Construction of the Azepinoindole Core Tricycle of the *Stemona* Alkaloids

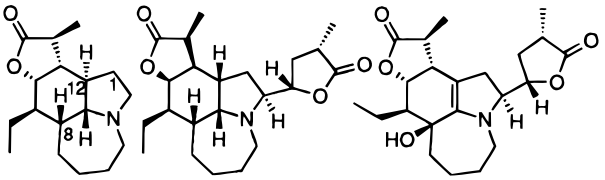
James H. Rigby,* Stéphane Laurent, Alexandre Cavezza, and Mary Jane Heeg†

Department of Chemistry, Wayne State University, Detroit, Michigan 48202-3489

Received May 13, 1998

The azepinoindole substructure common to a number of *Stemona* alkaloids is constructed by employing a 7-endo radical cyclization of a readily available N-alkylated hydroindolone substrate. The indolone precursors are prepared via [1 + 4] cycloaddition between a vinyl isocyanate and either dimethoxycarbene or cyclohexylisocyanide.

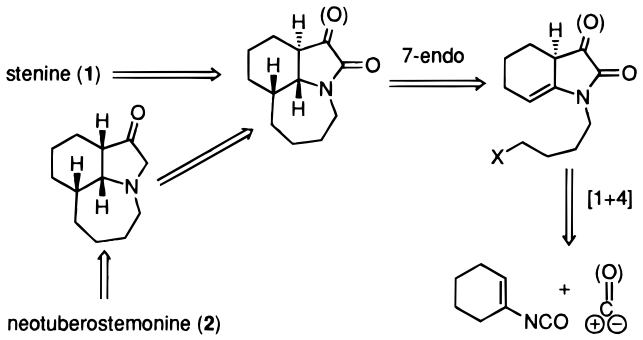
Traditional Chinese and Japanese folk medicines have long employed extracts of *Stemona tuberosa* as treatments for various respiratory diseases, including bronchitis, pertussis, and tuberculosis, and a number of structurally interesting alkaloids have recently been isolated from these extracts that may be responsible for much of this pharmacological activity.[1] The azepinoindole skeleton is a common structural motif shared by several of the *Stemona* alkaloids, including stenine (**1**),[2a] neotuberostemonine (**2**),[2b] and tuberostemonol (**3**),[2c] which has attracted considerable attention recently in the synthetic community.[3−5] We wish to report a novel strategy into this tricyclic ring system that is capable of selectively delivering each of the ring fusion themes present in compounds **1**−**3**.



1 **2** **3**

Scheme 1 depicts the basic features of our strategy directed toward azepinoindole construction within the context of stenine and neotuberostemonine as the target alkaloids. Rapid assembly of a highly functionalized hydroindolone building block via [1 + 4] cycloaddition between an appropriate vinyl isocyanate and one of several nucleophilic 1,1-dipole equivalents recently developed in our laboratory[6,7] followed by N-alkylation of the resultant enamide with a terminally functionalized four-carbon chain would set the stage for the crucial 7-*endo-trig* radical cyclization to produce the azepine ring moiety.[8,9] It is noteworthy that this strategy differs from most extant approaches into this ring system in that the stereochemical information in the vicinity of the azepine ring is set *during* the cycloheptannulation step. Most previous syntheses set this stereochemistry prior to closing the seven-membered ring onto the pyrrolidine nitrogen. It was anticipated that the syn-anti stereochemical relationship at the incipient ring fusion sites,

Scheme 1



† To whom correspondence regarding the X-ray structure determination should be addressed.

(1) Götz, M.; Strunz, G. M. In *Alkaloids: MTP International Review of Sciences*; Wiesner, K., Ed.; Series One; Butterworths: London, 1973; Vol. IX, pp 143−60.

(2) (a) Uyeo, S.; Irie, H.; Harada, H. *Chem. Pharm. Bull.* **1967**, *15*, 768. (b) Ye, Y.; Qin, G.-W.; Xu, R.-S. *Phytochemistry* **1994**, *37*, 1201. (c) Lin, W.-H.; Ye, Y.; Xu, R.-S. *J. Nat. Prod.* **1992**, *55*, 571.

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

(4) For additional approaches into the azepinoindole system, see: (a) Xiang, L.; Kozikowski, A. P. *Synlett* **1990**, 279. (b) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477. (c) Goldstein, D. M.; Wipf, P. *Ibid.* **1996**, *37*, 739.

(5) For approaches to other Stemona alkaloids not possessing the azepinoindole substructure, see: (a) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923. (b) Beddoes, R. L.; Davies, M. P. H.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1992**, 538. (c) Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, 55. (d) Morimoto, Y.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 5773. (e) Williams, D. R.; Reddy, J. P.; Amato, G. S. *Ibid.* **1994**, *35*, 6417. (f) Morimoto, Y.; Iwahashi, M. *Synlett* **1995**, 1221.

(6) Rigby, J. H.; Cavezza, A.; Ahmed, G. *J. Am. Chem. Soc.* **1996**, *118*, 12848.

