2.38–2.90 (m, 2 H), 3.09 (ddd, 1 H, J = 17, 5, 1 Hz), 3.64–3.91 (m, 1 H), 4.18, 4.19, (2 q, 2 H, J = 6 Hz), 6.73, 7.0 (2 s, 1 H); mass spectrum, m/e 171 ($M^{+\cdot}$), 143. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.10; H, 7.80; N, 8.02.

Preparation of 4-(4-Methoxy-2,4-dioxobutyl)azetidin-2-one (6j) and 4-(1-Methoxy-1,3-dioxo-2-butyl)azetidin-2-one (6k). As in the foregoing examples, reaction of diene **11**[12] and β-lactam **10** and chromatography on Kieselgel H (eluant EtOAc–pentane) gave **6j**[14] (524 mg, 56%) as a colorless oil: IR (CH_2Cl_2) 3400, 1750, 1715 cm^{-1}; NMR ($CDCl_3$) δ 2.62 (ddd, 1 H, J = 15, 2.5, 1 H), 2.85 (dd, 1 H, J = 18, 8.5 Hz), 3.06 (dd, 1 H, J = 18, 4 Hz), 3.17 (ddd, 1 H, J = 15, 5, 2.5 Hz), 3.5 (s, 2 H), 3.73 (s, 3 H), 3.96 (m, 1 H), 6.40 (br s, 1 H). **6k**[14] (281 mg, 30%) as a colorless oil: IR (CH_2Cl_2) 3400, 1770, 1740, 1715 cm^{-1}; NMR ($CDCl_3$) δ 2.29 (s, 3 H), 2.68 (dt, 1 H, J = 15, 3 Hz), 3.18 (ddd, 1 H, J = 15, 5, 3 Hz), 3.7 (m, 1 H), 3.8 (s, 3 H), 4.15 (m, 1 H), 6.2 (br s, 1 H).

Attempted Preparation of 4-(4-Methoxy-2,4-dioxobutyl)-azetidin-2-one (6j) from Diketene. Me_3SiOMe (490 mg) and $Me_3SiOSO_2CF_3$ (0.1 g) were added to β-lactam **10** (1.005 g) and diketene (420 mg) in dry CH_2Cl_2 (20 mL) at −78 °C. After stirring for 1 h at −78 °C the mixture was added to KF in MeOH (5% w/v, 100 mL) and stirred for 0.5 h. After evaporation in vacuo the residue was extracted with CH_2Cl_2 (4 × 40 mL), filtered, and concentrated in vacuo. Chromatography on Kieselgel H (15 g) gave (eluant EtOAc–pentane) methyl acetoacetate (522 mg, 90%) and 4-methoxyazetidin-2-one (**2b**)[3] (450 mg, 89%) both identical with authentic samples.

4-[[Methoxy(thiocarbonyl)]thio]azetidin-2-one (2g). Carbon disulfide (760 mg) was added dropwise to NaOMe [from Na (0.23 g) in dry MeOH (5 mL)]. The resulting solution was added to β-lactam (**2a**)[3] (1.29 g) in dry THF (30 mL) at −40 °C. The mixture was subsequently stirred at room temperature for 1 h, added to ice, and extracted with EtOAc (3 × 50 mL). The extract was washed with water, dried ($MgSO_4$), and evaporated, and the residue was chromatographed on Kieselgel H to give (eluant EtOAc:hexane 1:9) β-lactam **2g** (965 mg, 54%) as colorless needles: mp 54–55 °C (from Et_2O–i-Pr_2O); NMR ($CDCl_3$) δ 2.97 (ddd, 1 H, J = 15, 3, 1 Hz), 3.49 (ddd, 1 H, J = 15, 6, 2 Hz), 4.2 (s, 3 H), 5.41 (dd, 1 H, J = 6, 3 Hz), 7.18 (br s, 1 H); mass spectrum, m/e 177 ($M^{+\cdot}$), 149, 117, 108. Anal. Calcd for $C_5H_7NO_2S_2$: C, 33.86; H, 3.98; N, 7.90; S, 36.18. Found: C, 34.16; H, 4.01; N, 7.62; S, 35.89.

4-[(Thiobenzoyl)thio]azetidin-2-one (2h). Zinc bis(dithiobenzoate)[21] (2 g) and β-lactam **2a** (1.29 g) in dry PhH (70 mL) were stirred for 24 h at room temperature. Evaporation in vacuo and chromatography on the residue on Kieselgel H gave (eluant hexane:EtOAc 9:1) **2h** (940 mg, 42%) as red plates: mp 89–90 °C (from Me_2CO); IR 3410, 1770 cm^{-1}; NMR ($CDCl_3$) δ 3.12 (ddd, 1 H, J = 15, 3, 1 Hz), 3.56 (ddd, 1 H, J = 15, 6, 2 Hz), 5.5 (dd, 1 H, J = 6, 3 Hz), 6.9 (br s, 1 H), 7.2–8.1 (m, 5 H); mass spectrum, m/e $M^{+\cdot}$ absent, 176, 105, 85, 83. Anal. Calcd for $C_{10}H_9NOS_2$: C, 53.79; H, 4.06; N, 6.27; S, 28.71. Found: C, 53.67; H, 4.0; N, 6.3; S, 28.76.

