A Diels-Alder Approach to *Stemona* Alkaloids: Total Synthesis of Stenine

Cheng-Yi Chen and David J. Hart*

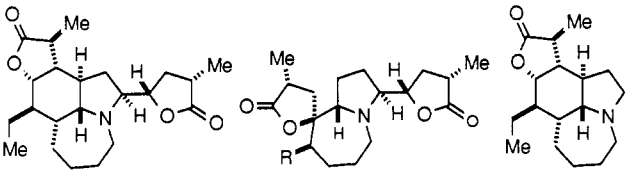
Department of Chemistry, The Ohio State University, 120 West 18th Avenue, Columbus, Ohio 43210

Received February 9, 1993

A total synthesis of *dl*-stenine (**4**) is described. Key features involve (1) use of an intramolecular Diels-Alder cycloaddition-aminimide rearrangement sequence to construct the perhydroindole substructure (**29** → **36** → **27**), (2) application of an Eschenmoser-Claisen rearrangement-iodolactonization sequence to prepare the butenolide substructure (**58** → **59** → **61**), (3) use of a free-radical allylation to introduce the C(9)-ethyl group (**61** → **62**), and (4) thermal cyclization of an amino ester to afford azepinone **68**. A variety of intermolecular and intramolecular Diels-Alder reactions, including examples in which α,β-unsaturated thioesters play the role of dienophile, are also described.

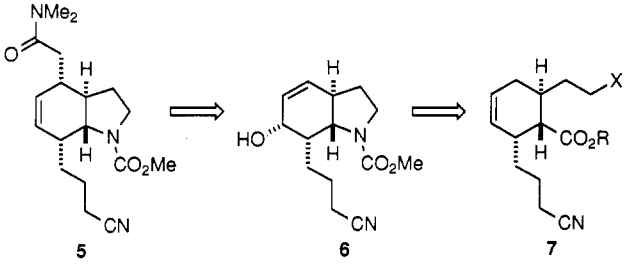
Introduction

Extracts of the roots of *Stemona* species of plants have been used in China and Japan as cough remedies for humans and as anthelmintics for domestic animals.[1-3] A number of alkaloids have been isolated from these extracts, and their pharmacological properties indicate they may be responsible for some of the effects of the crude extracts. For example, tuberostemonine (**1**) has been shown to possess anthelmintic and neurotoxic properties[4,5] and other *Stemona* alkaloids, such as stemspironine (**2**), exhibit insecticidal activity (Figure 1).[6] These alkaloids have recently been the subject of several synthesis efforts. For example, the first total synthesis of a *Stemona* alkaloid was reported in 1989 by the Williams group, who prepared (+)-croomine (**3**).[7] Other synthetic efforts have been described, and in 1990 we described the first synthesis of *dl*-stenine (**4**), a structural relative of tuberostemonine (**1**).[8-10] A full account of this study is presented here.[11]



1 **2** R = OMe, **3** R = H **4**

Figure 1.



5 **6** **7**

Figure 2.

Preliminary Studies

Our approach to stenine was not unlike most other approaches to this type of *Stemona* alkaloid as it relied on a Diels-Alder reaction to construct and control stereochemistry around the cyclohexane ring. Our initial plan is outlined briefly in Figure 2. We felt that amido nitrile **5** contained functionality appropriate for completion of the synthesis and imagined that it could be prepared from allylic alcohol **6** using a Claisen rearrangement. Ester **7** was projected to be a suitable precursor to **6** as the ester could serve as a handle for introducing the nitrogen and also be used to install the allylic alcohol using a halolactonization-dehydrohalogenation sequence. Ester **7** was to be prepared by a cycloaddition reaction between (*E*)-octa-5,7-dienenitrile (**8**) and an appropriate β-substituted acrylate.

We began by examining cycloaddition reactions between **8** and selected α,β-unsaturated esters.[12] Pentenoates **10a-10e** were prepared by treating aldehydes **9a-9c** with the appropriate stabilized phosphoranes in dichloromethane or benzene at reflux.[13-15] The yields of **10a-10e** are

(1) Gotz, M.; Edwards, O. E. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. IX, pp 545-551.
(2) Gotz, M.; Strunz, G. M. In *Alkaloids: MTP International Review of Sciences, Series One*; Wiesner, K., Ed.; Butterworth: London, 1973; Vol. IX, pp 143-160.
(3) For a recent lead reference on structures of *Stemona* alkaloids, see: Lin, W.-H.; Ye, Y.; Xu, R.-S. *J. Nat. Prod.* **1992**, *55*, 571.
(4) Tereda, M.; Sano, M.; Ishii, A. I.; Kino, H.; Fukushima, S.; Noro, T. *Nippon Yakurigaku Zasshi* (*J. Pharm. Soc. Jpn.*) **1982**, *79*, 93.
(5) Shinozaki, H.; Ishida, M. *Brain Res.* **1985**, *334*, 33.
(6) Sakata, K.; Aoki, K.; Chang, C.-F.; Sakurai, A.; Tamura, S.; Murakoshi, S. *Agric. Biol. Chem.* **1978**, *42*, 457.
(7) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923.
(8) For the structure of stenine see: Uyeo, S.; Irie, H.; Harada, H. *Chem. Pharm. Bull.* **1967**, *15*, 768.
(9) Chen, C.-Y.; Hart, D. J. *J. Org. Chem.* **1990**, *55*, 6236.
(10) For other approaches to structurally related *Stemona* alkaloids see: Mitsumasa, H.; Toshiro, I.; Kauzuo, T. *Tennen Yuki, Kagobutsu Toronkai Koen Yoshishu* **1985**, *27*, 200. Xiang, L.; Kozikowski, A. P. *Synlett* **1990**, *2*, 279. Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477. Martin, S. F.; Corbet, J. W. *Synthesis* **1992**, 55. Beddoes, R. L.; Davies, M. P. H.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1992**, 538.
(11) For additional studies see: Chen, C.-Y. Ph.D. Thesis, The Ohio State University, 1990.
(12) Diene **8** was prepared using the method of Roush et al. (Roush, W. R.; Gils, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269) and by alkylation of acetonitrile using (*E*)-1-bromo-3,5-hexadiene (Corey, E. J.; Petrzilka, M. *Tetrahedron Lett.* **1975**, *16*, 2537) in 64% yield as described in the supplementary material.
(13) Tufariello, J. J.; Tegeler, J. J. *Tetrahedron Lett.* **1976**, *17*, 4037. Danieli, B.; Lesma, G.; Palmisano, G.; Tollari, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1237.
(14) Hagemeyer, H. J.; Perry, M. A. U. S. Patent 3,267,133 (*Chem. Abstr.* **1966**, *65*, 13552h).
(15) The Wittig reactions give both *E* and *Z* isomers with the former being predominate (85-90%).

0022-3263/93/1958-3840$04.00/0

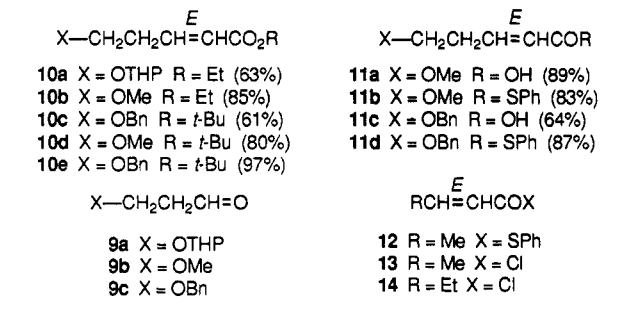
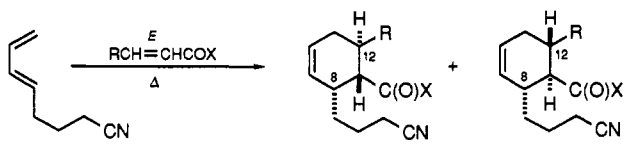


Figure 3.

Table I. Cycloadditions between 8 and Selected Thioesters and Acid Chlorides



entry	dienophile	R	X	condns[a]	% yield	15:16
1	**11b**	$MeOCH_2CH_2$	SPh	150, 24 (1:1)	22	52:48[c]
2	**11d**	$BnOCH_2CH_2$	SPh	150, 20 (1:2)	37	56:44[c]
3	**12**	Me	SPh	150, 24 (1:1)	43	60:40[c]
4	**13**	Me	Cl	170, 2 (1:4)	77[b]	55:(30:15)[e]
5	**14**	Et	Cl	170, 2 (1:4)	85[b]	48:(40:12)[f]

[a] Temperature (°C), time (h). Numbers in parentheses refer to the ratio of 8 to dienophile, respectively. Reactions were run without solvent in a sealed tube. [b] Reactions were quenched with methanol, and products were isolated as methyl esters. [c] Determined by ^{1}H-NMR. Stereochemical assignments are based on expectations and may be reversed. [d] Ratio of 15:16:third isomer = 55:30:15. The structures of the minor isomers were not rigorously proven. [e] Ratio of 15:16:third isomer = 48:40:12. The structures of the minor isomers were not rigorously proven.

indicated in parentheses in Figure 3. Unfortunately, all of the esters were unreactive toward 8 under various conditions. Polymerization of the diene was observed under thermal conditions, and destruction of the dienophile was observed in a few attempts to mediate the reaction using Lewis acid catalysis. We decided to next examine reactions between 8 and carboxylic acid derivatives that would be more reactive than esters. Rate studies described by Sauer suggested acid chlorides as an obvious choice.[16] Because we feared that elimination of HX might complicate attempted cycloadditions with the required acid chlorides, we decided to also examine α,β-unsaturated thioesters.[16] Although there was surprisingly little known about Diels–Alder reactions of unsaturated thioesters, we expected them to react with dienes at rates greater than those of the aforementioned esters.[17] Thus, thioesters **11b** and **11d** were prepared from *tert*-butyl esters **10d** and **10e**, respectively. For example, treatment of **10d** with trifluoroacetic acid in benzene gave carboxylic acid **11a** (89%), which was coupled with thiophenol using DCC to afford **11b** in 83% yield. An identical reaction sequence was used to prepare **11d**.

The results of cycloaddition studies between diene 8 and thioesters **11b**, **11d**, and **12**, as well acid chlorides **13** and **14**, are documented in Table I. These five dienophiles all react with 8 to give a mixture of cycloadducts. Since ethyl crotonate and esters **10a–10e** did not react with 8 under the conditions noted in entries 1–3, we conclude that thioesters are more reactive than the corresponding esters in Diels–Alder cycloadditions.

The reactions shown in Table I did not proceed with the degree of stereocontrol needed to continue with the synthesis in an efficient manner. The cycloadducts derived from entry 5, however, were used to probe subsequent steps in the event an appropriate dienophile was eventually identified. Thus, treatment of the mixture of acid chlorides derived from 8 and **14** with iodine and aqueous sodium bicarbonate in a two-phase system gave a single iodo lactone in 35% overall yield from 8 (Scheme I). The iodo lactone was assigned to structure **17** based on the expectation that if only one of the cycloadducts underwent iodolactonization, it would be **15** since a severe 1,3-diaxial interaction would occur between the C(8) and C(12) substituents in iodolactonization of **16**.[18,19] Dehydrohalogenation of **17** using DBU gave **18** in 93% yield. Treatment of **18** with hydrazine and exhaustive methylation of the intermediate acyl hydrazide **19** gave aminimide **20** in quantitative yield.[20] Finally, thermolysis of **20** in mesitylene at reflux gave cyclic carbamate **21** in 76% yield.[21]

Several other relevant cycloaddition studies are also described in Scheme I. Treatment of diene 8 with methyl fumaroyl chloride, followed by hydrolysis, once again gave an inseparable mixture of carboxylic acids. Only one of the acids underwent lactonization, however, upon treatment with iodine and sodium bicarbonate in ether and aqueous tetrahydrofuran. The resulting iodolactone, formed in 42% overall yield from 8, was assigned structure **22** based on the aforementioned expected iodolactonization rates and the appearance of H_{12} as a multiplet with no large vicinal couplings at δ 2.96. Diene 8 also reacted with maleic anhydride to give 82% of a single cycloadduct assigned structure **23**. Treatment of **23** with methanol gave a single carboxylic acid in 75% yield. Iodolactonization of this acid gave a γ-lactone whose spectral data were consistent with structure **25** (85%). For example, H_{12} in **25** exhibited the expected large vicinal coupling constant (12 Hz) to the axial proton at C(11). Selectivity in the methanolysis of anhydride **23** is consistent with other reports and can be explained using the antiperiplanar effect.[22]

On the whole, the studies outlined in Table I and Scheme I were discouraging. Although the preparation of **21** indicated that some aspects of the strategy outlined in Figure 2 might be workable (introduction of the allylic alcohol and nitrogen substructures) poor stereoselectivity in the cycloaddition reactions led us to explore an intramolecular cycloaddition variant outlined in Figure 4.[23] We felt that allylic alcohol **26** might play much the

(16) Sauer, J.; Wiest, H.; Meilert, A. *Chem. Ber.* **1964**, *97*, 3183. In fact, the acid chloride derived from **11a** was prepared using thionyl chloride, but it decomposed rapidly when warmed with diene 8.