(7) Rigby, J. H.; Qabar, M.; Ahmed, G.; Hughes, R. C. *Tetrahedron* **1993**, *49*, 10219.

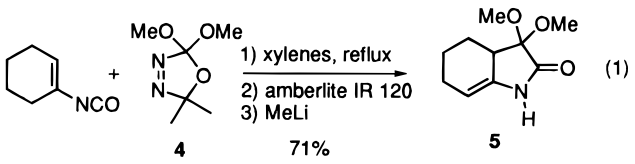
(8) For recent examples of 7-endo radical cyclizations, see: (a) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 84. (b) Andrés, C.; Duque-Soladana, J. P.; Iglesias, J. M.; Pedrosa, R. *Synlett* **1997**, 1391. (c) Lee, E.; Lim, J. W.; Yoon, C. H.; Sung, Y.-s.; Kim, Y. K.; Yun, M.; Kim, S. *J. Am. Chem. Soc.* **1997**, *119*, 8391. (d) Gibson, S. E.; Guillo, N.; Tozer, M. J. *J. Chem. Soc., Chem. Commun.* **1997**, 637. (e) Rodríguez, G.; Cid, M. M.; Saá, C.; Castedo, L.; Domínguez, D. *J. Org. Chem.* **1996**, *61*, 2780. (f) Mohanakrishnan, A. K.; Srinivasan, P. C. *Tetrahedron Lett.* **1996**, 37, 2659. (g) Moody, C. J.; Norton, C. L. *Ibid.* **1995**, *36*, 9051. (h) Brown, C. D. S.; Dishington, A. P.; Shishkin, O.; Simpkins, N. S. *Synlett* **1995**, 943. (i) Colombo, L.; Di Giacomo, M.; Papeo, G.; Carugo, O.; Scolastico, C.; Manzoni, L. *Tetrahedron Lett.* **1994**, *35*, 4031. (j) Ghosh, A. K.; Ghosh, K.; Pal, S.; Chatak, U. R. *J. Chem. Soc., Chem. Commun.* **1993**, 809. (k) Fidalgo, J.; Castedo, L.; Domínguez, D. *Tetrahedron Lett.* **1993**, *34*, 7317. (l) Koreeda, M.; Hamann, L. G. *J. Am. Chem. Soc.* **1990**, *112*, 8175. (m) Bachi, M. D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* **1983**, *48*, 1841. (n) Curran, D. P.; Chang, C. T. *J. Org. Chem.* **1989**, *54*, 3140.

(9) Rigby, J. H.; Qabar, M. N. *J. Org. Chem.* **1993**, *58*, 4473.

S0022-3263(98)00916-5 CCC: $15.00
Published on Web 07/09/1998

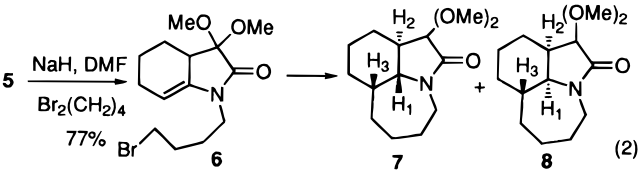
as present in stenine (**1**), would be obtained on the basis of the preferred stereochemical course of previous aryl radical cyclizations in related indolone substrates.[9] An additional feature of this strategy would be the capability of conveniently epimerizing the C-12 stereocenter to provide the presumably more stable all-cis arrangement as found in neotuberostemonine (**2**).[10]

A model study designed to test the feasibility of this concept began by exposure of 1-isocyanatocyclohexene to excess 2,2-dimethoxy-Δ^3-1,3,4-oxadiazoline (**4**) in refluxing xylenes to afford hydroindolone **5**[11] in excellent yield after selective removal of the N-substituent (eq 1).[6]



4 71% **5** (1)

Hydroindolone **5** was then treated with NaH in DMF followed by smooth N-alkylation with 1,4-dibromobutane to deliver the cyclization precursor **6**[11] in 77% yield. Exposure of **6** to several radical cyclization conditions led to various mixtures of isomeric azepinoindoles **7**[11] and **8**,[11] with the best yield and product ratio obtained using Ph_3SnH in refluxing benzene under slow addition conditions. The relevant coupling constants in the respective ^{1}H NMR spectra for **7** (J_{H1H2} = 10 Hz, J_{H1H3} = 5.5 Hz) and **8** (J_{H1H2} = 7.5 Hz, J_{H1H3} = 9.5 Hz) were fully consistent with the structures depicted in eq 2, and confirmation of the assignment for the major product **7** came from a single-crystal X-ray analysis of the corresponding thiolactam derivative (Lawesson's reagent/PhH, reflux).[12] It is presumed that the stereochemical course

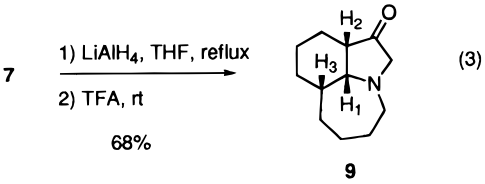


(2)