4-(Phenylseleno)azetidin-2-one (2i). $NaBH_4$ (400 mg) was added in portions to PhSeSePh (1.56 g) in dry EtOH (24 mL) and the mixture was stirred at room temperature for 30 min. β-Lactam **2a** (1.29 g) in EtOH (4 mL) was added and stirring continued for 1 h. After filtration through Kieselgel H, the solution was evaporated and the residue chromatographed on Kieselgel H to give (eluant hexane:EtOAc 9:1) **2i** (1.80 g, 79%) as colorless needles: mp 59–60 °C (from CCl_4); IR (CH_2Cl_2) 3400, 1770, 1340, 960, 940 cm^{-1}; NMR ($CDCl_3$) δ 3.02 (dt, 1 H, J = 17, 2 Hz), 3.49 (ddd, 1, H J = 17, 6, 2 Hz), 5.2 (dd, 1 H, J = 6, 2 Hz), 6.96 (br s, 1 H), 7.4–7.75 (m, 5 H); mass spectrum, m/e 226 ($M^{+\cdot}$), 157. Anal. Calcd for C_9H_9NOSe: C, 47.8; H, 4.0; N, 6.2. Found: C, 47.51; H, 3.96; N, 6.26.

Acknowledgment. We thank both the Science and Engineering Research Council and Imperial Chemical Industries PLC Pharmaceutical Division for generous support both at Imperial College and Northwestern University.

Registry No. **2a**, 28562-53-0; **2g**, 77705-30-7; **2h**, 89691-17-8; **2i**, 89691-18-9; **6c**, 76127-62-3; **6d**, 80675-57-6; **6e**, 80675-56-5; **6f**, 89691-19-0; **6g**, 76127-66-7; **6h**, 79260-92-7; **6i**, 79261-32-8; **6j**, 77960-47-5; **6k**, 77960-48-6; **8a**, 89691-20-3; **9a**, 13735-81-4; **9h**, 58518-76-6; **9c**, 54731-27-0; **9d**, 37471-46-8; **9e**, 80675-54-3; **9f**, 86593-93-3; **9g**, 80675-53-2; **10**, 80675-59-8; **11**, 67609-52-3; $EtCO_2CH_2Ph$, 122-63-4; PhSAc, 934-87-2; diethyl malonate, 105-53-3.

(21) Houben, J. *Chem. Ber.* **1906**, *39*, 3219.

Cationic Cyclizations of Ketene Dithioacetals. A General Synthesis of Pyrrolizidine, Indolizidine, and Quinolizidine Alkaloid Ring Systems

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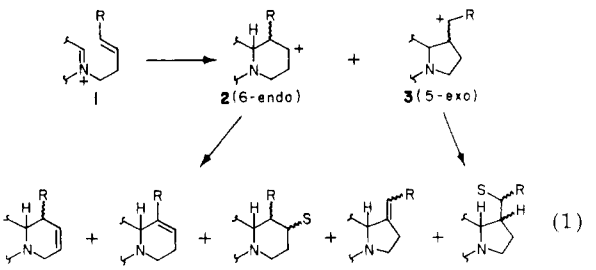
Received November 7, 1983

Cyclizations of ketene dithioacetals have been applied to the synthesis of pyrrolizidine, indolizidine, and quinolizidine alkaloid ring systems. This new cationic cyclization terminator allows the efficient formation of 5-, 6-, and 7-membered heterocyclic rings, as illustrated by the preparation of **10a–e**. Several of these products, available in three steps, have been converted into the known alkaloids (±)-supinidine, (±)-trachelanthamidine, (±)-elaeokanine A, and (±)-*epi*-lupinine.

Cationic cyclization is a common method of ring closure in alkaloid synthesis. Simple iminium ions, formed in any number of ways,[1] often initiate this process, although acyl iminium ions can prove to be superior because of their greater reactivity and ease of formation.[2] In planning such cyclizations one must give careful consideration not only



(1)

to the initiator but also to the internal nucleophile (terminator) for the reaction. The choice of a terminator can

(1) (a) Rapoport, H. *Lect. Heterocycl. Chem.* **1978**, *4*, 47. (b) Falling, S. N.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 1260 and references therein. (c) See also: Cook, A. G., Ed. "Enamines"; M. Dekker: New York, 1968.

(2) Acyliminium cyclizations in alkaloid synthesis have been reviewed: Speckamp, W. N. *Recl. Trav. Chem. Pays-Bas* **1981**, *100*, 345.

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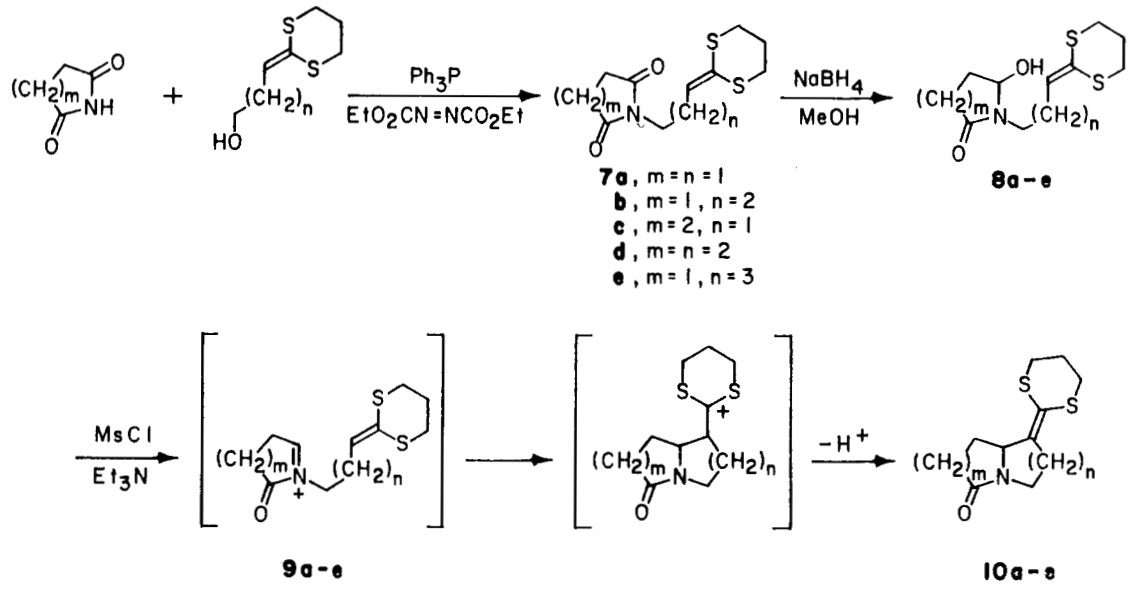