(17) Wu, H.-J.; Pan, K. *J. Chem. Soc., Chem. Commun.* **1987**, 898.

(18) The numbering scheme for stenine is used throughout the text of the paper.

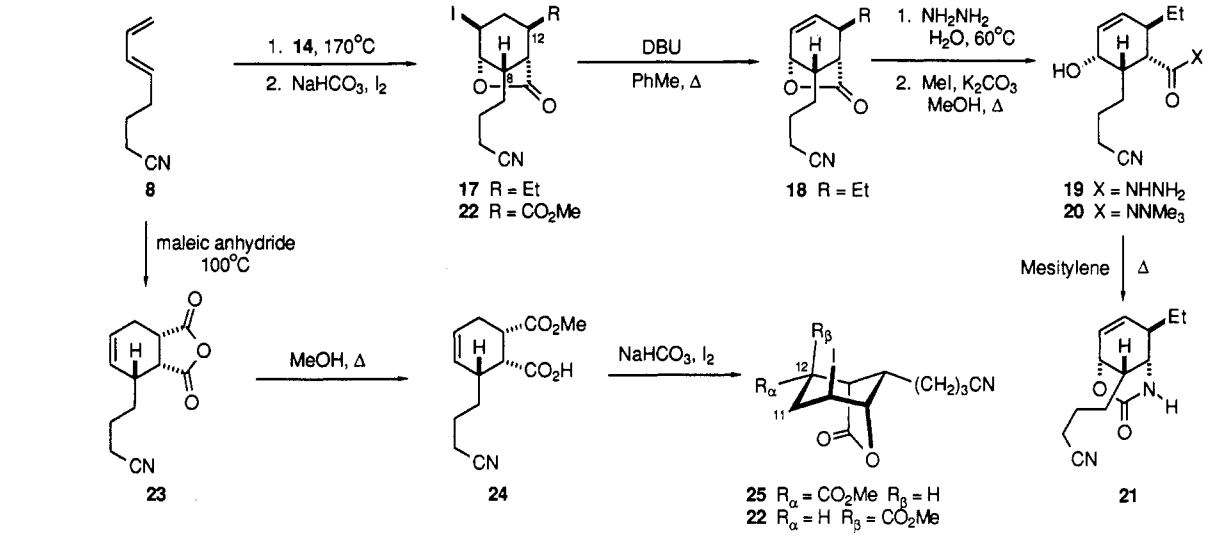
(19) For reviews on halolactonization see: Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, 171. Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 411–501.

(20) For a review of the chemistry of aminimides, see: McKillip, W. J.; Sedor, E. A.; Culbertson, B. M.; Wawzonek, S. *Chem. Rev.* **1973**, *73*, 255.

(21) Masuyama, A.; Tsuchiya, K.; Okahara, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2855. Benecke, H. P. *Tetrahedron Lett.* **1977**, *18*, 997. Benecke, H. P.; Wickel, J. H. *Tetrahedron Lett.* **1972**, *13*, 289.

(22) Kayser, M. M.; Wipff, G. *Can. J. Chem.* **1982**, *60*, 1192. Kayser, M. M.; Salvador, J.; Morand, P.; Krishnamurty, H. G. *Can. J. Chem.* **1982**, *60*, 1199. Kayser, M. M.; Salvador, J.; Morand, P. *Can. J. Chem.* **1983**, *61*, 439. Kraus, G.; Hagen, M. D. *J. Org. Chem.* **1983**, *48*, 3265.

Scheme I



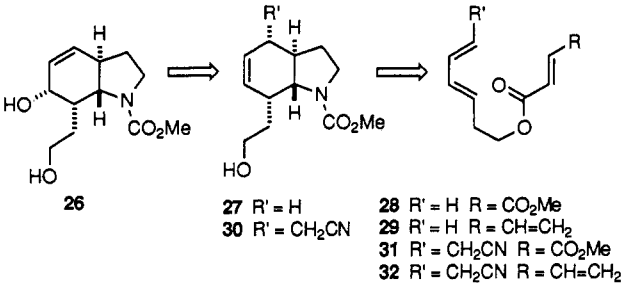
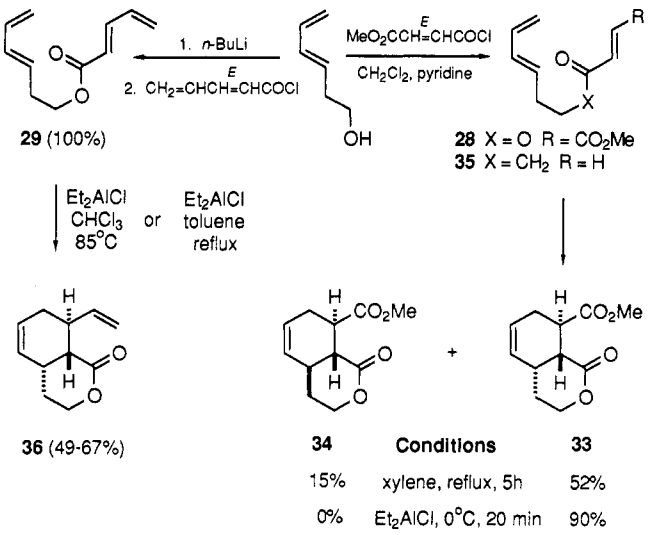


Figure 4.

Scheme II



same role anticipated for allylic alcohol **6** in Figure 2, although a two-carbon homologation would clearly be needed. We thought that **27** would be an appropriate precursor to **26**, as the hydroxyethyl group would be used to introduce the required allylic alcohol. Finally, esters such as **28** and **29** were thought to be reasonable precursors of perhydroindole **27**. We also thought compounds such as **30** could be prepared using this intramolecular Diels–Alder strategy (**31** or **32** → → **30**), eliminating the need for allylic alcohol intermediates such as **26**.

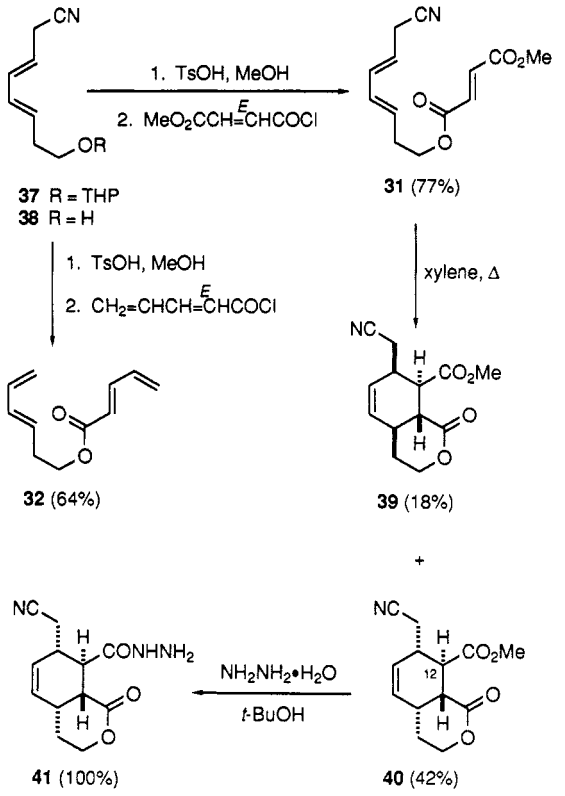
Preparation of cycloaddition substrates **28** and **29** is described in Scheme II. Treatment of (*E*)-3,5-hexadienol with methyl fumaroyl chloride or sequentially with *n*-butyllithium and (*E*)-2,4-pentadienoyl chloride gave **28** and **29** in quantitative yields. When **28** was heated in xylenes at reflux, a mixture of cycloadducts **33** (52%) and **34** (15%) was obtained. Selectivity in this cycloaddition is low relative to the cycloaddition of α,β-unsaturated ketone **35**, which occurs in several hours at 22 °C to give a 95:5 ratio of *cis*- and *trans*-perhydronaphthalenes, respectively.[24] Lewis acid promoted cycloaddition of **28** using diethylaluminum chloride, however, proceeded at 0 °C to give the desired cycloadduct **33** in 90% yield. Stereochemistry at the ring juncture was based on the appearance of H_1 as a doublet of doublets (J = 7.0, 3.2 Hz) at δ 3.22, the small coupling constants being indicative of a cis ring fusion. Thermolysis of **29** in xylenes gave only polymer, but Lewis acid promoted cycloaddition in chloroform at 80 °C or toluene at reflux gave **36** in 67% or 49% yields, respectively. Thus, both **28** and **29** provided cycloadducts with stereocontrol that could not be achieved in the intermolecular counterparts.

Preparation of cycloaddition substrates **31** and **32** is shown in Scheme III. Methanolysis of tetrahydropyranyl ether **37** gave crude alcohol **38**.[25] Acylation of **38** with methyl fumaroyl chloride and 2,4-pentadienoyl chloride gave triene **31** and tetraene **32** in 77% and 64% yields, respectively. It was disappointing to find that these substrates failed to undergo cycloaddition upon treatment with Lewis acids. Either no reaction was observed or complex product mixtures were obtained. Heating **31** in xylene did give the desired cycloadduct **40** (42%) along with isomeric cycloadduct **39** (18%), but similar treatment of **32** failed to afford any cycloadduct.

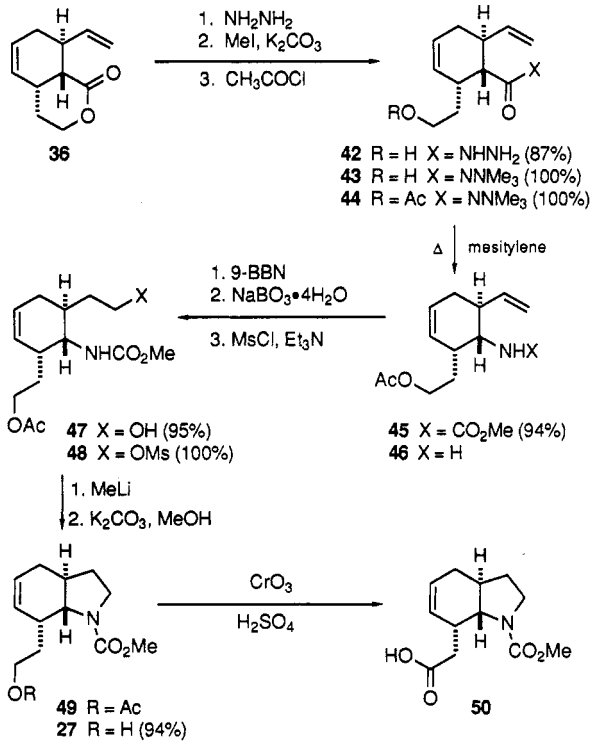
At this point it appeared that cycloadducts **36** and **40** might both be useful intermediates. The former was easiest to prepare on a large scale and was eventually selected as our point of departure. We briefly entertained thoughts of proceeding with cycloadduct **40**, although this would have required an awkward homologation of the C(12) substituent. When treatment of **40** with hydrazine gave

(23) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63.
(24) Gras, J.-L.; Bertrand, M. *Tetrahedron Lett.* **1979**, *20*, 4549.
(25) Diene **37** was prepared from **9a** by the following reaction sequence: (1) (*E*)-$(EtO)_2P(O)CH(Li)CH{=}CHCO_2Me$, THF (48%); (2) $LiAlH_4$, Et_2O (84%); (3) KI, KCN, 18-C-6, *n*-Bu_3P, CH_3CN (86%). Details are provided in the supplementary material.