$(TMS)_3SiH$, AIBN, PhH	2	1 (49%)
$NaBH_4$, cat. Bu_3SnCl, t-BuOH	3	1 (50%)
Ph_3SnH, AIBN, PhH, slow add'n	5	1 (85%)

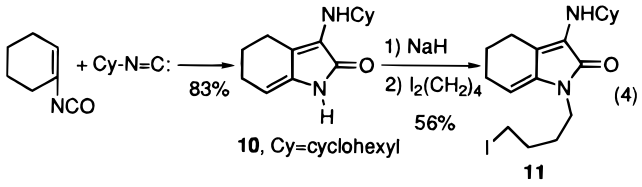
of the reaction producing **7** stems from steric approach controlled addition of the primary radical center to the enamide alkene followed by hydrogen atom abstraction from the more accessible face of the post-cyclization radical center to afford the desired stereochemical relationship at the three contiguous carbon centers. The stereochemical assignment for the minor product **8** remains tentative at this time. These results demonstrate that rapid access to the stereochemically correct azepinoindole moiety of stenine and related *Stemona* alkaloids can be achieved via a relatively rare 7-endo radical cyclization protocol.

With the syn-anti tricycle in hand, efforts to equilibrate the stereocenter at C-12 to the presumably more stable syn-syn isomer characteristic of neotuberostemonine (**2**) were then pursued. Thus, heating lactam **7** in the presence of lithium aluminum hydride (THF, reflux) followed by hydrolysis of the dimethoxy acetal afforded a new azepinoindole **9**[11] that exhibited bridgehead coupling patterns (J_{H1H2} = 4 Hz, J_{H1H3} = 4 Hz) in accord with those found in the natural product itself (J = 3.8, 3.9 Hz), suggesting that epimerization to the all cis isomer occurred rapidly during the acetal hydrolysis step.[2b] As a result of these events, two of the three ring fusion patterns frequently found among representatives of the *Stemona* alkaloid family can be accessed from a common hydroindolone precursor.



(3)

Entry into a third ring-fusion type, as exemplified by the recently isolated tuberostemonol (**3**),[2c] in which unsaturation is retained in the hydroindolone moiety required a slightly modified synthetic sequence, since it was envisioned that the cycloheptannulation was best accomplished in this case via an anion alkylation approach. In this instance, the functionalized hydroindolone intermediate could be derived from a [1 + 4] cycloaddition between a vinyl isocyanate and an alkyl isocyanide serving as the 1,1-dipole equivalent.[7] In the event, room-temperature cycloaddition between 1-isocyanatocyclohexene and cyclohexyl isocyanide afforded hydroindolone **10**[11] in 83% yield,[13] and routine enamide N-alkylation with 1,4-diiodobutane followed to give cyclization precursor **11**[11] in good yield. Heating this



(4)

material in the presence of EtMgBr (diglyme, 120 °C) afforded the desired tricyclic enamide **12**[11] in 70% yield, presumably through the intermediacy of the corresponding metalloenamine.[14] Mild hydrolysis of the enamine function to the corresponding hydroisatin derivative, which exists primarily in the enol form,[15] followed by treatment with *m*-CPBA at −15 °C afforded exclusively the desired oxidation product **14**[11,16] in 93% yield, wherein reaction occurred at the γ-position of the extended enol to give the ring fusion pattern found in tuberostemonol (**3**).[2c] The regioselectively exhibited during this oxidation

(10) Calculations (SYBYL force field) performed on Spartan SGI (copyright 1991−95, Wave Function, Inc.) suggest that the all-cis ring fusion stereochemistry is more stable than the cis−trans isomer by at least 1 kcal/mol. We thank Sylvie Bosio of this department for performing these calculations.

(11) This compound exhibited spectral (^{1}H NMR, ^{13}C NMR, IR) and analytical (combustion analysis and/or HRMS) data in complete accord with the assigned structure.

(12) X-ray data for this compound have been deposited with the Cambridge Crystallographic Data Centre.

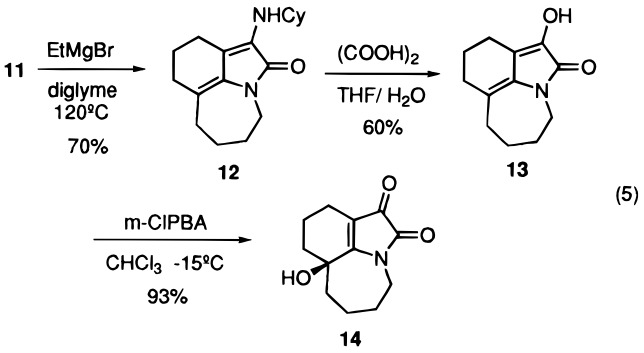
(13) Rigby, J. H.; Qabar, M. *J. Am. Chem. Soc.* **1991**, *113*, 8975.

(14) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178.

(15) Rigby, J. H.; Mateo, M. E. *Tetrahedron* **1996**, *52*, 10569.