(2)

Table I. Ring Systems Prepared by Reduction/Cyclization of 7a-e

imide	m	n	cyclized product	overall yield, %
7a	1	1	10a	86
7b	1	2	10b	70
7c	2	1	10c	71
7d	2	2	10d	79
7e	1	3	10e	48

be a critical one because two modes of ring closure, endo and exo,[3] often are competitive. The cyclization of 1, for example, can give two carbocationic intermediates, 2 and 3, and it can be difficult to control which of these ring sizes will predominate.[4] Furthermore, either of these carbocations can go on to several different products via elimination or trapping by various nucleophiles (for example, solvent SH), as shown. Thus, even if only one of the two possible carbocations is produced, a number of cyclized products may be formed. Both of these problems tend to limit the usefulness of such cationic cyclizations unless a judicious choice of terminator and/or reaction conditions is made. In an attempt to find a terminator that would overcome these drawbacks, we reasoned that a ketene dithioacetal (2-dithianylalkylidene) group would have a number of the attributes of an ideal terminator, and in this paper we report our studies on acyl iminium ion initiated cyclizations of ketene dithioacetals for the synthesis of pyrrolizidine, indolizidine, and quinolizidine alkaloid ring systems.

Results and Discussion

The rationale for choosing the ketene dithioacetal terminator was based in part on earlier reports that protonation of this type of electron-rich alkene, while surprisingly difficult, generates exclusively the sulfur-stabilized carbocation, as might be expected.[5] While several other electrophiles exhibit similar regioselectivities,[6] there were no examples of *intramolecular* electrophilic attack on ketene dithioacetals. We therefore prepared the precursor **8a** and in a preliminary published study[7] described its clean cyclization to the 5,5-ring system **10a**, bearing out our prediction.

Two modifications of conventional methodology for acyl iminium formation were made for this cyclization. First, although the usual procedure[8] for reduction of *N*-alkyl imides to hydroxy lactams calls for sodium borohydride in ethanol, with the repeated addition of sulfuric acid, we found that it is more convenient to carry out the reaction simply with an excess of sodium borohydride in *methanol*[9] at −4 °C. Stopping the reaction before overreduction occurs is easily accomplished extractively by simply pouring the reaction mixture into a stirred aqueous bicarbonate–methylene chloride mixture. The resulting hydroxy lactam recovered from the organic layer is suitable for cyclization with no further purification other than drying. This procedure works well in all cases attempted (**7a-e**).

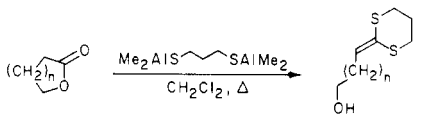
The second modification was to develop conditions for forming acyl iminium ions in a nonacidic medium. The usual conditions (formic acid or ethanolic HCl)[2] were presumed to be too acidic for the assured survival of the electron-rich terminator, so that we instead converted the hydroxy lactam into the mesylate (CH_3SO_2Cl, Et_3N, CH_3Cl_2, −20 °C → 20 °C).[10] This product is not observed, however, because it undergoes rapid elimination to the desired acyl iminium ion, followed by cyclization (exclusively "exo" with respect to the terminator) and loss of a proton to give a new, cyclic ketene dithioacetal in good yield.

We have tested the generality of this mesyl chloride induced cyclization sequence in a number of other ring systems, and the reaction proves to be general for 5-, 6-, and 7-membered ring formation. Examples are shown in Table I. In all cases the appropriate ketene dithioacetal

(3) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(4) Iminium ion cyclizations usually give 6-membered rings in preference to five when the internal nucleophile is a double bond, although there are a number of examples in which either mixtures or mainly the 5-membered rings are obtained.[1,2]
(5) Carey, F. A.; Neergaard, J. R. *J. Org. Chem.* **1971**, *36*, 2731.
(6) For a review of ketene dithioacetal chemistry, see: Kolb, M. In "The Chemistry of Functional Groups"; Patai, S., Ed.; Wiley: New York, 1980; Chapter 16.
(7) (a) Chamberlin, A. R.; Chung, J. Y. L. *Tetrahedron Lett.* **1982**, *23*, 2619. (b) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1982**, *105*, 3653.
(8) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437. Dibal has also been used for this reduction: Hart, D. J.; Kanai, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 1255.
(9) This reduction succeeds in methanol (whereas overreduction occurs in ethanol without added acid) presumably because of the greater solubility of $NaBH_4$ in methanol. The reduction step thus can proceed at a faster rate relative to unimolecular opening of the hydroxy lactam, the step which leads to overreduction. An excess of borohydride is essential.
(10) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.

alcohol was coupled with either succinimide or glutarimide via the Mitsunobu reaction.[11] Imide reduction followed by cyclization of the crude hydroxy lactam afforded in most cases 70–80% yields, after flash chromatography, of the bicyclic products shown. Formation of the 7-membered ring suffers somewhat from competitive transformation of the acyl iminium ion into double bond isomers; however, the yield of pure cyclic product is still approximately 50%. Attempted formation of a 4-membered ring failed.

