of 0.003 mL (0.05 mmol) of methyl iodide. After being stirred for 1 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography on hexamethyldisilzane treated silica (20 wt %) (5% EtOAc/hexane) to give 0.002 g (65%) of stenine (**15**) as a light yellow oil: IR (neat) 1794, 1774, 1381, 1327, and 1172 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 7.5 Hz), 1.29 (d, 3H, J = 7.2 Hz), 1.24−1.70 (m, 8H), 1.87−1.99 (m, 4H), 2.07−2.14 (m, 2H), 2.19−2.22 (m, 1H), 2.29−2.37 (m, 2H), 2.47−2.52 (m, 1H), 2.86−2.88 (m, 1H), 3.16−3.19 (m, 1H), 4.48 (dd, 1H, J = 11.7 and 9.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.0, 15.2, 22.5, 26.4, 27.8, 29.8, 30.0, 40.1, 40.7, 42.7, 43.4, 47.7, 53.3, 55.3, 68.2, 80.7, and 179.9. Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.59; H, 9.82; N, 5.05. Found: C, 73.47; H, 9.66; N, 4.83.

Acknowledgment. We appreciate the financial support provided by the National Science Foundation (Grant No. CHE-0450779) and the National Institutes of Health (GM 059384) for generous support of this work. 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 wish to thank Professors David Hart and Peter Wipf for providing spectral data for stenine as well as an authentic sample.

Supporting Information Available: An ORTEP drawing for structure **29** as well as NMR data of various key compounds. The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050515E