(16) Compound **14** exhibited a UV spectrum (MeOH, λ_{max} (nm) = 256, 430) characteristic of the chromophore present in the assigned structure.

process finds ample precedent in the reactions of this functionality with other electrophilic reagents in related hydroindolone substrates.[17]



(5)

In conclusion, rapid access to three azepinoindole substructures commonly found among the *Stemona* alkaloids can be efficiently achieved from a reaction sequence involving either a radical or a metalloenamine-based cycloheptannulation step.

Experimental Section[18]

3,3-Dimethoxy-3a,4,5,6-tetrahydroindol-2-one (5). Cyclohexene-1-carboxylic acid (2.5 g, 19.8 mmol) and triethylamine (3.3 mL) were dissolved in benzene (25 mL), and the solution was stirred at room temperature for 30 min. After the solution was cooled to 0 °C, diphenyl phosphorazidate (6.54 g, 23.8 mmol) was added dropwise to the reaction mixture, and stirring was continued for an additional 30 min at this temperature. After removal of the benzene, the residue was filtered through a plug of silica gel [pentane/1% ether] to afford 2.76 g (92%) of the pure acyl azide as a colorless oil. This compound (2.76 g, 18.3 mmol) was then dissolved in a solution containing xylenes (30 mL) and 2,2-dimethoxy-Δ^3-1,3,4-oxadiazoline (7.31 g, 45.7 mmol), and the reaction mixture was gently refluxed for 2 h. After being cooled to room temperature, the reaction was diluted in H_2O (50 mL) and extracted with EtOAc (3 × 50 mL), the combined organic layers were dried (anhydrous $MgSO_4$), and as much solvent as possible was removed in vacuo. The residue was chromatographed (4:1 hexanes/EtOAc) to afford 3,3-dimethoxy-1-(dimethoxymethyl)-3a,4,5,6-tetrahydroindol-2-one (3.91 g, 79% from the acyl azide) as a white solid: mp = 86−7 °C (pentane).

To this oxoindole (3.60 g, 13.3 mmol) in acetone (50 mL) was added Amberlite IR-120 (6.0 g) at −15 °C. The solution was stirred at that temperature for 7 days. The Amberlite was removed by filtration and the acetone evaporated in vacuo. The residue was chromatographed (4:1 hexanes/EtOAc) to afford 3,3-dimethoxy-1-formyl-3a,4,5,6-tetrahydroindol-2-one (2.51 g, 84%): mp = 74−5 °C (pentane).

To this indole (2.30 g, 10.2 mmol) in dry THF (80 mL) was added dropwise MeLi (1.4 M in ether, 8.8 mL, 12.3 mmol) at −78 °C. The reaction was then immediately quenched with saturated aqueous ammonium chloride solution (80 mL). The aqueous layer was extracted with EtOAc (3 × 80 mL), and the combined organic layers were washed with brine and dried (anhydrous $MgSO_4$). Column chromatography (2:1 hexanes/EtOAc) afforded the product **5** (2 g, 100%) as a white solid: mp = 148−50 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00−1.60 (m, 1H), 1.70−1.95 (m, 3H), 2.00−2.16 (m, 2H), 2.70−2.75 (m, 1H), 3.40 (s, 6H), 5.03 (q, J = 3.6 Hz, 1H), 8.74 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 22.3, 22.8, 44.9, 50.5, 51.2, 99.3, 101.4, 133.9, 170.7; IR ($CDCl_3$) 3272, 2931, 1738, 1683, 1035 cm^{-1}; mass spectrum (EI) *m/e* (rel int) 197 (55), 169 (100), 122 (33), 101 (35); HRMS calcd for $C_{10}H_{15}O_3N$ 197.1052, found 197.1050. Anal. Calcd for $C_{10}H_{15}O_3N$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.96; H, 7.69; N, 7.12.

1-(4-Bromobutyl)-3,3-dimethoxy-1,3,3a,4,5,6-hexahydroindol-2-one (6). To a stirred suspension of NaH (60% dispersion in mineral oil, 0.609 g, 15.2 mmol) in DMF (60 mL) was added dropwise a solution of **5** (2 g, 10.1 mmol) in DMF (10 mL) at 0 °C. The reaction mixture was allowed to come to room temperature over 1 h, after which time 1,4-dibromobutane (4.38 g, 20.3 mmol) was added dropwise at 0 °C. The reaction mixture was stirred overnight at room temperature and then quenched with water (150 mL) and the aqueous layer extracted with ether (3 × 100 mL). The combined organic layers were dried (anhydrous $MgSO_4$), and the solvent was removed in vacuo. The crude product was chromatographed (4:1 hexanes/EtOAc) to afford 2.61 g (77%) of **6** as a white solid: mp 65−6 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.97 (q, J = 3.0 Hz, 1H), 3.57 (m, 1H), 3.44−3.41 (m, 2H), 3.40 (s, 3H), 3.37 (s, 3H), 2.70−2.61 (m, 1H), 2.20−1.00 (m, 10H); ^{13}C NMR ($CDCl_3$, DEPT, 75 MHz) δ 168.4 (C), 136.4 (C), 99.5 (CH), 99.2 (C), 51.2 (CH_3), 50.5 (CH_3), 44.1 (CH), 38.5 (CH_2), 33.1 (CH_2), 29.6 (CH_2), 25.3 (CH_2), 23.0 (CH_2), 22.5 (CH_2), 21.5 (CH_2); IR ($CHCl_3$) 1717, 1675 cm^{-1}; mass spectrum (EI) *m/e* (rel int) 331 (M^+, 13), 303 (13), 252 (21), 55 (100); HRMS calcd for $C_{14}H_{21}BrNO_3$ (M^+) 331.0783, found 331.0781. Anal. Calcd for $C_{14}H_{21}BrNO_3$: C, 50.61; H, 6.67; N, 4.22. Found: C, 50.67; H, 6.73; N, 4.17.