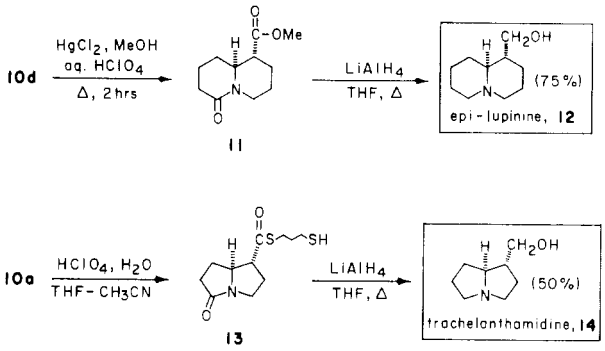
The homologous ketene dithioacetal alcohols used in the coupling reaction were prepared in one step by modification of Corey's method of protecting lactones as their cyclic dithio ortho esters.[12] By avoiding the acid-catalyzed ring closure called for in this procedure, a high yield of the desired ketene dithioacetal alcohol is obtained, and it is coupled with the appropriate imide without further purification.



(3)

4a, n = 1 (butyrolactone) **4b**, n = 1
5a, n = 2 (valerolactone) **5b**, n = 2
6a, n = 3 (caprolactone) **6b**, n = 3

Two major advantages of the ketene dithioacetal cyclizations described in this paper are predictable ring size and production of only one major cyclization product. A third attribute is that the product contains a synthetically versatile group for further elaboration of the newly formed ring. To illustrate this latter point, and to assist in proving the structures, several of the products shown in Table I were converted into known alkaloids. For example, **10d**

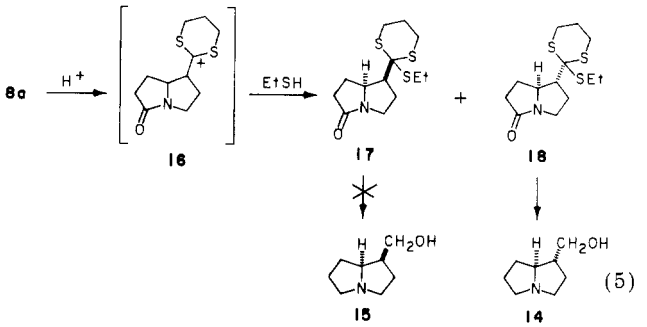


(4)

undergoes hydrolysis/methanolysis followed by reduction to give (±)-*epi*-lupinine (**12**)[13] in 75% yield. Note that the first step produces only the thermodynamically more stable equatorial ester diastereomer. Little or none of the corresponding carboxylic acid is produced despite the fact that aqueous perchloric acid is used. A related sequence in the 5,5-ring system (**10a**) produces (±)-trachelanthamidine (**14**),[14] again illustrating production of the thermodynamically more stable ester diastereomer (**13**) in the hydrolysis step.

Many unsuccessful attempts were made in this 5,5-ring system to achieve "kinetic protonation" from the convex face during the hydrolysis step, a reaction that would give the ester diastereomer leading to (±)-isoretronecanol (**15**).[14] Because that strategy failed, we were forced to consider alternative methods. One possibility was to trap the initial cyclized sulfur-stabilized carbocation (**16**), formed from **8a** by treatment with mesyl chloride, *before* elimination to the usual ketene dithioacetatal product, in hopes that cyclization itself would produce the desired stereochemistry (normally lost during elimination). Conflicting literature precedents[15] made it unclear as to which diastereomer should prevail, in addition to the obvious potential problem in this case of competitive trapping of the acyl iminium ion by the nucleophile. A number of mesyl chloride induced cyclizations were nevertheless attempted in the presence of added nucleophiles, but without success.

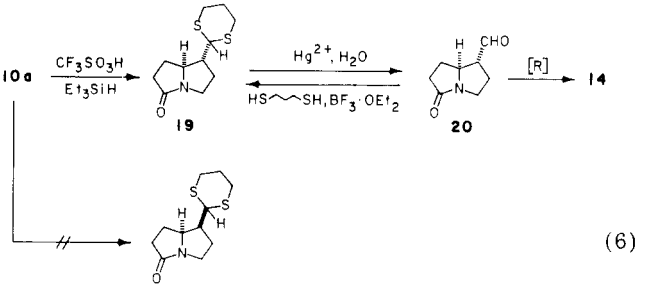
We then conducted the analogous acid-catalyzed cyclizations and found, somewhat to our surprise, that cyclization proceeded quite smoothly. For example, **8a** was



(5)

converted into **10a** simply by treatment with trifluoroacetic acid in methylene chloride at room temperature (89% yield). This ketene dithioacetal product predominated in the presence of large excesses of most nucleophiles tested, including mild aqueous acid solution (dilute aqueous HCl is sufficiently acidic to induce cyclization of **8a** but *not* hydrolysis of the product **10a**. See Experimental Section). Finally, we were able to trap **16** (generated from **8a** by treatment with CF_3SO_3H in dichloromethane) with ethanethiol to give what we believe is a 3:1 mixture of the diastereomeric trithio ortho esters (**17** and **18**), but we have as yet been unable to achieve clean hydrolysis of **17** to the ester corresponding to isoretronecanol (**15**), although **18** was converted into **14**.