Scheme III



Scheme IV



only the product derived from reaction at the ester group, however, we decided to commit to cycloadduct **36**. This turned out to be a fortunate decision as the remainder of the synthesis was remarkably straightforward.

Total Synthesis of Stenine. Our first goal was to prepare **27**, projected to be a key intermediate as shown in Figure 3. This was accomplished as outlined in Scheme IV. Installation of the lone nitrogen of stenine (**4**) was accomplished using an aminimide variant of the Hoffman rearrangement.[21] This method was well-suited to the problem as it was anticipated that the hydroxyethyl side chain and olefins would cause difficulties if other Hoffman-type procedures were used. Thus, treatment of **36** with hydrazine in deoxygenated methanol gave acyl hydrazide **42** (87%).[26] Exhaustive methylation of **42** followed by acylation of the resulting aminimide **43** gave **44** in quantitative yield. Thermolysis of **44** in mesitylene at 160 °C followed by addition of methanol to the intermediate isocyanate gave carbamate **45** (94%) and 2% of the urea derived from amine **46**. Hydroboration of **45** using 9-BBN followed by oxidation with basic hydrogen peroxide gave **47** in 75% yield.[27] Using sodium perborate as the oxidant improved the yield of **47** to 95%.[28] Treatment of **47** with methanesulfonyl chloride gave mesylate **48** (100%) to set the stage for construction of **27**. Although treatment of **48** with sodium hydride failed to afford cyclization products, use of 2 equiv of methyllithium gave **27** (83%) and acetate **49** (13%). Hydrolysis of **49** was accomplished using aqueous potassium carbonate in methanol at room temperature to provide **27** in 94% overall yield from **48**.

The next objective was introduction of the allylic alcohol substructure. This was accomplished using halolactonization–dehydrohalogenation methodology. Thus, oxidation of alcohol **27** gave carboxylic acid **50** in 83% yield (Scheme IV). Treatment of **50** with iodine and sodium bicarbonate in a two-phase system afforded **51** (95%). Proton NMR coupling constants (J_{10-11} = 11 Hz and 6 Hz, J_{9-10} = 9 Hz) suggest that the lactone oxygen and halide both occupy equatorial sites on the six-membered ring. Nonetheless, **51** is most likely born with the six-membered ring in a boatlike conformation due to the normal stereoelectronic requirements for opening of an iodonium ion. Dehydrohalogenation of **51** using DBU proceeded smoothly to afford **52** (98%) whose structure was confirmed by X-ray crystallography (Scheme V).[29] We next performed the required two-carbon homologation of the C(8) side chain. Reduction of **52** followed by Wittig olefination of the resulting lactol gave α,β-unsaturated ester **53** (75%). This set the stage for introduction of the C(11) acetic acid side chain. Treatment of **53** with *N,N*-dimethylacetamide dimethyl acetal did afford the desired product **54** (43%), but tetrahydrofuran **55** was also produced in 45% yield. Not surprisingly, cyclization was competitive with the desired Eschenmoser–Claisen rearrangement.[30,31] Attempts to reduce the unsaturated ester prior to conducting the rearrangement also provided **55**. Thus, we decided to circumvent this problem by postponing the two-carbon homologation. Reduction of lactone **52** with sodium borohydride gave allylic alcohol **26** (100%). Once again, problems were encountered with the Claisen rearrangement as treatment of **26** with *N,N*-dimethylacetamide dimethyl acetal gave tetrahydrofuran **56** (75%) and acetate

(26) Reduction of the terminal olefin, presumably by diimide, complicated this reaction if solvent was not deoxygenated.

(27) Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 5280, 5281.

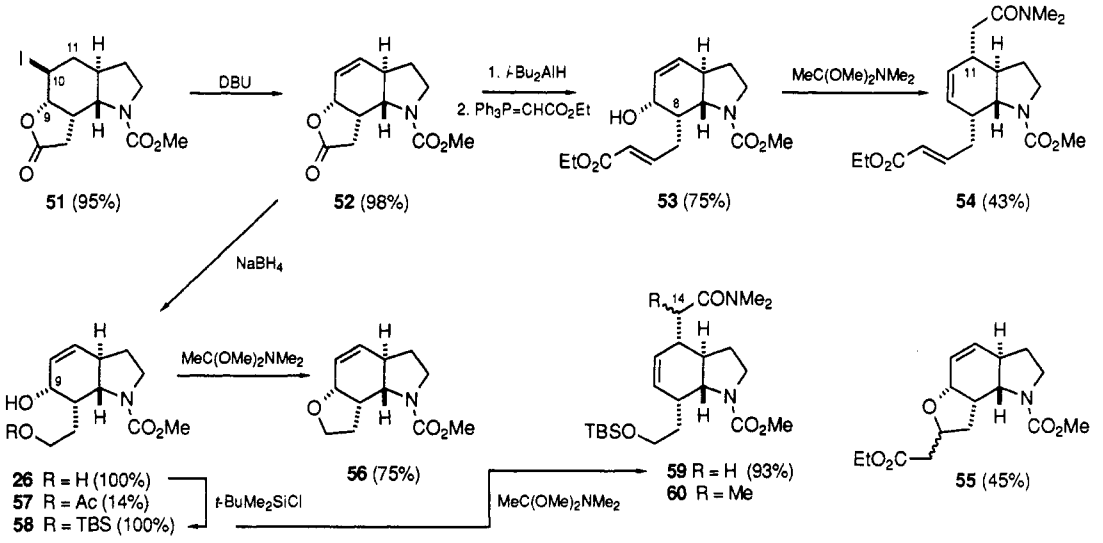
(28) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *Tetrahedron Lett.* **1989**, *30*, 1483.

(29) We thank Dr. Judith C. Gallucci, for performing X-ray crystallographic analyses of **52** and **68** at The Ohio State University Department of Chemistry Crystallographic Facility. The author has deposited atomic coordinates for **52** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

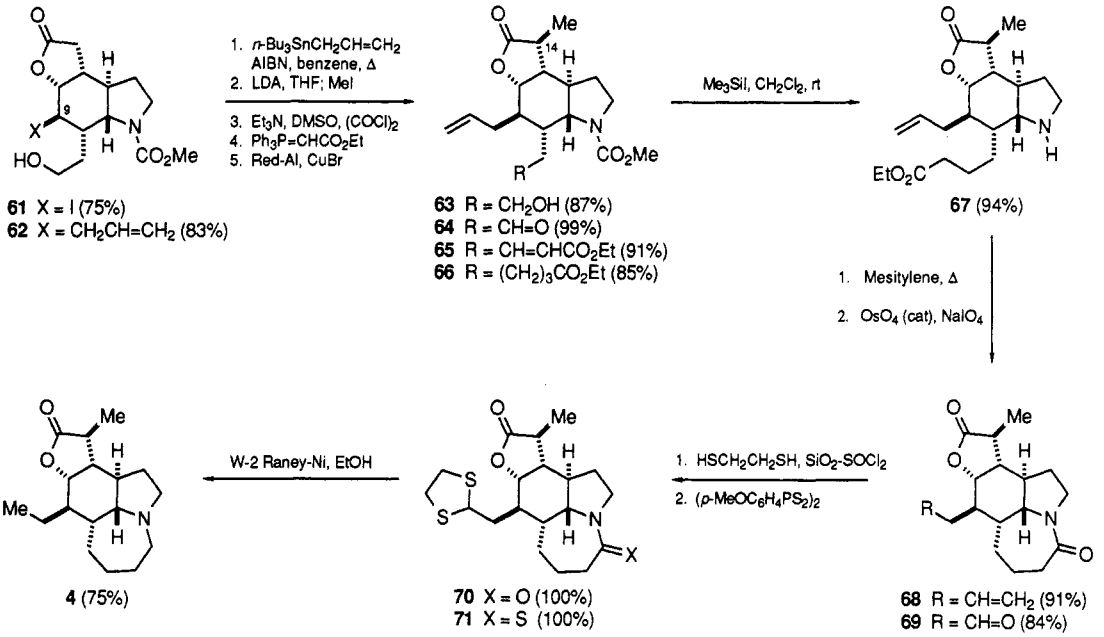
(30) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chem. Acta* **1964**, *47*, 2425.

(31) Ohrui, H.; Jones, G. H.; Moffatt, J. F.; Maddox, M. L.; Christensen, A. T.; Bryan, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4601.

Scheme V



Scheme VI



57 (14%). Activation of the primary hydroxyl group and subsequent cyclization apparently occurs faster than functionalization of the C(9) hydroxyl group. This problem was solved by protecting the primary alcohol as *tert*-butyldimethylsilyl ether **58** (100%) prior to conducting the Claisen rearrangement.[32] Treatment of **58** with the appropriate amide acetal then gave the desired amide **59** (93%), presumably through a transition state in which the six-membered ring adopts a boatlike conformation. We recognized that the C(14) methyl group of stenine might also be introduced at this stage of the synthesis. Treatment of **58** with *N,N*-dimethylpropionamide dimethyl acetal, however, gave what was tentatively assigned structure **60** (63%) as a 1:1 mixture of diastereomers. Since this stereochemical problem was solved in another manner, this approach to controlling stereochemistry at C(14) was not investigated further.

We next turned to the tasks of (1) lactone construction, (2) introduction of the C(9) ethyl group, (3) the aforementioned two-carbon homologation, and (4) construction of the azepine as outlined in Scheme VI. Electrophile-initiated cyclization of **59** was accompanied by loss of the *tert*-butyldimethylsilyl group to give iodo lactone **61** in 75% yield. Keck allylation of **61** proceeded with excellent diastereoselectivity, presumably the result of steric effects, to give **62** (83%).[33] Alkylation of the enolate derived from **62** gave **63** (87%), also the product expected on the basis of steric effects.[34] Swern oxidation of **63** followed by Wittig olefination of the resulting aldehyde **64** gave α,β-unsaturated ester **65** in 90% overall yield.[35] Conjugate reduction of **65** gave **66** (85%)[36] and removal of the carbamate protecting group afforded **67** (94%), setting the stage for construction of the azepine.[37] Attempts to convert **67** to

(32) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

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

(34) A minor product of this reaction, isolated in 8% yield, was the methyl ether derived from alkylation of the primary hydroxyl group of **63**. The stereochemistry of **63** was established by NOE studies that indicated a cis relationship between the C(14) methyl group and C(10) hydrogen.

(35) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

68 using trimethylaluminum failed, as did efforts to cyclize the amino acid derived from hydrolysis of the ethyl ester.[38] In the end, simply heating 67 in mesitylene at reflux for 4 h gave 68 in 91% yield. The structure of 68 was confirmed by X-ray crystallography.[29]

The synthesis was completed in a straightforward manner. Johnson–Lemieux oxidation of 68 gave aldehyde 69 (84%) which was converted to thioketal 70 in quantitative yield using 1,2-ethanedithiol and silica gel coated with thionyl chloride.[39,40] Treatment of 70 with Lawesson's reagent gave thiolactam 71 and simultaneous reduction of the thioketal and thiolactam using Raney-Ni afforded racemic stenine (4) in 75% yield from 70.[41–43]

In summary, the first total synthesis of stenine has been accomplished. The synthesis makes use of an intramolecular Diels–Alder reaction, an aminimide variant of the Curtius rearrangement, an Eschenmoser–Claisen rearrangement, a halolactonization, and a Keck allylation to control the six stereogenic centers of the cyclohexane substructure.

Experimental Section

All melting points were taken using a Thomas-Hoover capillary melting point apparatus and are uncorrected as are all boiling points. ^{1}H NMR spectra are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz, integration, interpretation]. ^{13}C NMR data are reported as follows: chemical shift (multiplicity determined from off resonance decoupled, DEPT or INEPT spectra). Some NMR spectra were recorded at 323 or 348 K to ease interpretation due to carbamate geometrical isomerism. Mass spectra were obtained at an ionization energy of 70 eV. Compounds for which an exact mass is reported exhibited no significant peaks at m/z greater than that of the parent.