3,3-Dimethoxydodecahydroazepino[3,2,1-*hi*]indol-2-one (7, 8). To a refluxing solution of **6** (200 mg, 0.60 mmol) dissolved in degassed benzene (60 mL) was added a solution of Ph_3SnH (254 mg, 0.72 mmol) and AIBN (20 mg, 0.12 mmol) in degassed benzene (60 mL) via a syringe pump over 2.5 h. Upon completion of the addition, the reaction mixture was refluxed for 30 min and then allowed to come to room temperature. After evaporation of the solvent, the residue was dissolved in MeOH (20 mL), KF (160 mg) was added, and the suspension was stirred for 1.5 h. The MeOH was replaced by 30 mL of CH_2Cl_2 and filtered through Celite 512 to give, after evaporation, a thick oil. The crude ^{1}H NMR spectrum indicated a 5:1 mixture of diastereomers for the cyclized product. Column chromatography (2:1 hexanes/EtOAc) gave 130 mg (85%) of **7** and **8** as a thick colorless oil that consisted of a 5:1 mixture of the two diastereomers. Compounds **7** and **8** were detected by TLC as blue spots of R_f = 0.15 (2:1 hexanes/EtOAc) using cobalt(II) thiocyanate as a reagent for visualization. The two diastereomers were separated by chromatography (Chromatotron 2 mm plate, 4:1 hexanes/EtOAc) to afford the pure compounds as colorless oils. Major isomer **7**: ^{1}H NMR (CD_3OD, 500 MHz) δ 3.98−3.93 (m, 1H), 3.48 (dd, J = 10.0, 5.5 Hz, 1H), 3.41 (s, 3H), 3.32 (s, 3H), 2.75 (dt, J = 12.0, 1.0 Hz, 1H), 2.20 (m, 1H), 1.96 (dt, J = 10.0, 3.0 Hz, 1H), 1.91−1.19 (m, 12H); ^{13}C NMR ($CDCl_3$, DEPT, 125 MHz) δ 168.6 (C), 100.2 (C), 60.2 (CH), 51.5 (CH_3), 50.6 (CH_3), 47.0 (CH), 40.2 (CH_2), 38.0 (CH), 31.3 (CH_2), 31.0 (CH_2), 29.7 (CH_2), 28.9 (CH_2), 24.3 (CH_2), 21.8 (CH_2); IR (film) 1696 cm^{-1}; mass spectrum (EI) *m/e* (rel int) 253 (M^+, 7), 238 (13), 223 (81), 208 (100), 101 (58); HRMS calcd for $C_{14}H_{23}NO_3$ (M^+) 253.1678, found 253.1683.

Minor isomer **8**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.59 (dt, J = 13.5, 3.5 Hz, 1H), 3.43 (s, 3H), 3.41 (s, 3H), 3.36 (dt, J = 14.0, 4.5 Hz, 1H), 3.23 (dd, J = 9.5, 7.5 Hz, 1H), 2.39 (m, 1H), 2.0−0.9 (m, 13H); ^{13}C NMR (CD_3OD, DEPT, 125 MHz) δ 169.8 (C), 101.3 (C), 59.8 (CH), 49.7 (CH_3), 49.5 (CH_3), 43.8 (CH_2), 42.1 (CH), 40.7 (CH), 37.6 (CH_2), 30.5 (CH_2), 27.1 (CH_2), 25.4 (CH_2), 22.8 (CH_2), 21.6 (CH_2); IR (film) 1696 cm^{-1}; mass spectrum (EI) *m/e* (rel int) 253 (M^+, 7), 238 (13), 223 (81), 208 (100), 101 (58); HRMS calcd for $C_{14}H_{23}NO_3$ (M^+) 253.1678, found 253.1683.

3,3-Dimethoxy-dodecahydroazepino[3,2,1-*hi*]indole-2-thione. To a stirred solution of **7** (53 mg, 0.21 mmol) in toluene (4 mL) was added Lawesson's reagent (85 mg, 0.21 mmol). The reaction mixture was refluxed for 1.5 h and then allowed to come to room temperature, at which point the solvent was removed in vacuo. The residue was directly chromatographed (10:1 hexanes/EtOAc) to afford 48 mg (85%) of the expected product as a yellow solid: mp 128 °C (hexanes/

(17) Qabar, M. Ph.D. Thesis, Wayne State University, 1991.