Other attempts at obtaining the isoretonecanol stereochemistry by nonaqueous protonation of **10a** from the



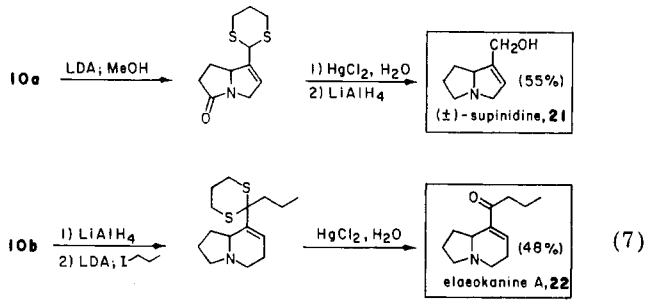
(6)

convex face followed by trapping of the thiolenium ion with triethylsilane[16] also were unsuccessful, giving mainly the dithiane **19** as shown by hydrolysis and reduction to trachelanthamidine (**14**).[14] The aldehyde intermediate **20** could be reconverted into **19**, ($HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$), confirming the stereochemical assignments as shown, and ruling out epimerization during dithiane hydrolysis or handling of the aldehyde. These acid-catalyzed cyclizations, while not achieving their intended purpose of pro-

(11) Mitsunobu, O. *Synthesis* **1981**, 1.
(12) Corey, E. J.; Beames, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 5829.
(13) (a) Van Tamelen, E. E.; Foltz, A. L. *J. Am. Chem. Soc.* **1960**, *82*, 502. (b) Weinreb, S. M.; Bremmer, M. L. *Tetrahedron Lett.* **1983**, 261.
(14) For a comprehensive review of pyrrolizidine alkaloids, see: Robins, D. J. *Fortschritte Chem. Org. Naturst.* **1981**, *41*, 8.
(15) (a) Stevens, R. V.; Luh, Y.; Sheu, J. T. *Tetrahedron Lett.* **1976**, 3799. (b) Takano, S.; Ogawa, N.; Ogasawara, K. *Heterocycles* **1981**, *16*, 915. The differing stereochemical results might be attributable to epimerization of the sensitive aldehyde under conditions described in ref b.
(16) Carey, F. A.; Court, A. S. *J. Org. Chem.* **1982**, *37*, 1926.

viding access to isoretronecanol (**15**), do clearly illustrate that the ketene dithioacetal terminator is compatible with an acidic cyclization medium, despite our earlier supposition to the contrary.

It is also possible to carry out regioselective double bond migration, based on the earlier work of Seebach in carbocyclic and acyclic systems.[17] Specifically, deprotonation of **10a** (LDA, HMPT) followed by protonation α to sulfur produces a protected α,β-unsaturated aldehyde, which is hydrolyzed and reduced to give (±)-supinidine (**21**)[14] in



(7)

55% yield for the three steps. In an analogous manner, **10b**, after reduction to the amine with lithium aluminum hydride, undergoes deprotonation and α-alkylation with propyl iodide.[17] Mercuric ion hydrolysis gives elaeokanine A (**22**)[18] in 50% yield. In this case the alkylation sequence returns ca. 20% of starting material, either because of incomplete deprotonation or competitive E_2 elimination. Conditions for deprotonation/alkylation in this system were not optimized, however.

In conclusion, the ketene dithioacetal group has proved to be an excellent cationic cyclization terminator in acyl iminium ion initiated cyclizations. The annulation sequence described requires only simple precursors and proceeds in good yield. The ring size is predictable in all cases examined, "exo" cyclization being the exclusive mode of ring closure. The product of the reaction is itself a ketene dithioacetal, which is a versatile group for further elaboration of the newly formed ring. Studies on the use of this terminator in the synthesis of other alkaloids and of carbocyclic ring systems are in progress.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 283 spectrophotometer. ^{1}H magnetic resonance spectra were obtained on a Bruker WM 250 (250 MHz) spectrometer unless otherwise stated; a Varian Associates FT 80A (80 MHz) was used where specified. Spectra are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), and integration. Melting points were taken on a Laboratory Devices melting point apparatus and are reported uncorrected. Mass spectra were recorded on a Finnegan 9610 spectrometer at 70 eV. Elemental analyses were performed either by Galbraith Laboratories, Inc. or by Atlantic Microlab, Inc.

When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran (THF) was distilled from potassium benzophenone ketyl. Dichloromethane was dried over activated alumina and distilled from calcium hydride. Thin-layer chromatography (TLC) was performed on E. Merck precoated silica gel plates (60F-254). Flash chromatography was performed on silica gel 200–400 mesh (Merck).

General Procedure for Preparation of Ketene Dithioacetals.[12] 1,3-Propanedithiol (10 mL, 0.10 mol) was added dropwise to a solution of trimethylaluminum (110 mL of a 2 M solution in toluene, 0.22 mol) and dichloromethane (200 mL) at −78 °C. The resulting solution was removed from the ice bath and stirred for 30 min. To the reaction flask was then added a solution of either butyrolactone, valerolactone, or caprolactone (0.10 mol) and dichloromethane (200 mL). The resulting clear solution was heated at reflux for 20 h, cooled to room temperature, concentrated in vacuo, and taken up in ether. Water was added dropwise very slowly until bubbling ceased. The resulting suspension was dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo to give the crude ketene dithioacetal alcohol, which was used immediately in the next reaction without purification. All ketene dithioacetal alcohols showed characteristic triplets for the vinyl proton (δ ~5.9) and for the two protons on the carbon bearing the -OH group (δ ~3.6). The ketene dithioacetal alcohol was converted cleanly to the cyclic protected lactone in the NMR tube after 1 day. This transformation can be monitored by TLC (ketene dithioacetal alcohol R_f ~0.50 in ether, cyclic protected lactone R_f ~0.70 in ether).

General Procedure for Preparation of N-Substituted Imides (7a–e).[11] To a solution of the ketene dithioacetal alcohol (36 mmol, crude), triphenylphosphine (10.4 g, 40 mmol), either succinimide or glutarimide (36 mmol), and THF (30 mL) was added dropwise a solution of diethyl azodicarboxylate (6.96 g, 40 mmol) in THF (16 mL). The resulting solution was stirred overnight and then concentrated in vacuo. Ether was added to the residue, and after removal of a white precipitate the solution was concentrated and purified by flash chromatography to give the N-substituted imides (**7a–e**) described below.