Solvents and reagents were dried and purified prior to use when deemed necessary: THF, Et_2O, and benzene were distilled from sodium metal; CH_2Cl_2 was distilled over calcium hydride. Reactions requiring an inert atmosphere were run under argon. Analytical thin-layer chromatography was conducted using 0.25-mm thick precoated silica gel 60F-254 plates. Column chromatography was performed over silica gel (70–230 mesh). Medium-pressure liquid chromatography (MPLC) was performed using Lobar prepacked silica gel columns. All Grignard reagents and organolithiums were titrated prior to use with 2-butanol using 1,10-phenanthroline as the indicator.[44]

Tetraene 29. To a solution of 11.3 g (110 mmol) of (*E*)-3,5-hexadienol[45] in 150 mL of Et_2O at −78 °C was added dropwise of 68.8 mL of *n*-BuLi (1.6 M in hexane). The mixture was stirred at −78 °C for 30 min, followed by dropwise addition of 16.0 g (130 mmol) of (*E*)-2,4-pentadienoyl chloride.[46] The mixture was stirred at −78 °C for 30 min, warmed to rt and stirred for 30 min. The mixture was diluted with 600 mL of Et_2O and washed with 200 mL of saturated aqueous $NaHCO_3$. The organic solution was dried ($MgSO_4$) and concentrated in vacuo to afford 20 g (100%) of tetraene 29 as pale yellow liquid. This material was used in the subsequent reaction without further purification: IR (CCl_4) 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.45 (q, J = 6.8 Hz, 2 H, CH_2C=), 4.22 (t, J = 6.8 Hz, 2 H, CH_2O), 5.00 (d, J = 9.9 Hz, 1 H, =CH_2), 5.14 (d, J = 16.3 Hz, 1 H, =CH_2), 5.46 (dt, J = 10.0, 0.6 Hz, 1 H, =CH_2), 5.63 (dt, J = 16.3, 0.7 Hz, 1 H, =CH_2), 5.66 (dd, J = 14.4, 6.9 Hz, 1 H, =CH), 5.90 (dd, J = 15.4, 0.5 Hz, 1 H, =CH), 6.12–6.53 (m, 3 H, =CH), 7.28 (dd, J = 15.4, 11.0 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 31.7 (t), 63.3 (t), 115.8 (t), 121.9 (d), 125.3 (t), 129.5 (d), 133.2 (d), 134.6 (d), 136.6 (d), 144.6 (d), 166.4 (s); exact mass calcd for $C_{11}H_{14}O_2$ m/z 178.0994, found m/z 178.0994.

Lactone 36. To a solution of 20 g (110 mmol) of tetraene 29 in 3.7 L of toluene was added 94 mL (170 mmol) of Et_2AlCl (1.8 M in toluene). The mixture was heated under reflux for 5 h, cooled to rt, and 15 mL of saturated aqueous $NaHCO_3$ was added dropwise. The mixture was filtered and the filtrate was concentrated in vacuo and chromatographed on 300 g of silica gel (eluted with EtOAc-hexane (1:1)) to afford 9.8 g (49%) of lactone 36 as pale yellow oil: IR (CH_2Cl_2) 1720, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.77 (m, 1 H), 1.92–2.14 (m, 2 H), 2.32 (m, 1 H), 2.63 (dd, J = 6.5, 3.7 Hz, 1 H, CHCO), 2.72 (m, 1 H, =CCH), 3.17 (m, 1 H, CHCC(O)), 4.24 (m, 2 H, CH_2O), 5.06 (dd, J = 10.3, 1.5 Hz, 1 H, =CH_2), 5.13 (dd, J = 17.3, 1.5 Hz, 1 H, =CH_2), 5.53 (m, J = 10.1 Hz, 1 H, =C*H*CH_2), 5.75–5.95 (m, 2 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 25.7 (t), 28.14 (t), 28.2 (d), 36.4 (d), 34.7 (d), 66.4 (t), 115.2 (t), 127.6 (d), 128.4 (d), 139.4 (d), 172.5 (s); exact mass calcd for $C_{11}H_{14}O_2$ m/z 178.0994, found m/z 178.0994. A 67% yield of 36 was obtained when the reaction was conducted in chloroform on a 2.0 mmol scale using 4.0 mmol of Et_2AlCl in a sealed tube at 80 °C for 20 h.

Hydrazide 42. A mixture of 10.5 g (59 mmol) of lactone 36 and 30 g (0.6 mol) of degassed 80% aqueous hydrazine in 150 mL of degassed methanol was heated under reflux for 12 h. The mixture was cooled to rt and concentrated in vacuo to afford a white solid which was recrystallized from THF and Et_2O (1:3) to afford 10.8 g (87%) of hydrazide 42 as white crystals: mp 140–141 °C; IR (KBr) 3470, 3320, 1675 cm^{-1}; ^{1}H NMR (D_2O, 250 MHz) δ 1.35–1.57 (m, 2 H, CH_2), 1.72–1.82 (m, 1 H, CHC=), 2.10 (m, 1 H, CHC=), 2.30–2.47 (m, 3 H, CHC= and CHCON), 3.54 (m, 2 H, CH_2O), 4.60 (br s, 4 H, $NHNH_2$ and OH), 4.90 (dd, J = 10.5, 1.6 Hz, 1 H, =CH_2), 5.00 (dd, J = 17.3, 1.6 Hz, 1 H, =CH_2), 5.62 (m, 3 H, =CH); ^{13}C NMR (D_2O, 62.5 MHz) δ 30.3 (t), 32.6 (d), 34.0 (t), 34.7 (d), 46.9 (d), 59.6 (t), 114.6 (t), 126.1 (d), 128.5 (d), 141.2 (d), 175.1 (s); exact mass calcd for $C_{11}H_{18}N_2O_2$ m/z 210.1369, found m/z 210.1381.

Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.82; H, 8.63. Found: C, 62.73; H, 8.72.

Aminimide 43. A mixture of 12.3 g (58.6 mmol) of hydrazide 42, 14.0 g (100 mmol) of K_2CO_3, and 49.5 g (350 mmol) of methyl iodide in 30 mL of anhydrous methanol was heated under reflux for 4 h. The resulting homogeneous solution was cooled to rt and concentrated in vacuo. The residual white oily solid was suspended in 300 mL of CH_2Cl_2 and filtered. The filtrate was concentrated in vacuo to afford 15.1 g (100%) of aminimide 43 as pale yellow oil: IR (neat film) 3400, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.82–1.93 (m, 3 H, CH_2 and CHC=), 2.24 (dt, J = 18.0, 5.2 Hz, 1 H, =CCH_2), 2.37 (dd, J = 10.9, 6.3 Hz, 1 H, CHCON), 2.58 (m, 1 H, =CCH), 2.76 (m, 1 H, =CCH_2), 3.36 (s, 9 H, CH_3), 3.62 (m, 1 H, CH_2O), 3.74 (m, 1 H, CH_2O), 4.91 (dd, J = 10.7, 2.2 Hz, 1 H, =CH_2), 5.10 (ddd, J = 16.6, 1.3, 1.1 Hz, 1 H, =CH_2), 5.52 (m, 1 H, =C*H*CH), 5.72 (m, 1 H, =C*H*CH_2), 5.82 (ddd, J = 17.0, 10.2, 7.5 Hz, 1 H, C*H*=CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 30.9 (t), 34.4 (t) 35.9 (d), 36.0 (d), 47.9 (d), 55.2 (q), 59.6 (t), 113.3 (t), 125.9 (d), 129.9 (d), 142.2 (d), 177.0 (s); exact mass calcd for $C_{14}H_{24}N_2O_2$ m/z 252.3596, found m/z 252.1794.

Acetate 44. To 14.5 g (58.5 mmol) of aminimide 43 at 0 °C was added dropwise 80 mL of acetyl chloride. The mixture was stirred at 0 °C for 3 h, warmed to rt, stirred at rt for 1 h, and concentrated in vacuo to give a white solid. This material was dissolved in 300 mL of CH_2Cl_2 and washed with three 100-mL portions of saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), concentrated in vacuo to afford 17.3 g (100%) of

(36) Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. *J. Org. Chem.* **1977**, *42*, 3180.
(37) Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun.* **1978**, 315.
(38) For a lead reference describing lactamization methods see: Mader, M.; Helquist, P. *Tetrahedron Lett.* **1988**, *29*, 3049.
(39) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
(40) Kamitori, T.; Hojo, M.; Masuda, R.; Kimura, T.; Yoshida, T. *J. Org. Chem.* **1986**, *51*, 1427.
(41) Scheibye, S.; Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.
(42) Kornfeld, E. C. *J. Org. Chem.* **1951**, *16*, 131. Wolfrom, M. L.; Karabinos, J. V. *J. Am. Chem. Soc.* **1944**, *66*, 909.
(43) We thank Professor M. Haruna (Meijo University, Nagoya, Japan) for supplying a 400-MHz ^{1}H NMR spectrum of (−)-4 for the purpose of comparison with our 300-MHz spectrum of *dl*-4.
(44) Walton, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
(45) Martin, S. F.; Tu, C.-Y.; Chou, T. S. *J. Am. Chem. Soc.* **1980**, *102*, 5274.
(46) Davies, C. R.; Davies, J. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2390.

acetate **44** as white solid: mp 91–92 °C; IR (CH_2Cl_2) 1730, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.68 (m, 1 H, CH_2), 1.92 (m, 1 H, CH_2), 2.02 (s, 3 H, CH_3), 2.03–2.65 (m, 5 H, CH_2C=, CHC=, C*H*C=CH_2 and CHCON), 3.39 (s, 9 H, NCH_3), 4.16 (t, J = 7.1 Hz, 2 H, CH_2OAc), 4.92 (ddd, J = 10.4, 1.9, 0.8 Hz, 1 H, =CH_2), 5.08 (ddd, J = 16.1, 1.9, 0.8 Hz, 1 H, =CH_2), 5.67 (m, 2 H, CH=CH), 5.87 (ddd, J = 16.1, 10.4, 7.2 Hz, 1 H, C*H*=CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 20.8 (q), 30.6 (t), 31.0 (t), 34.0 (d), 35.9 (d), 42.3 (d), 55.0 (q), 63.7 (t), 112.9 (t), 125.4 (d), 129.6 (d), 142.4 (d), 170.9 (s), 176.2 (s); exact mass calcd for $C_{16}H_{26}N_2O_3$ m/z 294.1972, found m/z 294.1944.

Anal. Calcd for $C_{16}H_{26}N_2O_3$: C, 65.26; H, 8.91. Found: C, 65.73; H, 8.97.

Carbamate 45. A solution of 10.0 g (34.0 mmol) of aminimide **44** in 120 mL of mesitylene was heated under reflux for 4 h. The reaction mixture was cooled to rt followed by the addition of 10 mL of anhydrous methanol. The mixture was heated under reflux for 12 h, cooled to rt, and concentrated in vacuo. The residue was chromatographed on 200 g of silica gel (eluted with EtOAc–hexane (1:1)) to afford 8.53 g (94%) of carbamate **45** as colorless oil: IR (neat film) 1730, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.55 (m, 1 H, CH_2), 1.78 (m, 1 H, CH_2), 2.04 (s, 3 H, CH_3), 2.08 (m, 1 H, =CCH_2), 2.25 (m, 1 H, =CCH), 2.54 (m, 2 H, C*H*C=CH_2 and =CCH_2), 3.67 (s, 3 H, OCH_3), 3.82 (m, 1 H, CHN), 4.14 (dt, J = 6.9, 1.2 Hz, 2 H, CH_2OAc), 4.70 (m, 1 H, NH), 5.12 (m, 2 H, =CH_2), 5.54 (m, 1 H, =C*H*CH), 5.72 (m, 2 H, =C*H*CH_2 and C*H*=CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 20.6 (q), 27.8 (t), 29.6 (t), 32.4 (d), 39.6 (d), 51.6 (d), 51.6 (q, DEPT editing), 62.2 (t), 115.6 (t), 125.7 (d), 128.0 (d), 139.2 (d), 156.4 (s), 170.6 (s); exact mass calcd for $C_{14}H_{21}NO_4$ m/z 267.1471, found m/z 267.1459.