(18) General experimental details have been described previously: Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Cuisiat, S. V.; Ferguson, M. D.; Henshilwood, J. A.; Krueger, A. C.; Ogbu, C. O.; Short, K. M.; Heeg, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 1382.

EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.77 (m, 1H), 3.49 (s, 3H), 3.48 (s, 3H), 3.70 (dd, J = 10.2, 5.7 Hz, 1H), 2.90 (t, J = 12.6 Hz, 1H), 2.24 (m, 1H), 2.00−1.25 (m, 13H); ^{13}C NMR ($CDCl_3$, DEPT, 75 MHz) δ 195.9 (C), 103.6 (C), 66.8 (CH), 51.3 (CH_3), 50.9 (CH_3), 47.8 (CH), 45.6 (CH_2), 37.6 (CH), 31.6 (CH_2), 29.5 (CH_2), 28.8 (CH_2), 28.3 (CH_2), 25.0 (CH_2), 21.5 (CH_2); IR ($CHCl_3$) 1477, 1421 cm^{-1}; msss spectrum (EI) *m/e* (rel int) 269 (M^+, 12), 239 (34), 224 (100); HRMS calcd for $C_{14}H_{23}NO_2S$ (M^+) 269.1449, found 269.1456;

Dodecahydroazepino[3,2,1-*hi*]indol-3-one (9). To a stirred solution of LAH (516 mg, 13.60 mmol in 40 mL of dry THF) was added **7** (688 mg, 2.72 mmol) in solution in THF (20 mL) at room temperature. The reaction mixture was gently refluxed for 2 h. After cooling to 0 °C, the reaction was quenched by adding dropwise a saturated aqueous potassium sodium tartrate solution (60 mL), and the biphasic mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with EtOAc (3 × 70 mL), and the combined organic layers were dried (anhydrous $MgSO_4$) and evaporated in vacuo to give the crude 3,3-dimethoxy-dodecahydroazepino-[3,2,1-*hi*]indole that was used in the next step without purification. Alternatively, the pure product can be isolated by chromatography (1:1 $CHCl_3$/MeOH) as a colorless oil in 80% yield: ^{1}H NMR (CD_3OD, 500 MHz) δ 3.22 (s, 3H), 3.20 (s, 3H), 2.91 (d, J = 10.5 Hz, 1H), 2.84 (d, J = 10.5 Hz, 1H), 2.83 (m, 1H), 2.64 (dd, J = 12.0, 6.0 Hz, 1H), 2.46 (ddd, J = 14.0, 9.5, 3.0 Hz, 1H), 2.04 (m, 2H), 1.89−1.35 (m, 12H); ^{13}C NMR (CD_3-OD, DEPT, 125 MHz) δ 107.3 (C), 68.8 (CH), 63.1 (CH_2), 50.6 (CH_2), 48.7 (CH_3), 47.7 (CH_3), 44.9 (CH), 38.3 (CH), 31.9 (CH_2), 28.1 (CH_2), 27.9 (CH_2), 27.3 (CH_2), 25.0 (CH_2), 20.6 (CH_2); IR (film) 2914, 1142 cm^{-1}; mass spectrum (EI) *m/e* (rel int) 239 (M^+, 14), 224 (100), 192 (22); HRMS calcd for $C_{14}H_{25}NO_2$ (M^+) 239.1885, found 239.1885. Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.00; H, 10.40; N, 5.78.

The crude compound was dissolved in CH_2Cl_2 (10 mL), and trifluoroacetic acid (12 mL) was added dropwise at 0 °C. The reaction mixture was allowed to come to room temperature and then stirred for 2 h. After completion of the reaction, a 1.0 M solution of $NaHCO_3$ was added until the pH became neutral. The biphasic solution was stirred for 30 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried (anhydrous $MgSO_4$) and concentrated in vacuo. The residue was chromatographed (2:1 hexanes/EtOAc + 1% triethylamine) to afford 356 mg (68% yield from **7**) of **9** as a light yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.62 (d, J = 18.5 Hz, 1H), 2.9 (dt, J = 13.0, 3.5 Hz, 1H), 2.78 (d, J = 18.5 Hz, 1H), 2.70 (t, J = 4.0 Hz, 1H), 2.38 (m, 2H), 1.86−1.25 (m, 13H); ^{13}C NMR ($CDCl_3$, DEPT, 125 MHz) δ 216.3 (C), 69.1 (CH), 65.1 (CH_2), 55.6 (CH_2), 50.3 (CH), 37.4 (CH), 31.4 (CH_2), 27.8 (CH_2), 26.6 (CH_2), 24.9 (CH_2), 23.7 (CH_2), 20.8 (CH_2); IR (film) 1752 cm^{-1}; mass spectrum (EI) *m/e* (rel int) 193 (M^+, 33), 165 (100), 164 (57), 122 (54); HRMS calcd for $C_{12}H_{19}NO$ (M^+) 193.1466, found 193.1465.