***N*-(3-(1,3-Dithian-2-ylidene)propyl)-2,5-pyrrolidinedione (7a).** Flash chromatography (silica gel, ether) of the crude product from the reaction of succinimide with **4b** gave a 51% yield of **7a** as a white solid: IR ($CDCl_3$) 1713, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.84 (t, J = 7.6 Hz, 1 H), 3.57 (t, J = 6.9 Hz, 2 H), 2.84 (m, 4 H), 2.69 (br s, 4 H), 2.50 (q, J = 6.9 Hz, 2 H), 2.13 (m, 2 H); MS (EI, 70 eV), m/e (relative intensity) 257 (M^+, 19).

***N*-(4-(1,3-Dithian-2-ylidene)-*n*-butyl)-2,5-pyrrolidinedione (7b).** Flash chromatography (silica gel, ether) of the crude product from the reaction of succinimide with **5b** gave a 62% yield of **7b** as an oil: IR (thin film) 1705, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.87 (t, J = 7.3 Hz, 1 H), 3.50 (t, J = 7.3 Hz, 2 H), 2.81 (m, 4 H), 2.69 (s, 4 H), 2.16 (m, 4 H), 1.83 (m, 2 H); MS (EI, 70 eV), m/e (relative intensity) 271 (M^+, 23).

***N*-(3-(1,3-Dithian-2-ylidene)propyl)-2,6-piperidinedione (7c).** Flash chromatography (silica gel, ether:petroleum ether (3:1)) of the crude product from the reaction of glutarimide with **4b** gave a 37% yield of **7c** as an oil: IR (thin film) 1736, 1680, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.86 (t, J = 7.7 Hz, 1 H), 3.83 (t, J = 7.0 Hz, 2 H), 2.82 (m, 4 H), 2.63 (m, 4 H), 2.47 (q, J = 7.2 Hz, 2 H), 2.12 (m, 2 H), 1.93 (m, 2 H); MS (EI, 70 eV), m/e (relative intensity) 271 (M^+, 14).

***N*-(4-(1,3-Dithian-2-ylidene)-*n*-butyl)-2,6-piperidinedione (7d).** Flash chromatography (silica gel, ether:petroleum ether (4:1)) of the crude product from the reaction of glutarimide with **5b** gave a 60% yield of **7d** as an oil: IR (thin film) 1730, 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.21 (t, J = 7.3 Hz, 1 H), 3.74 (m, 2 H), 2.84 (m, 2 H), 2.63 (t, J = 6.5 Hz, 2 H), 2.19 (m, 2 H), 2.14 (m, 4 H), 1.92 (m, 2 H), 1.84 (m, 2 H), 1.60 (m, 2 H); MS (EI, 70 eV), m/e (relative intensity) 285 (M^+, 13).

***N*-(5-(1,3-Dithian-2-ylidene)-*n*-pentyl)-2,5-pyrrolidinedione (7e).** Flash chromatography (silica gel, ether) of the crude product from the reaction of succinimide with **6b** gave a 65% yield of **7e** as an oil: IR (thin film) 1698, 1585 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 5.84 (t, J = 7.2 Hz, 1 H), 3.47 (t, J = 7.2 Hz, 2 H), 2.83 (m, 4 H), 2.67 (s, 4 H), 2.10 (m, 4 H), 1.5 (m, 4 H).

General Procedure for Reduction and Mesyl Chloride Cyclization (10a–e). Excess sodium borohydride (0.60 g, 16.0 mmol) was added to a solution of the N-substituted imide (1.60 mmol) in methanol (16 mL) at −4 °C. The resulting solution was stirred at −4 °C for 1 h and then poured into a mixture of saturated aqueous $NaHCO_3$ (16 mL) and dichloromethane (16 mL) rapidly stirred at 0 °C. The aqueous phase was extracted with more dichloromethane, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo overnight to give the hydroxy lactam. To this crude product in 10 mL of dichloromethane at −20 °C were added triethylamine (0.24 mL,

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(18) (a) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1972**, *25* 817. (b) Overman, L. E.; Malone, T.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6993. We thank Professor Overman for providing a reference sample and spectra of his synthetic material.

1.7 mmol) and methanesulfonyl chloride (0.13 mL, 1.7 mmol). The resulting solution was removed from the cold bath and stirred overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography to give the bicyclic compounds, **10a–e**, described below.

1-Aza-4-[2-(1,3-dithianylidene)]bicyclo[3.3.0]octan-8-one (10a). Reduction of **7a** (0.410g, 1.60 mmol) and subsequent cyclization afforded 0.33 g (86%) of **10a** after flash chromatography (silica gel, ethyl acetate: hexane (4:1)) as a white solid: mp 110–111 °C; IR ($CDCl_3$) 1685, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.58 (br t, J = 6.7 Hz, 1 H), 4.05 (t, J = 10.0 Hz, 1 H), 2.25–3.05 (m, 9 H), 2.15 (m, 2 H), 1.75 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 175.8, 142.6, 119.4, 64.1, 41.6, 33.8, 33.2, 29.7, 29.6, 29.0, 24.6; MS (EI, 70 eV), m/e (relative intensity) 241 (M^+, 100), 167 (M – C_3H_6S, 52.2), 123 (M – $C_4H_6S_2$, 24.3).

Anal. Calcd for $C_{11}H_{12}NOS_2$: C, 54.76; H, 6.26; N, 5.80. Found: C, 54.78; H, 6.27; N, 5.76.