Continued elution gave 0.18 g (2%) of the diastereomeric ureas derived from **46** as a pale yellow oil: IR (CH_2Cl_2) 3400 (br), 1730, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.6 (m, 1 H), 1.8 (m, 1 H), 2.04 (s, 3 H, CH_3), 2.08 (m, 1 H), 2.21 (m, 1 H), 2.50 (m, 2 H), 3.86 (m, 1 H, CHN), 4.14 (t, J = 6.9 Hz, 2 H, CH_2OAc), 4.35 (m, 1 H, NH), 5.08 (m, 2 H, =CH_2), 5.54 (m, 1 H, =C*H*CH), 5.72 (m, 2 H, =C*H*CH_2 and C*H*=CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 20.8 (q), 27.9 (t), 28.1 (t), 29.8 (t), 32.7 (d), 32.8 (d), 40.2 (d), 50.5 (d), 50.6 (d), 62.5 (t), 62.6 (t), 115.4 (t), 125.8 (d), 128.4 (d), 139.7 (d), 139.8 (d), 157.4 (d), 157.4 (s), 171.0 (s), 171.0 (s) (several carbons not observed due to magnetic equivalence); exact mass calcd for $C_{28}H_{36}N_2O_5$ m/z 444.2624, found m/z 444.2650.

Alcohol 47. To a solution of 5.9 g (22.1 mmol) of carbamate **45** in 40 mL of dry THF at 0 °C was added dropwise 48.6 mL (24.3 mmol) of 9-BBN (0.5 M in THF). The mixture was warmed to rt and stirred for 2 h, followed by addition of 24 mL of water and 11.2 g (72.9 mmol) of sodium perborate tetrahydrate. The mixture was stirred at rt for 2 h and diluted with 200 mL of Et_2O. The aqueous layer was extracted with three 100-mL portions of CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on 200 g of silica gel (eluted with CH_2Cl_2–methanol (95:5)) to afford 6.01 g (95%) of alcohol **47** as colorless liquid: IR (CH_2Cl_2) 3610, 3440, 1725, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.43–1.90 (m, 5 H), 1.91–2.00 (m, 2 H), 2.04 (s, 3 H, CH_3), 2.25 (m, 1 H), 2.46 (m, 1 H), 3.65 (s, 3 H, OCH_3), 3.67–3.85 (m, 3 H, CHN, C*H*$_2$OH), 4.15 (t, J = 6.7 Hz, 2 H, CH_2OAc), 4.94 (d, J = 9.1 Hz, 1 H, NH), 5.03 (m, 1 H, =C*H*CH), 5.20 (m, 1 H, =C*H*CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 20.9 (q), 27.3 (t), 30.0 (t), 31.9 (d), 32.2 (d), 35.2 (t), 51.5 (d), 52.0 (q), 60.6 (t), 62.3 (t), 126.4 (d), 127.6 (d), 156.8 (s), 171.0 (s); exact mass calcd for $C_{14}H_{23}NO_5$ m/z 285.1577, found m/z 285.1612.

Mesylate 48. To a solution of 13.0 g (45.6 mmol) of alcohol **47** and 9.2 g (91 mmol) of Et_3N in 80 mL of CH_2Cl_2 at 0 °C was added dropwise 7.8 g (68 mmol) of MsCl. The mixture was warmed to rt, stirred for 1 h, diluted with 200 mL of CH_2Cl_2, and washed sequentially with 150 mL of 3 N aqueous HCl, 100 mL of water, and 150 mL of saturated aqueous $NaHCO_3$. The organic solution was dried ($MgSO_4$) and concentrated in vacuo to afford 16.6 g (100%) of carbamate **48** as pale yellow liquid: IR (CH_2Cl_2) 1730, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.58–1.94 (m, 5 H), 2.02 (m, 1 H, =CCH_2), 2.03 (s, 3 H, CH_3), 2.27 (m, 1 H, =CCH_2), 2.42 (m, 1 H, =CCH), 3.02 (s, 3 H, SCH_3), 3.64 (s, 3 H, OCH_3), 3.84 (m, 1 H, CHN), 4.14 (t, J = 6.6 Hz, 2 H, CH_2OAc), 4.28 (m, 2 H, CH_2OMs), 4.82 (d, J = 9.6 Hz, 1 H, NH), 5.51 (m, 1 H, =C*H*CH), 5.64 (m, 1 H, =C*H*CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 20.8 (q), 26.7 (t), 29.9 (t), 31.6 (t), 31.8 (d), 32.1 (d), 37.4 (q), 51.0 (d), 52.0 (q), 62.1 (t), 67.7 (t), 125.8 (d), 127.7 (d), 156.6 (s), 170.9 (s); exact mass calcd for $C_{12}H_{19}NO_3$ (M^+ – MsOH – MeCO) m/z 225.1366, found m/z 225.1391.

Hexahydroindole 27 and Hexahydroindole 49. To a solution of 16.6 g (45.6 mmol) of mesylate **48** in 300 mL of THF at –78 °C was added dropwise 65.1 mL (91.2 mmol) of MeLi (1.4 M in hexane) over a period of 15 min. The mixture was gradually warmed to rt and stirred for 30 min, followed by addition of 200 mL of Et_2O and 150 mL of water. The aqueous layer was separated and extracted with three 100-mL portions of Et_2O. The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on 200 g of silica gel (eluted with EtOAc) to afford 1.59 g (13%) of acetate **49** as a pale yellow oil: IR (CH_2Cl_2) 1735, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.3–2.0 (m, 7 H), 2.04 (s, 3 H, CH_3), 2.30 (m, 1 H, =CCH), 2.80–3.34 (m, 2 H), 3.70 (s, 3 H, OCH_3), 3.52–3.78 (m, 1 H), 4.14 (m, 2 H, CH_2O), 5.72 (m, 2 H, CH=CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz, 328 K) δ 20.4 (q), 28.1 (t), 29.4 (t), 30.9 (t), 35.3 (d, two carbons), 36.3 (d), 47.4 (t), 51.6 (q), 62.8 (t), 126.4 (d), 129.7 (d), 155.9 (s), 170.3 (s); exact mass calcd for $C_{14}H_{21}NO_4$ m/z 267.1470, found m/z 267.1471.

Continued elution afforded 8.5 g (83%) of hexahydroindole **27** as colorless liquid: IR (CH_2Cl_2) 3450 (br), 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.34–1.44 (m, 2 H, CH_2CO), 1.68 (m, 1 H, CHCN), 1.80–2.04 (m, 4 H, CH_2CN, =CCH_2 and =CCH), 2.30 (m, 1 H, =CCH_2), 3.08 (br s, 1 H, OH), 3.20–3.36 (m, 2 H, CH_2N), 3.64 (s, 3 H, OCH_3), 3.62–3.74 (m, 3 H, CHN and CH_2O), 5.62–5.80 (m, 2 H, CH=CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 29.2 (t), 31.3 (t), 32.6 (t), 34.9 (d), 36.4 (d), 47.6 (t), 52.2 (q), 61.3 (t), 63.3 (d), 126.1 (d), 130.7 (d), 156.6 (s); exact mass calcd for $C_{12}H_{19}NO_3$ m/z 225.1366, found m/z 225.1343.

A mixture of 1.59 g (6.0 mmol) of **49** and 2 g (14.3 mmol) of potassium carbonate in 5 mL of methanol and 3 mL of water was stirred at rt for 12 h. The mixture was concentrated in vacuo to a volume of 3.5 mL and extracted with three 25-mL portions of CH_2Cl_2. The organic solution was dried ($MgSO_4$) and concentrated in vacuo to afford 1.13 g (85%) of hexahydroindole **27**.

Carboxylic Acid 50. To a solution of 23.8 mL (67 mmol) of 8.0 N Jones reagent at 0 °C was added a solution of 7.5 g (33.3 mmol) of alcohol **27** in 100 mL of acetone in five portions over a period of 15 min. The mixture was stirred at 0 °C for 30 min, diluted with 200 mL of acetone, and filtered. The filtrate was diluted with 100 mL of water, concentrated in vacuo to a volume of 125 mL, and extracted with three 200-mL portions of CH_2Cl_2. The organic solution was dried ($MgSO_4$), concentrated in vacuo, and recrystallized (EtOAc–hexane (1:4)) to afford 6.61 g (83%) of acid **50** as white solid: IR (CH_2Cl_2) 3100 (br), 1680 cm^{-1}; mp 141–143 °C; ^1H NMR ($CDCl_3$, 250 MHz, 323 K) δ 1.47 (m, 1 H), 1.81–2.04 (m, 3 H), 2.11 (dd, J = 15.3, 9.9 Hz, 1 H, CH_2CO_2H), 2.30 (m, 1 H), 2.50 (dd, J = 15.3, 4.4 Hz, 1 H, CH_2CO_2H), 3.2–3.5 (m, 3 H), 3.69 (s, 3 H, OCH_3), 3.7 (m, 1 H), 5.68 (m, 1 H, =CH), 5.86 (m, 1 H, =CH), 9.82 (br s, 1 H, OH); ^{13}C NMR ($CDCl_3$, 62.5 MHz, 323 K) δ 29.7 (t), 31.1 (t), 34.2 (t), 35.2 (d), 36.7 (d), 47.8 (t), 52.3 (q), 62.6 (d), 127.2 (d), 129.6 (d), 156.7 (s), 177.5 (s); exact mass calcd for $C_{12}H_{17}NO_4$ m/z 239.1157, found m/z 239.1179.

Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.22; H, 7.16. Found: C, 60.24; H, 7.17.

Iodo Lactone 51. To a solution of 5.0 g (20.9 mmol) of acid **50** in 130 mL of THF–Et_2O–saturated aqueous $NaHCO_3$ (1:1:2) at 0 °C was added 15.9 g (62.6 mmol) of iodine in one portion. The mixture was stirred at 0 °C for 3 h and rt for 12 h, diluted with 100 mL of Et_2O, and washed with 100 mL of saturated aqueous $NaHSO_3$. The aqueous layer was extracted with three 100-mL portions of Et_2O. The organic solution was dried ($MgSO_4$) and concentrated in vacuo to afford 7.2 (95%) of iodo lactone **51** as white crystals: mp 166–168 °C; IR (CH_2Cl_2) 1790, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz, 323 K) δ 1.53 (m, 1 H, CH_2CN), 1.81–2.05 (m, 3 H, CH_2CI and CH_2CN), 2.43 (m, 2 H, CH_2CO), 2.53 (ddd, J = 13.1, 5.5, 2.7 Hz, 1 H, CHCN), 3.35 (ddd, J = 11.0, 11.0, 6.5 Hz, 1 H, CH_2N), 3.48 (dd, J = 11.0, 5.6 Hz, 1 H, CHN), 3.50–3.75 (m, with s at 3.64, 5 H, CHCO, OCH_3 and CH_2N), 3.93 (ddd, J = 10.7, 8.8, 5.5 Hz, 1 H, CHI), 4.84 (dd, J = 8.5, 7.5 Hz, 1 H, CHO); ^{13}C NMR ($CDCl_3$, 62.5 MHz, 323 K) δ 23.9 (d), 28.0 (t), 28.1 (t), 37.9 (t), 29.6 (d), 39.9 (d), 47.6 (t), 52.3 (q), 60.7 (d),

85.3 (d), 155.8 (s), 174.8 (s); exact mass calcd for $C_{12}H_{16}INO_4$ *m/z* 365.0152, found *m/z* 365.0125.

Anal. Calcd for $C_{12}H_{16}INO_4$: C, 39.45; H, 4.38. Found: C, 38.95; H, 4.47.

Lactone 52. To a solution of 2.61 g (7.2 mmol) of iodo lactone **51** in 25 mL of toluene was added 1.62 g (10.7 mmol) of DBU in one portion. The reaction mixture was warmed under reflux for 3 h, cooled to rt, and chromatographed on 60 g of silica gel (eluted with EtOAc–hexane (2:1)) to afford 1.67 g (98%) of lactone **52** as white crystals: mp 109–110 °C; IR (CH_2Cl_2) 1770, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz, 323 K) δ 1.58 (m, 1 H, CH_2CN), 2.10 (m, 1 H, CH_2CN), 2.50 (m with d at 2.48, J = 10 Hz, 3 H, CH_2CO and =CCH), 3.31 (dd, J = 10.7, 4.9 Hz, 1 H, CHN), 3.36 (dt, J = 11.0, 6.7 Hz, 1 H, CH_2N), 3.61 (m, 1 H, CH_2N), 3.67 (s, 3 H, OCH_3), 3.88 (m, 1 H, CHCO), 5.19 (ddd, J = 8.5, 3.9, 1.9 Hz, 1 H, CHO), 5.85 (ddd, J = 9.8, 3.9, 3.2 Hz, 1 H, =CH), 6.12 (dd, J = 9.8, 1.9 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz, 323 K) δ 27.1 (t), 27.3 (t), 35.2 (d), 36.5 (d), 47.3 (t), 52.1 (q), 61.8 (d), 77.1 (d), 126.8 (d), 132.5 (d), 155.8 (s), 176.0 (s); exact mass calcd for $C_{12}H_{15}NO_4$ *m/z* 237.1001, found *m/z* 237.0998.