3-(Cyclohexylamino)-5,6-dihydro-2-oxo-4*H*-indole (10). To 1-cyclohexene-1-carboxylic acid (10.0 g, 80 mmol) in toluene (35 mL) at room temperature was added Et_3N (8.1 g, 80 mmol) followed, after 20 min, by the addition of diphenyl phosphorazidate (21.74 g, 80.0 mmol) at 0 °C over a period of 20 min. After 30 min, the solution was reduced in volume to 10 mL followed by passing through a plug of silica gel (pentane/2% ether) to give, after solvent evaporation under reduced pressure, the pure acyl azide (10.0 g, 67.0 mmol). Heating the azide in acetonitrile (50 mL) at reflux for 30−40 min afforded the isocyanate, which after cooling to room temperature was treated with cyclohexyl isocyanide (7.3 g, 67.0 mmol) and allowed to stir at that temperature overnight. The precipitate was filtered and washed with a minimun amount of acetonitrile to afford the pure product (11.9 g, 83% from acyl azide): mp 145−146 °C (CH_3CN); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (br s, 1H), 5.32 (t, J = 4.5 Hz, 1H), 3.94 (d, J = 9.3 Hz, 1H), 3.29 (m, 1H), 2.60 (dd, J = 6.0, 6.0 Hz, 2H), 2.24 (q, J = 5.4 Hz, 2H), 1.95 (m, 2H), 1.81−1.72 (m, 4H), 1.61 (m, 1H), 1.33−1.09 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.5, 136.6, 130.4, 106.5, 104.5, 52.1, 34.3, 25.7, 24.8, 23.8, 23.7, 22.5; IR (KBr) 3372, 1685 cm^{-1}; mass spectrum (EI) *m/e* (rel int) 232 (M^+, 100), 189 (64), 150 (98), 135 (15); HRMS calcd for $C_{14}H_{20}N_2O$ 232.1575, found 232.1578. Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.39; H, 8.67; N, 12.06. Found: C, 72.38; H, 8.61; N, 12.09.

3-(Cyclohexylamino)-1-(4-iodobutyl)-1,4,5,6-tetrahydroindol-2-one (11). To a stirred suspension of NaH (60% dispersion in mineral oil, 450 mg, 11.2 mmol) in DMF (80 mL) was added dropwise a solution of **10** (2 g, 8.62 mmol) in DMF (10 mL) at 0 °C. The reaction mixture was allowed to come to room temperature over 1 h, after which time 1,4-diiodobutane (13.4 g, 43.10 mmol) was added dropwise at 0 °C. The reaction mixture was stirred overnight at room temperature and then quenched with water (180 mL). The aqueous layer was extracted with ether (3 × 100 mL), and the combined organic layers were dried (anhydrous $MgSO_4$) and evaporated in vacuo. The crude product was chromatographed (10:1 hexanes/EtOAc) to afford 2 g (56%) of **11** as a yellow solid: mp 83 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.27 (t, J = 5.0 Hz, 1H), 3.94 (br s, 1H), 3.53 (t, J = 7.0 Hz, 2H), 3.27 (m, 1H), 3.18 (t, J = 6.5 Hz, 2H), 2.57 (t, J = 6.0 Hz, 2H), 2.25 (q, J = 6.0 Hz, 2H), 1.93 (m, 2 H), 1.80−1.10 (m, 14H); ^{13}C NMR ($CDCl_3$, DEPT, 125 MHz) δ 166.8 (C), 138.8 (C), 129.8 (C), 104.4 (C), 102.4 (CH), 52.1 (CH), 37.8 (CH_2), 34.3 (CH_2), 30.5 (CH_2), 29.9 (CH_2), 25.7 (CH_2), 24.8 (CH_2), 23.8 (CH_2), 23.6 (CH_2), 22.5 (CH_2), 6.5 (CH_2); IR ($CHCl_3$) 3365, 1682, 1639 cm^{-1}; mass spectrum (EI) *m/e* (rel int) 414 (M^+, 95), 287 (77), 205 (100); HRMS calcd for $C_{18}H_{27}IN_2O$ (M^+) 414.1168, found 414.1174. Anal. Calcd for $C_{18}H_{27}IN_2O$: C, 52.16; H, 6.57; N, 6.76. Found: C, 52.27; H, 6.55; N, 6.69.