1-Aza-5-[2-(1,3-dithianylidene)]bicyclo[4.3.0]nonan-9-one (10b). Reduction of **7b** (1.46 g, 5.38 mmol) and subsequent cyclization afforded 0.92 g (70%) of **10b** after flash chromatography (silica gel, ethyl acetate eluant) as a white solid: mp 69–70 °C; IR ($CDCl_3$) 1682, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.63 (m, 1 H), 3.95 (m, 1 H), 2.95 (m, 1 H), 2.80 (m, 4 H), 2.45 (m, 2 H), 2.30 (m, 2 H), 2.10 (m, 2 H), 1.85 (m, 2 H), 1.55 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 174.3, 141.1, 121.2, 59.6, 35.6, 31.1, 29.8, 29.7, 25.9, 24.8, 24.2, 21.3; MS (EI, 70 eV), m/e (relative intensity) 255 (M^+, 77), 181 (M – C_3H_6S, 55), 137 (M – $C_4H_6S_2$, 60) 136 (M – $C_4H_7S_2$, 100).

Attempts to obtain an elemental analysis for the compound were unsuccessful due to rapid decomposition.

1-Aza-7-[2-(1,3-dithianylidene)]bicyclo[4.3.0]nonan-2-one (10c). Reduction of *7c* (0.390 g, 1.43 mmol) and subsequent cyclization afforded 0.26 g (71%) of **10c** after flash chromatography (silica gel, ethyl acetate) as an oil: IR ($CDCl_3$) 1630, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.29 (m, 2 H), 2.70–3.20 (m, 5 H), 2.30–2.60 (m, 4 H), 2.17 (m, 2 H), 1.85 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 169.0, 142.6, 119.6, 61.0, 44.0, 30.5, 30.3, 29.6, 28.0, 24.5, 20.3,; MS (EI, 70 eV), m/e (relative intensity) 255 (M^+, 82), 181 (M – C_3H_6S, 50), 137 (M – $C_4H_6S_2$, 5 H), 136 (M – $C_4H_7S_2$, 100).

Attempts to obtain an elemental analysis for the compound were unsuccessful due to rapid decomposition.

1-Aza-5-[2-(1,3-dithianylidene)]bicyclo[4.4.0]decan-10-one (10d). Reduction of **7d** (0.230 g, 0.81 mmol) and subsequent cyclization afforded 0.17 g (79%) of **10d** after flash chromatography (silica gel, ethyl acetate) as an oil: IR (thin film) 1645, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.65 (dd, J = 11.2 Hz, J = 4.3 Hz, 1 H), 4.54 (dd, J = 13.1 Hz, J = 8.5 Hz, 1 H), 2.95 (m, 4 H), 2.80 (m, 1 H), 2.10–2.50 (m, 6 H), 1.50–2.10 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 169.0, 140.3, 120.5, 60.7, 37.8, 31.5, 29.7, 29.6, 26.9, 24.5, 23.1, 22.5, 19.9; MS (EI, 70 eV), m/e (relative intensity) 269 (M^+, 49), 195 (M – C_3H_6S, 15), 151 (M – $C_4H_6S_2$, 45), 150 (M – $C_4H_7S_2$, 100).

Anal. Calcd for $C_{13}H_{19}NOS_2$: C, 57.96; H, 7.11; N, 5.20. Found: C, 58.22; H, 7.18; N, 5.12.

1-Aza-6-[2-(1,3-dithianylidene)]bicyclo[5.3.0]decan-10-one (10e). Reduction of **7e** (0.620 g, 2.17 mmol) and subsequent cyclization afforded 0.27 g (48%) of **10e** after flash chromatography (silica gel, ethyl acetate) as an oil: IR (thin film) 1670, 1578 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.93 (t, J = 8.7 Hz, 1H), 4.05 (dm, J = 14 Hz, 1 H), 3.10 (m, 2 H), 2.10–2.90 (m, 9 H), 1.20–1.95 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 174.6, 141.2, 125.9, 67.3, 42.9, 31.1, 29.8, 29.4, 28.7, 28.3, 24.9, 24.6; MS (EI, 70 eV), m/e (relative intensity) 269 (M^+, 33.2), 194 (M – C_3H_7S, 100), 150 (M – $C_4H_7S_2$, 38.6).

Anal. Calcd for $C_{13}H_{19}NOS_2$: C, 57.96; H, 7.11, N, 5.20. Found: C, 57.71; H, 7.15; N, 5.06.

Acid-Catalyzed Cyclization of 8a to 10a. A solution of **8a** (17 mg, 0.065 mmol) in dichloromethane (0.6 mL) was treated with trifluoroacetic acid (5 μL, 0.007 mmol). After 5 min the reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated. Purification as described above gave 14 mg (89%) of pure product that was spectrally and chromatographically identical with **10a**. Other acids such as perchloric acid, hydrochloric acid, methanesulfonic acid, and trifluoromethane sulfonic acid were also used to effect the cyclization although these reactions gave larger amounts of byproducts and somewhat lower yields.

Synthesis of *epi*-Lupinine (12). *rac*-(5*S*,6*S*)-1-Aza-5-carbomethoxybicyclo[4.4.0]decan-10-one (11). A solution of **10d** (0.980 g, 3.64 mmol), mercuric chloride (4.00 g, 14.7 mmol), methanol (36 mL), and perchloric acid (1.60 mL of a 70% aqueous solution, 11.2 mmol) was heated at reflux for 2 h. After cooling and filtration, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (silica gel, ethyl acetate) of the crude product gave 0.54 g (76%) of 11 as a white solid, mp 90–91 °C. An analytical sample was prepared by recrystallization from ethyl acetate–petroleum ether: mp 92.0–92.5 °C [lit.[19] 94–95 °C]; IR ($CDCl_3$) 1740, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.74 (dm, J = 13.2 Hz, 1 H), 3.63 (s, 3 H), 3.39 (m, 1 H), 2.30 (m 4 H), 1.92 (m, 2 H), 1.50–1.80 (m, 4 H), 1.30–1.50 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 174.1, 169.4, 57.7, 51.9, 49.6, 42.2, 32.9, 28.9, 28.0, 24.1, 18.8; MS (EI, 70 ev), m/e (relative intensity) 211 (M^+, 47), 196 (M – 15, 16), 183 (M – 28, 27), 155 (M – 56, 100), 96 (M – 115, 77).