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.73; H, 6.33. Found: C, 60.22; H, 6.52.

Unsaturated Ester 53. To a solution of 0.20 g (0.84 mmol) of lactone **52** in 5 mL of THF at −78 °C was added dropwise of 1.0 mL (1 mmol) of diisobutylaluminum hydride (1.0 M in THF). The mixture was stirred at −78 °C for 5 h, followed by the addition of 0.5 mL of saturated aqueous $NaHCO_3$. The mixture was warmed to rt, dried ($MgSO_4$), and concentrated in vacuo to afford 0.18 g of a pale yellow oil. To 0.13 g of the oil in 3 mL of chloroform was added 0.60 g (1.7 mmol) of Ph_3P=$CHCO_2Et$ in 3 mL of chloroform. The mixture was stirred at rt for 12 h, concentrated in vacuo and chromatographed on 10 g of silica gel (eluted with EtOAc-hexane (1:1)) to afford 0.13 g (68%) of unsaturated ester **53** as a pale yellow liquid: IR (CH_2Cl_2) 3660, 3600, 3400 (br), 1710, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.24 (t, J = 7.1 Hz, 3 H, CH_3), 1.44 (m, 1 H), 1.93–2.18 (m, 2 H), 2.46 (m, 2 H), 3.22 (m, 2 H), 3.53 (m, 2 H), 3.65 (s,.3 H, OCH_3), 4.13 (q, J = 7.1 Hz, 2 H, OCH_2), 4.58 (m, 1 H, CHO), 5.58 (m, 1 H, =CH), 5.81 (m, 2 H, =CH and $CHCO_2Et$), 7.07 (m, 1 H, CH=CCO_2Et); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.1 (q), 26.9 (t), 27.7 (t), 37.6 (d), 40.9 (d), 47.5 (t), 52.1 (q), 59.9 (t), 63.0 (d), 70.4 (d), 121.0 (d), 126.6 (d), 131.5 (d), 149.8 (d), 156.1 (s), 166.6 (s); exact mass calcd for $C_{16}H_{23}NO_5$ *m/z* 309.1576, found *m/z* 309.1563.

Amide 54 and Tetrahydrofuran 55. To a solution of 58.3 mg (0.19 mmol) of unsaturated ester **53** in 2 mL of xylenes was added 0.13 g (0.94 mmol) of *N,N*-dimethylacetamide dimethyl acetal in one portion. The mixture was warmed to reflux, heated for 3 h, cooled to rt, concentrated in vacuo, and chromatographed over 4 g of silica gel (eluted with EtOAc) to afford 32 mg (45%) of a mixture of tetrahydrofurans **55** as colorless oil: IR (CH_2Cl_2) 1710, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.24 (t, J = 7 Hz, 3 H, CH_3), 1.3–1.6 (m, 2 H), 2.0 (m, 2 H), 2.4–2.5 (m, 2 H), 2.63 (dd, J = 15.4, 6.7 Hz, 1 H, CH_2CO_2Et), 3.19–3.40 (m, 2 H), 3.41–3.65 (m, 2 H), 3.68 (s, 3 H, OCH_3), 4.14 (q, J = 7.1 Hz, 2 H, CH_2Me), 4.23 (m, 1 H, CHO), 4.54 (ddd, J = 8.6, 4.4, 1.3 Hz, 0.7 H, =CCHO), 4.73 (ddd, J = 9.7, 4.1, 3.1 Hz, 0.3 H, =CCHO), 5.84 (ddd, J = 9.6, 4.4, 3.0 Hz, 1 H, =CHCO), 5.90 (m, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 Mhz) δ 14.0 (q), 27.1 (d), 27.3 (t), 30.7 (t), 31.1 (t), 36.4 (d), 36.6 (d), 37.5 (d), 39.6 (d), 39.8 (t), 40.0 (t), 47.4 (t), 51.9 (q), 60.2 (t), 62.8 (d), 63.2 (d), 73.8 (d), 74.0 (d), 77.0 (d), 77.5 (d), 128.9 (d), 129.1 (d), 131.0 (d), 155.8 (s), 170.7 (s), 170.8 (s); exact mass calcd for $C_{16}H_{23}NO_5$ *m/z* 309.1576, found *m/z* 309.1539.

Continued elution afforded 29 mg (43%) of amide **54** as pale yellow oil: IR (CH_2Cl_2) 1750, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.28 (t, J = 7.1 Hz, 3 H, CH_3), 1.40–1.80 (m, 4 H), 1.98 (m, 1 H), 2.20–2.53 (m with dd at 2.45, J = 15.4, 5.5 Hz, 3 H, $CH_2C(O)NMe_2$), 2.68 (m, 1 H), 2.97 (s, 3 H, NCH_3), 3.02 (s, 3 H, NCH_3), 3.22 (m, 1 H), 3.48 (m, 1 H, NCH_2), 3.64–3.90 (m with s at 3.70, 4 H, OCH_3), 4.19 (q, J = 7.1 Hz, 2 H, OCH_2), 5.52–5.72 (m, 2 H, CH=CH), 5.83 (d, J = 15.5 Hz, 1 H, CHC(O)OEt), 7.0 (m, 1 H, CH=CC(O)OEt); mass spectrum *m/z* (relative intensity) 378 (M^+, 3), 333 (12), 265 (78), 178 (100); exact mass calcd for $C_{20}H_{30}N_2O_5$ *m/z* 378.2154, found *m/z* 378.2189.

Diol 26. To a mixture of 1.35 g (5.71 mmol) of lactone **52** and 0.54 g (14.3 mmol) of sodium borohydride in 29 mL of 2-methyl-2-propanol at 50 °C was added 6 mL of methanol over a period of 20 min. The mixture was stirred at 50 °C for 1 h and cooled to rt followed by addition of 20 mL of water. The solution was extracted with three 50-mL portions of CH_2Cl_2. The organic solution was dried ($MgSO_4$) and concentrated in vacuo to afford 1.38 g (100%) of diol **26** as colorless oil: IR (CH_2Cl_2) 3700, 3600, 3400, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz, 323 K) δ 1.42 (m, 2 H), 1.67 (m, 1 H), 1.95 (m, 1 H), 2.40 (m, 1 H), 3.22 (m, 3 H), 3.44–3.78 (m with s at 3.61, 6 H), 4.50 (m, 1 H, *CH*OH), 4.4–4.9 (br s, 2 H, OH, exchanges with D_2O), 5.60 (m, 1 H, =CH), 5.78 (m, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz, 323 K) δ 25.6 (t), 27.6 (t), 38.2 (d), 39.7 (d), 47.8 (t), 51.9 (q), 62.3 (t), 63.6 (d), 69.7 (d), 125.7 (d), 132.1 (d), 156.23 (s); exact mass calcd for $C_{12}H_{19}NO_4$ *m/z* 241.1314, found *m/z* 241.1341.

Tetrahydrofuran 56 and Acetate 57. To a solution of 76.5 mg (0.32 mmol) of diol **26** in 3 mL of xylenes was added 0.30 mL of *N,N*-dimethylacetamide dimethyl acetal in one portion. The mixture was warmed under reflux for 12 h, cooled to rt, concentrated in vacuo and chromatographed on 5 g of silica gel (eluted with EtOAc–hexane (1:1)) to afford 53.6 mg (75%) of tetrahydrofuran **56** as pale yellow oil: IR (CH_2Cl_2) 1710 cm^{-1}; ^1H NMR (C_6D_6, 250 MHz, 348 K) δ 1.02 (m, 1 H, CH_2CN), 1.38–1.58 (m, 2 H, CH_2CO and CH_2CN), 1.73 (m, 1 H, CH_2CO), 2.12 (m, 1 H, CHC=), 3.06 (m, 2 H, CHN and CH_2N), 3.38 (m, 2 H, CH_2O), 3.51 (s, 3 H, OCH_3), 3.47–3.67 (m, 3 H, CHCO and CH_2N), 4.45 (m, 1 H, CHO), 5.64 (m, 1 H, CH=CH); ^{13}C NMR (C_6D_6, 62.5 MHz, 348 K) δ 25.9 (t), 27.8 (t), 37.1 (d), 40.0 (d), 47.8 (t), 51.6 (q), 63.9 (d), 66.8 (t), 77.0 (d), 130.2 (d), 130.8 (d), 155.8 (s); exact mass calcd for $C_{12}H_{17}NO_3$ *m/z* 223.1208, found *m/z* 223.1177.

Continued elution afforded 12.0 mg (14%) of acetate **57** as a pale yellow oil: IR (neat film) 3465 (br), 1770, 1694 cm^{-1}; ^1H NMR (C_6D_6, 250 MHz, 348 K) δ 0.96 (m, 1 H), 1.32–1.78 (m, 4 H), 1.77 (s, 3 H, CH_3), 2.10 (m, 1 H), 2.94 (dd, J = 10.8, 3.0 Hz, 1 H), 3.08 (m, 1 H), 3.34 (m, 2 H), 3.50 (s, 3 H, OCH_3), 4.28 (br s, 1 H, OH), 4.33 (t, J = 7.3 Hz, 2 H, CH_2O), 5.41 (m, 2 H, CH=CH); ^{13}C NMR (C_6D_6, 62.5 MHz, 348 K) δ 20.6 (q), 23.5 (t), 27.9 (t), 37.8 (d), 39.3 (d), 48.0 (t), 51.6 (q), 63.7 (d), 64.7 (t), 71.1 (d), 126.4 (d), 132.5 (d), 156.1 (s), 170.4 (s); exact mass calcd for $C_{14}H_{21}NO_4$ *m/z* 267.1470, found *m/z* 267.1447.

Silyl Ether 58. To a solution of 92.4 mg (0.38 mmol) of diol **26** in 1.5 mL of CH_2Cl_2 was sequentially added 46.5 mg (0.46 mmol) of triethylamine, 1.8 mg (0.015 mmol) of 4-DMAP, and 69.3 mg (0.46 mmol) of *tert*-butyldimethylsilyl chloride. The mixture was stirred at rt for 2 h, concentrated in vacuo, and chromatographed on 5 g of alumina (eluted with EtOAc) to afford 131.4 mg (97%) of silyl ether **58** as a colorless oil: IR (neat film) 3418, 1681 cm^{-1}; ^1H NMR ($CDCl_3$, 500 Mhz, 323 K) δ 0.06 (s, 3 H, CH_3), 0.07 (s, 3 H, CH_3), 0.88 (s, 9 H, CH_3), 1.38 (m, 2 H, CH_2CN, CH_2COSi), 1.68 (m, 1 H, CH_2COSi), 1.94 (m, 1 H, CH_2CN), 2.35 (m, 1 H, CHC=), 3.18 (dd, J = 10.7, 2.9 Hz, 1 H, CHN), 3.19–3.32 (m, 2 H, CH_2N, CHCN), 3.57 (m, 2 H, CH_2O), 3.63 (s, 3 H, CH_3), 3.76 (ddd, J = 5.9, 4.8, 3.4 Hz, 1 H, CHO), 4.45 (s, 1 H, OH), 5.59 (m, 1 H, =CH), 5.66 (m, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 125 MHz, 323 K) δ −5.6 (q), 18.2 (s), 25.2 (t), 25.9 (q), 27.7 (t), 38.4 (d), 40.2 (d), 48.0 (t), 51.8 (q), 63.7 (d), 63.8 (t), 69.3 (d), 124.9 (d), 132.6 (d), 156.1 (s); mass spectrum *m/z* (relative intensity) 355 (M^+, 1), 298 ($M^+ - t$-Bu, 100); exact mass calcd for $C_{18}H_{33}NO_4Si$ *m/z* 355.2178, found *m/z* 355.2211.