1-(Cyclohexylamino)-4,5,6,7,8,9-hexahydro-10*H*-azepino-[3,2,1-*hi*]indol-2-one (12). A solution of **11** (400 mg, 0.96 mmol) in dry diglyme (10 mL) was cooled to 0 °C, and a fresh solution of EtMgBr (1.16 mL, 1.0 M in THF) was added dropwise. Stirring was continued at 0 °C for 30 min, after which time a dark brown solution was obtained. This solution was heated to 120 °C for 30 min, and the reaction color changed from dark brown to light red. After being cooled to 0 °C, the reaction was quenched with water (10 mL) and stirring was continued for 30 min at room temperature. After extraction of the crude product with CH_2Cl_2 (3 × 20 mL), the solvent was removed in vacuo and the excess of diglyme was evaporated under vacuum (0.3 mmHg/30 °C). The residue was chromatographed (10:1 hexanes/EtOAc) to afford 194 mg (70%) of **12** as a yellow solid that became greenish on standing at room temperature: mp 95 °C dec (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.80 (br s, 1H), 3.70 (m, 2H), 3.27 (m, 1H), 2.52 (t, J = 6.5 Hz, 2H), 2.33 (m, 2H), 2.19 (t, J = 5.0 Hz, 2H), 1.94 (m, 2H), 1.82−1.10 (m, 14 H); ^{13}C NMR ($CDCl_3$, DEPT, 125 MHz) δ 167.7 (C), 134.9 (C), 128.9 (C), 120.1 (C), 108.5 (C), 52.3 (CH), 43.5 (CH_2), 34.8 (CH_2), 34.4 (CH_2), 31.9 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 25.8 (CH_2), 24.8 (CH_2), 23.4 (CH_2), 22.5 (CH_2); IR ($CHCl_3$) 3351, 1668 cm^{-1}; mass spectrum (EI) *m/e* (rel int) 286 (M^+, 100), 243 (51), 204 (65); HRMS calcd for $C_{18}H_{26}N_2O$ (M^+) 286.2045, found 286.2042.

1-Hydroxy-4,5,6,7,8,9-hexahydro-10*H*-azepino[3,2,1-*hi*]-indol-1-one (13). In THF (10 mL) was dissolved **12** (460 mg, 1.60 mmol), an aqueous solution of oxalic acid dihydrate (2.03 g, 16.1 mmol, 4 mL of water) was added, and the resulting red mixture was gently refluxed for 24 h. Water (20 mL) was then added, and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic layers were dried (anhydrous $MgSO_4$) and evaporated in vacuo to give the crude product, which was recrystallized from acetone to afford 160 mg of **13** as light orange needles. The mother liquor was chromatographed (2:1 hexanes/EtOAc) to give 38 mg of **13**. The overall yield of the hydrolysis was 60%: mp 193 °C (acetone); ^{1}H NMR($CDCl_3$, 500 MHz) δ 7.88 (br s, 1H), 3.72 (m, 2H), 2.49 (t, J = 6.0 Hz, 2H), 2.37 (m, 2H), 2.22 (t, J = 6.0 Hz, 2H), 1.85−1.71 (m, 6H); ^{13}C NMR ($CDCl_3$, DEPT, 125 MHz) δ 166.6 (C), 138.2 (C), 132.5 (C), 125.9 (C), 116.1 (C), 44.5 (CH_2), 35.7 (CH_2), 32.2 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 22.8 (CH_2), 20.2 (CH_2); IR ($CHCl_3$) 3224, 1647 cm^{-1}; mass spectrum (EI) *m/e* (rel int) 205 (M^+, 100), 188 (25), 177 (29); HRMS calcd for $C_{12}H_{15}NO_2$ (M^+) 205.1102, found 205.1100. Anal. Calcd for

$C_{12}H_{15}NO_2$: C, 70.21; H, 7.37; N, 6.83. Found: C, 70.06; H, 7.41; N, 6.74.

7a-Hydroxy-4,5,6,7,8,9-hexahydro-10*H*-azepino[3,2,1-*hi*]indole-1,2-dione (14). In $CHCl_3$ (1.5 mL) was dissolved **13** (37 mg, 0.18 mmol); after the reaction mixture was cooled to −10 °C (MeOH/ice bath), *m*-CPBA (38 mg, 0.22 mmol) in $CHCl_3$ (0.5 mL) was added dropwise. After the reaction mixture was stirred at −10 °C for 30 min, it was allowed to come to room temperature. The solvent was evaporated, and the red residue was applied directly to a chromatography column (2:1 hexanes/EtOAc) to afford 37 mg (93%) of **14** as dark red crystals: mp 186 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.24 (m, 1H), 3.21 (t, J = 12.5 Hz, 1H), 2.37 (br s, 1H), 2.21 (dt, J = 16.5 Hz, 4.5 Hz, 1H), 2.07 (m, 1H), 2.01−1.92 (m, 4H), 1.84 (m, 1H), 1.77−1.65 (m, 4H), 1.29 (dq, J = 12.5, 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, DEPT, 125 MHz) δ 185.3 (C), 169.7 (C), 157.8 (C), 108.8 (C), 69.1 (C), 41.5 (CH_2), 40.9 (CH_2), 40.2 (CH_2), 29.6 (CH_2), 23.5 (CH_2), 18.9 (CH_2), 18.5 (CH_2); IR ($CHCl_3$) 3457, 1717, 1604 cm^{-1}; UV λ_{max} 256, 430 nm; mass spectrum (EI) *m*/*e* (rel int) 221 (M^+, 100), 175 (98), 109 (40); HRMS calcd for $C_{12}H_{15}NO_3$ (M^+) 221.1052, found 221.1054. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.13; H, 6.83; N, 6.33. Found: C, 65.14; H, 6.82; N, 6.29.

Acknowledgment. The authors wish to thank the National Science Foundation for their generous support of this research.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for **12**, **13** and **14**. Crystallographic data for the thiolactam derivative of **7** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO980916C