Amide 59. To a solution of 0.76 g (2.14 mmol) of silyl ether **58** in 12 mL of xylenes was added 2.5 mL (17.1 mmol) of *N,N*-dimethylacetamide dimethyl acetal in one portion. The mixture was warmed under reflux for 4 h, cooled to rt, concentrated in vacuo, and chromatographed on 30 g of silica gel (eluted with EtOAc) to afford 0.84 g (93%) of amide **59** as pale yellow oil: IR (CH_2Cl_2) 1750, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 323 K) δ 0.06 (s, 6 H, $SiCH_3$), 0.82 (s, 9 H, CH_3), 1.22 (m, 1 H, CH_2CN), 1.38 (m, 1 H, CH_2CO), 1.61 (m, 2 H, CH_2CN and CH_2CO), 1.89 (m, 1 H, $CHCCONMe_2$), 2.19 (dd, J = 15.3, 8.4 Hz, 1 H, CH_2CONMe_2), 2.37 (dd, J = 15.3, 5.7 Hz, 1 H, CH_2CONMe_2), 2.58 (m, 1 H, CHCC=), 2.88 (s, 3 H, NCH_3), 2.94 (s, 3 H, NCH_3), 2.95 (m, 1 H, CHC=), 3.16 (m, 1 H, CH_2N), 3.32 (dd, J = 11.1, 5.3 Hz, 1 H, CHN), 3.60 (s, 3 H, OCH_3), 3.62–3.83 (m, 3 H, CH_2O and CH_2N), 5.48 (m, 1 H, =CH), 5.71 (m, 1 H, =CH); ^{13}C NMR (C_6D_6, 62.5 MHz, 348 K) δ −5.1 (q), 18.5 (s), 26.2 (q), 28.6 (t), 33.4 (t), 36.1 (d), 35.0–36.8 (br), 37.8 (t), 39.6 (d), 43.1 (t), 48.1 (t), 51.7 (q), 62.4 (t), 63.2 (d), 131.2 (d), 131.3 (d), 156.1 (s), 170.5 (s); mass

spectrum m/z (relative intensity) 424 (M^+, 1), 367 (89), 240 (q), 127 (6), 57 (4); exact mass calcd for $C_{22}H_{40}N_2O_4Si$ m/z 424.2757, found m/z 424.2704.

Iodo Lactone 61. A mixture of 0.54 g (1.27 mmol) of amide **59** and 1.0 g (3.93 mmol) of iodine in 4 mL of THF and 4 mL of water was stirred at rt under argon for 24 h. A solution of 2.0 g of sodium thiosulfate in 3 mL of water was added, the organic layer was separated, and the aqueous layer was extracted with two 15-mL portions of CH_2Cl_2. The organic solution was dried ($MgSO_4$), concentrated in vacuo, and chromatographed on 10 g of silica gel (eluted with EtOAc) to afford 0.39 g (75%) of iodo lactone **61** as white foam: IR (CH_2Cl_2) 3600, 1785, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.42–1.88 (m, 5 H), 2.06 (m, 1 H), 2.46 (d, J = 16.6 Hz, 1 H, CH_2CO), 2.67–2.85 (m, 2 H), 3.30 (m, 2 H), 3.69 (s, 3 H, OCH_3), 3.73 (m, 3 H, CH_2N and CH_2O), 3.97 (dd, J = 11.3, 3.9 Hz, 1 H, CHI), 4.89 (m, 1 H, CHO), 5.10 (s, 1 H, OH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 27.3 (t, d, two carbons), 30.9 (t), 35.9 (t), 37.7 (d), 38.6 (d), 41.3 (d), 46.9 (t), 52.4 (q), 60.0 (d), 61.3 (t), 84.1 (d), 156.2 (s), 174.9 (s); exact mass calcd for $C_{14}H_{20}INO_5$ m/z 409.0388, found m/z 409.0405.

Allylated Lactone 62. A mixture of 0.35 g (0.86 mmol) of iodo lactone **61**, 0.57 g (1.71 mmol) of allyltributyltin, and 28 mg (0.17 mmol) of AIBN in 10 mL of benzene was heated under reflux for 1 h. The solution was cooled to rt, followed by addition of 0.34 g (2.0 mmol) of DBU. The mixture was chromatographed on 10 g of silica gel (eluted with EtOAc) to afford 0.23 g (83%) of lactone **62** as colorless oil: IR (CH_2Cl_2) 3600, 1775, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.32–1.80 (m, 5 H), 2.03 (m, 1 H), 2.09–2.48 (m, 5 H), 2.70 (dd, J = 17.1, 6.7 Hz, 1 H, $CH_2C(O)$), 2.88 (br s, 1 H), 3.25 (ddd, J = 17.6, 11.1, 6.2 Hz, 1 H), 3.34 (dd, J = 11.7, 5.1 Hz, 1 H), 3.57–3.78 (m with s at δ 3.68, 6 H), 4.41 (dd, J = 4.3, 1.4 Hz, 1 H, CHO), 5.12 (m, 2 H, $=CH_2$), 5.85 (m, 1 H, $=CH$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 27.5 (t), 30.2 (t), 34.7 (d), 35.6 (t), 37.0 (t), 38.7 (d), 38.8 (d), 29.2 (d), 47.2 (t), 52.2 (q), 60.0 (d), 61.2 (t), 82.5 (d), 117.5 (t), 135.8 (d), 156.1 (s), 175.6 (s); exact mass calcd for $C_{17}H_{25}NO_5$ m/z 323.1733, found m/z 323.1722.

Alkylated Lactone 63. To a solution of 0.33 mL (2.32 mmol) of diisopropylamine in 14 mL of THF at 0 °C was added dropwise of 1.4 mL (2.23 mmol) of n-BuLi (1.6 M in hexane). The mixture was stirred at 0 °C for 10 min and cooled to −78 °C, followed by sequential addition of 1.5 mL of HMPA and a solution of 0.30 g (0.93 mmol) of lactone **62** in 0.5 mL of HMPA and 1.5 mL of THF. The mixture was stirred at −78 °C for 40 min followed by the dropwise addition of 0.60 mL (9.64 mmol) of methyl iodide. The mixture was stirred at −78 °C for 20 min, followed by addition of 0.5 mL of saturated aqueous NH_4Cl. The mixture was warmed to rt, dried ($MgSO_4$), concentrated in vacuo, and chromatographed on 6.0 g of silica gel (eluted with EtOAc–hexane (2:1)) to afford 26.4 mg (8%) of the methyl ether of **63** as pale yellow oil: IR (CCl_4) 1782, 1703 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz, 323 K) δ 1.23 (d, J = 7.5 Hz, 3 H, CH_3), 1.24–2.22 (m, 9 H), 2.44 (dq, J = 7.5, 2.6 Hz, 1 H, CHMe), 2.55 (m, 1 H), 3.12–3.28 (m, 4 H), 3.21 (s, 3 H, OCH_3), 3.31 (s, 3 H, OMe), 3.68 (m, 1 H), 4.40 (m, 1 H, CHO), 5.02 (m, 2 H, $=CH_2$), 5.73 (m, 1 H, $=CH$); ^{13}C NMR ($CDCl_3$, 62.5 MHz, 323 K) δ 14.2 (q), 27.4 (t), 28.2 (t), 35.0 (d), 36.4 (t), 40.2 (d, two carbons), 41.3 (d), 46.1 (d), 47.9 (t), 51.9 (q), 58.1 (q), 60.1 (d), 71.4 (t), 80.0 (d), 117.3 (t), 135.5 (d), 156.0 (s), 178.4 (s); exact mass calcd for $C_{19}H_{29}NO_5$ m/z 351.2046, found m/z 351.2027.

Continued elution afforded 0.27 g (87%) of alkylated lactone **63** as colorless oil: IR (CH_2Cl_2) 3600, 1780, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.30 (d, J = 7.5 Hz, 3 H, CH_3), 1.42 (m, 1 H, CH_2CN), 1.59 (m, 2 H), 1.80 (m, 2 H), 2.03 (m, 2 H), 2.22 (m, 3 H), 2.52 (dq, J = 7.5, 2.6 Hz, 1 H, CHMe), 2.79 (br s, 1 H), 3.28 (ddd, J = 17.5, 11.2, 6.2 Hz, 1 H, CH_2N), 3.33 (dd, J = 11.3, 4.9 Hz, 1 H, CHN), 3.64 (m, 3 H, OCH_2 and CH_2N), 3.67 (s, 3 H, OCH_3), 4.50 (dd, J = 5.5, 3.2 Hz, 1 H, CHO), 5.10 (m, 2 H, $=CH_2$), 5.82 (m, 1 H, $=CH$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.3 (q), 28.1 (t), 30.8 (t), 34.4 (d), 36.7 (t), 39.8 (d), 40.0 (d), 41.6 (d), 45.9 (d), 47.4 (t), 52.4 (q), 60.2 (d), 61.3 (t), 80.1 (d), 117.8 (t), 135.6 (d), 156.3 (s), 178.8 (s); exact mass calcd for $C_{18}H_{27}NO_5$ m/z 337.1889, found m/z 337.1908.

Aldehyde 64. To a solution of 35.9 mg (0.26 mmol) of oxalyl chloride in 3 mL of CH_2Cl_2 at −78 °C was added dropwise a solution of 44.2 mg (0.52 mmol) of DMSO in 1.5 mL of CH_2Cl_2. The mixture was stirred at −78 °C for 15 min followed by dropwise addition of 85.3 mg (0.25) of alkylated lactone **63** in 1.5 mL of CH_2Cl_2. The mixture was stirred at −78 °C for 15 min, followed by addition of 2 mL (14.4 mmol) of Et_3N. The solution was warmed to rt and partitioned between 20 mL of water and 20 mL of CH_2Cl_2. The aqueous layer was extracted with two 15-mL portions of CH_2Cl_2. The organic phase was dried ($MgSO_4$), concentrated in vacuo, and chromatographed on 10 g of silica gel (eluted with EtOAc–hexane (4:1)) to afford 84.3 mg (99%) of the aldehyde **64** as colorless oil: IR (CH_2Cl_2) 1785, 1730, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.26 (d, J = 7.5 Hz, 3 H, CH_3), 1.40 (m, 1 H, CH_2CN), 1.80 (m, 1 H, CH_2CN), 2.0–2.5 (m, 8 H), 3.2–3.4 (m, 3 H), 3.62 (s, 3 H, OCH_3), 3.68 (m, 1 H, CH_2CN), 4.46 (t, J = 5.5 Hz, 1 H, CHO), 5.10 (m, 2 H, $=CH_2$), 5.82 (m, 1 H, $=CH$), 9.60 (br s, 1 H, CH=O); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.3 (q), 28.2 (t), 32.6 (d), 36.1 (t), 40.5 (d), 41.1 (d), 42.7 (t), 45.7 (d), 47.8 (t), 52.4 (q), 59.4 (d), 79.5 (d), 118.0 (t), 135.0 (d), 156.3 (s), 178.4 (s), 201.2 (d) (broad methine appears to be obscured at about δ 40.8); exact mass calcd for $C_{18}H_{25}NO_5$ m/z 335.1733, found m/z 335.1715.

Unsaturated Ester 65. A mixture of 80.2 mg (0.24 mmol) of aldehyde **64** and 0.10 g (0.29 mmol) of $Ph_3P{=}CHCO_2Et$ in 3.0 mL of chloroform was heated under reflux for 20 min, cooled to rt, concentrated in vacuo, and chromatographed on 10 g of silica gel (eluted with EtOAc–hexane (4:1)) to afford 88.5 mg (91%) of ester **65** as colorless oil: IR (CH_2Cl_2) 1775, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.25 (t, J = 7.1 Hz, 3 H, CH_3), 1.27 (d, J = 7.5 Hz, 3 H, CH_3), 1.24–1.50 (m, 1 H, CH_2CN), 1.80 (m, 1 H, CHCN), 1.9–2.3 (m, 7 H), 2.48 (dq, J = 7.5, 2.8 Hz, 1 H, CHMe), 2.75 (br m, 1 H), 3.18 (m, 1 H), 3.34 (m, 1 H), 3.64 (s, 3 H, OCH_3), 3.70 (m, 1 H), 4.13 (q, J = 7.1 Hz, 2 H, OCH_2Me), 4.46 (t, J = 5.5 Hz, 1 H, CHO), 5.06 (m, 2 H, $=CH_2$), 5.80 (m, 2 H, $=CH$ and $CHCO_2Et$), 6.84 (m, 1 H, $CH{=}CCO_2Et$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.2 (q), 14.4 (q), 28.4 (t), 30.8 (t), 36.2 (t), 37.2 (d), 39.2 (d), 41.0 (d), 41.2 (d), 45.9 (d), 47.5 (t), 52.3 (q), 59.5 (d), 60.1 (t), 79.7 (d), 118.0 (t), 122.7 (d), 135.0 (d), 147.2 (d), 157.5 (s), 166.2 (s), 178.6 (s); exact mass calcd for $C_{22}H_{31}NO_6$ m/z 405.2151, found m/z 405.2128.

Ester 66. To a suspension of 0.14 g (0.85 mmol) of CuBr in 3 mL of dry THF at 0 °C was added dropwise 0.51 mL (1.7 mmol) of Red-Al (3.4 M in toluene). The mixture was cooled to −78 °C, followed by dropwise addition of 0.5 mL (0.85 mmol) of 2-butanol. The mixture was stirred to −78 °C, followed by dropwise addition of a solution of 70.5 mg (0.17 mmol) of ester **65** in 2 mL of THF. The mixture was stirred at −78 °C for 10 min and −20 °C for 1 h, followed by addition of 0.2 mL of saturated aqueous $NaHCO_3$. The mixture was warmed to rt, dried ($MgSO_4$), and concentrated in vacuo to afford 58.9 mg (85%) of ester **66** as pale yellow oil: IR (CH_2Cl_2) 1775, 1730, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.22 (t, J = 7.1 Hz, 3 H, CH_3), 1.29 (d, J = 7.5 Hz, 3 H, CH_3), 1.25–1.90 (m, 7 H), 1.9–2.05 (m, 2 H), 2.1–2.6 (m with dq (J = 7.5, 2.8 Hz), at δ 2.48 (6 H, =CCH), 3.25 (m, 2 H), 3.65 (s, 3 H, OCH_3), 3.70 (m, 1 H), 4.08 (q, J = 7.1 Hz, 2 H, OCH_2Me), 4.46 (m, 1 H, CHO), 5.08 (m, 2 H, $=CH_2$), 5.79 (m, 1 H, $=CH$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.1 (q), 14.3 (q), 23.2 (t), 26.9 (t), 28.2 (t), 34.4 (t), 36.5 (t), 37.5 (d), 39.3 (d), 40.2 (d), 41.5 (d), 46.0 (d), 47.8 (t), 52.1 (q), 60.1 (t, d, two carbons), 80.2 (d), 117.6 (t), 135.6 (d), 156.1 (s), 173.3 (s), 178.7 (s); exact mass calcd for $C_{22}H_{33}NO_6$ m/z 407.2308, found m/z 407.2280.

Amine 67. To a solution of 58.9 mg (0.15 mmol) of ester **66** in 0.5 mL of chloroform was added 0.10 mL (0.60 mmol) of iodotrimethylsilane in one portion. The mixture was stirred at rt for 2 h and partitioned between 10 mL of CH_2Cl_2, 1 mL of methanol, 3 mL of saturated aqueous sodium thiosulfate, and 10 mL of saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to afford 47.4 mg (94%) of amine **67** as pale yellow oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.23 (t, J = 7.1 Hz, 3 H, CH_3), 1.25 (d, J = 7.5 Hz, 3 H, CH_3), 1.25–2.3 (m, 14 H), 2.46 (dq, J = 7.5, 2.8 Hz, 1 H, CHMe), 2.78 (dd, J = 11.3, 5.1 Hz, 1 H, CHN), 2.90 (br s, 1 H), 3.08 (dd, J = 8.3, 6.1 Hz, 2 H, CH_2N), 4.09 (q, J = 7.1 Hz, 2 H, OCH_2Me), 4.45 (dd, J = 5.2, 3.8 Hz, 1 H, CHO), 5.07 (m, 2 H, $=CH_2$), 5.79 (m, 1 H, $=CH$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.1 (q), 14.3 (q), 24.1 (t), 26.5 (t), 29.4 (t), 34.1 (t), 36.4 (t), 37.9 (d), 39.7 (d), 39.7 (d), 42.1 (d), 44.7 (t), 46.7 (d), 60.3 (t), 60.4 (d), 80.6 (d), 117.6 (t), 135.6 (d), 173.7 (s), 179.1 (s); exact mass calcd for $C_{20}H_{31}NO_4$ m/z 249.2253, found m/z 349.2225.

Lactam 68. A solution of 54.2 mg (0.16 mmol) of amino ester **67** in 20 mL of mesitylene was heated under reflux for 4 h, cooled to rt, concentrated in vacuo, and chromatographed on 2 g of silica gel (eluted with EtOAc) to afford 43 mg (91%) of lactam **68** as white solid: mp 121–125 °C; IR (CH_2Cl_2) 1780, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.34 (d, J = 7.1 Hz, 3 H, CH_3), 1.30–2.50 (m, 15 H), 3.47 (m, 2 H, CH_2N), 3.74 (dd, J = 12.2, 9.0 Hz, 1 H, CHN), 4.42 (dd, J = 12.3, 9.2 Hz, 1 H, CHO), 5.12 (m, 2 H, $=CH_2$), 5.85 (m, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 15.41 (q), 22.2 (t), 23.0 (t), 27.8 (t), 33.0 (t), 33.8 (t), 35.1 (d), 39.7 (d), 41.6 (d), 44.4 (d), 45.6 (d), 46.7 (t), 60.3 (d), 78.4 (d), 118.5 (t), 133.9 (d), 171.0 (s), 178.4 (s); mass spectrum m/z (relative intensity) 303 (M^+, 12), 260 ($M^+ - C_3H_7$, 100), 189 (2); exact mass calcd for $C_{18}H_{25}NO_3$ m/z 303.1834, found m/z 303.1825.

Aldehyde 69. To a mixture of 50.1 mg (0.16 mmol) of lactam **68** and 8.5 mg (0.03 mmol) of osmium tetraoxide (1% in water) and 2 mL of THF and 2 mL of water was added 0.11 g (0.50 mmol) of sodium periodate in one portion. The mixture was stirred at rt for 30 min and partitioned between 10 mL of water and 10 mL of CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with two 10-mL portions of CH_2Cl_2. The organic solution was dried ($MgSO_4$) and concentrated in vacuo to afford 42.2 mg (84%) of aldehyde **69** as a white foam: IR (CH_2Cl_2) 1775, 1725, 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.29 (d, J = 7.1 Hz, 3 H, CH_3), 1.50 (m, 4 H), 1.70–2.50 (m, 10 H), 2.70 (ddd, J = 16.2, 6.3, 1.6 Hz, 1 H, CH_2CON), 3.38 (m, 1 H, CH_2N), 3.55 (dd, J = 11.4, 8.6 Hz, 1 H, CH_2N), 3.70 (dd, J = 12.2, 8.9 Hz, 1 H, CHN), 4.47 (dd, J = 12.0, 9.0 Hz, 1 H, CHO), 9.94 (t, J = 1.2 Hz, 1 H, CHO); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 15.2 (q), 22.1 (t), 22.9 (t), 27.6 (t), 32.7 (t), 37.2 (d), 37.3 (d), 39.4 (d), 44.1 (d), 45.0 (t), 45.2 (d), 46.8 (t), 60.1 (d), 79.4 (d), 170.9 (s), 177.8 (s), 200.1 (d); mass spectrum m/z (relative intensity) 305 (M^+, 31), 260 (45), 232 (46), 69 (100); exact mass calcd for $C_{17}H_{23}NO_4$ m/z 305.1627, found m/z 305.1663.

Thioacetal 70. A mixture of 40.0 mg (0.13 mmol) of aldehyde **69**, 0.20 g (2.13 mmol) of 1,2-ethanediol, and 80.0 mg of thionyl chloride coated silica gel in 2.5 mL of CH_2Cl_2 was stirred at rt for 12 h. The mixture was concentrated in vacuo and chromatographed on 5 g of silica gel (eluted with EtOAc–methanol (6:1)) to afford 50.0 mg (100%) of thioacetal **70** as a white solid: mp 187–190 °C; IR (CH_2Cl_2) 1770, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.30 (d, J = 7.1 Hz, 3 H, CH_3), 1.38–2.48 (m, 15 H), 3.18 (m, 4 H, CH_2S), 3.42 (m, 2 H, CH_2N), 3.68 (dd, J = 12.0, 9.0 Hz, 1 H, CHN), 4.38 (dd, J = 11.6, 9.0 Hz, 1 H, CHO), 4.75 (dd, J = 10.5, 4.7 Hz, 1 H, CHS_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.2 (q), 22.5 (t), 23.0 (t), 27.7 (t), 32.9 (t), 37.9 (t), 38.1 (d), 38.5 (t), 39.4 (d), 42.2 (d), 43.4 (t), 44.1 (d), 45.9 (d), 46.8 (t), 52.0 (d), 60.3 (d), 81.5 (d), 179.9 (s), 178.0 (s); mass spectrum m/z (relative intensity) 381 (M^+, 5), 353 (31), 262 (100); exact mass calcd for $C_{19}H_{27}NO_3S_2$ m/z 381.1432, found m/z 381.1517.

Thiolactam 71. A mixture of 42.0 mg (0.09 mmol) of thioacetal **70** and 74.2 mg (0.18 mmol) of Lawesson's reagent in 3.0 mL of CH_2Cl_2 was stirred at rt for 2 h. The mixture was chromatographed directly over 8 g of silica gel (eluted with EtOAc) to afford 43.2 mg (100%) of thiolactam **71** as a white solid: mp 255–260 °C dec; IR (CH_2Cl_2) 1784 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.34 (d, J = 7.1 Hz, 3 H, CH_3), 1.4–2.3 (m, 12 H), 2.47 (dq, J = 7.1, 2.4 Hz, 1 H, CHMe), 2.80 (m, 1 H, $CH_2C(S)N$), 3.02 (m, 1 H, $CH_2C(S)N$), 3.15–3.30 (m, 4 H, CH_2S), 3.68 (m, 2 H, CH_2N), 4.12 (dd, J = 13.9, 8.7 Hz, 1 H, CHN), 4.38 (dd, J = 11.9, 8.8 Hz, 1 H, CHO), 4.76 (dd, J = 10.5, 4.6 Hz, 1 H, CHS_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.3 (q), 22.9 (t), 24.7 (t), 27.7 (t), 37.9 (d), 37.9 (t), 38.5 (t), 39.3 (d), 42.1 (d), 42.5 (t), 43.1 (t), 44.4 (d), 45.7 (d), 51.9 (d), 55.1 (t), 65.5 (d), 81.1 (d), 177.7 (s), 199.3 (s); mass spectrum m/z (relative intensity) 397 (M^+, 45), 369 (7), 292 (4); exact mass calcd for $C_{19}H_{27}NO_2S_3$ m/z 397.1204, found m/z 397.1187.

***dl*-Stenine (4).** A mixture of 20.1 mg of thiolactam **71** and 0.48 g of W-2 Raney nickel in 2.5 mL of ethanol was heated under reflux for 1 h. The mixture was cooled to rt and filtered to afford 11.2 mg (80%) of stenine (**4**) as pale yellow oil: IR (CH_2Cl_2) 1770 cm^{-1}; ^1H NMR (C_6D_6, 250 MHz) δ 0.8–2.0 (m with t (J = 7.5 Hz) and d (J = 7.3 Hz) at δ 0.91 and 1.03, 22 H), 2.02–2.27 (m, 2 H), 2.63 (m, 1 H), 2.94 (m, 1 H), 3.98 (dd, J = 8.7, 11.4 Hz, 1 H, CHO); ^{13}C NMR (C_6D_6, 62.5 MHz) δ 10.2 (q), 15.1 (q), 23.0 (t), 26.3 (t), 27.8 (t), 30.0 (t), 30.1 (t), 40.1 (d), 40.4 (d), 42.7 (d), 43.2 (d), 47.3 (d), 52.8 (t), 54.9 (t), 67.3 (d), 79.6 (d), 178.0 (s); mass spectrum m/z (relative intensity) 277 (M^+, 30), 276 (100); exact mass calcd for $C_{17}H_{27}NO_2$ m/z 277.2042, found m/z 277.2027.

Acknowledgment. We thank the National Institutes of Health for support of this research.

Supplementary Material Available: Experimental procedures for compounds described in Figure 3, Table I, and Schemes I–III, ^1H and ^{13}C NMR spectra for compounds in Schemes IV–VI, and ORTEP drawings for compounds **52** and **68** (92 pages). This material is contained in libraries on microfiche, immediately follow this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.