***epi*-Lupinine (12).** To a solution of lithium aluminum hydride (96 mg, 2.53 mmol) in THF (3 mL) was added a solution of 11 (100 mg, 0.51 mmol) in THF (3 mL). The resulting solution was heated at reflux for 17 h, cooled, then treated sequentially with 0.10 mL of H_2O, 0.10 mL of 15% aqueous NaOH, and 0.20 mL of H_2O, and then treated with solid Na_2SO_4. The mixture was filtered and the solid was washed with THF. The combined solutions were concentrated in vacuo to give 85 mg (99%) of 12 as a white solid: mp 79–80 °C [lit.[19] 81–82 °C; lupinine, mp 59–61 °C[19]]; IR ($CDCl_3$) 3640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (m, 2 H), 2.81 (m, 2 H), 1.50–2.10 (m, 10 H), 1.15–1.50 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 64.6, 64.2, 57.0, 56.7, 44.0, 29.8, 28.4, 25.6, 25.1, 24.6; MS (EI, 70 eV), m/e (relative intensity) 169 (M^+, 66), 168 (M – 1, 59), 152 (M – 17, 97), 138 (M – 31, 78), 83 (M – 86, 100).

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.95; H, 11.31; N, 8.27. Found: C, 70.65; H, 11.36; N, 8.21.

Synthesis of (+)-Trachelanthamidine (14). *rac*-(4*S*,5*S*)-1-Aza-4-(((3-mercaptopropyl)thio)carbonyl)bicyclo[3.3.0]octan-8-one (13). Aqueous perchloric acid (2.0 mL of a 0.5 M solution, 0.96 mmol) was added to a solution of **10a** (77 mg, 0.32 mmol), THF (1.5 mL), and acetonitrile (1.5 mL). The resulting solution was stirred overnight, neutralized with aqueous $NaHCO_3$, and extracted with dichloromethane (3 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica gel, ethyl acetate) of the residue gave a 68 mg (82%) of **13** as an oil: IR ($CDCl_3$) 1690, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.05 (q, J = 7.6 Hz, 1 H), 3.65 (dt, J = 8.2 Hz, 11.7 Hz, 1 H), 3.20 (m, 1 H), 3.04 (t, J = 6.9 Hz, 2 H), 2.30–2.80 (m, 8 H), 1.80–2.00 (m, 3 H), 1.38 (t, J = 7.4 Hz, 1 H).

(+)-Trachelanthamidine (14). To a solution of lithium aluminum hydride (36 mg, 0.95 mmol) in THF (1 mL) was added a solution of **13** (50 mg, 0.19 mmol) in THF (1 mL). After heating at reflux for 7 h the reaction mixture was cooled and then treated sequentially with 40 μL of H_2O, 40 μL of 15% aqueous NaOH, and 40 μL of H_2O. The mixture was dried (Na_2SO_4) and filtered, the solids were washed with ether, and the combined filtrates were concentrated in vacuo. Flash chromatography (silica gel, chloroform:methanol:trietylamine (5:4:1)) of the crude product gave 17 mg (62%) of **14** as an oil: IR ($CDCl_3$) 3340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (m, 2 H), 3.43 (m, 1 H), 3.27 (m, 1 H), 3.11 (m, 1 H), 2.61 (m, 2 H), 1.75–2.10 (m, 7 H), 1.65 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 67.8, 65.2, 56.9, 54.9, 48.7, 32.1, 30.2, 25.8; MS (EI, 70 eV), m/e (relative intensity) 141 (M^+, 26), 124 (M – 17, 15), 110 (M – 31, 9), 83 (M – 58, 100), 82 (M – 59, 50). The ^1H NMR is nearly identical with the published spectrum,[20] differing significantly from that of the diastereomer isoretronecanol.[20]

To further confirm the stereochemical outcome of the hydrolysis step, **13** was converted into the ethyl ester derivative. A solution of **13** (13 mg, 0.050 mmol) in ethanol (1.0 mL), previously saturated with HCl gas, was heated at reflux for 1 h. The cooled solution was neutralized with aqueous $NaHCO_3$, and the mixture was

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(20) Danishefsky, S.; McKee, R.; Singh, R. K. *J. Am. Chem. Soc.* **1977**, *99*, 4783.

extracted with dichloromethane. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 10 mg (100%) of an oil: IR ($CDCl_3$) 1735, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.13 (q, J = 7.1 Hz, 2 H), 4.01 (m, 1 H), 3.57 (m, 1 H), 3.15 (m, 1 H), 1.75–2.80 (m, 7 H), 1.23 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.9, 172.1 64.3, 61.1, 49.7, 40.8, 34.4, 30.7, 26.0, 14.3; MS (EI, 70 eV), m/e (relative intensity) 197 (M^+, 27), 152 (M - 45, 40), 140 (M - 57, 41), 97 (M - 100, 100). The ^{13}C NMR of this product closely resembles the published spectrum,[21] and it differs significantly from the reported spectrum[22] of the thermodynamically less stable diastereomer, especially at C-4, C-7, and C-9. This ester also gave **14** upon $LiAlH_4$ reduction.

Cyclization of 8a by Acid Followed by Trapping with Ethanethiol. Methanesulfonic acid (0.40 mL, 5.95 mmol) was added dropwise to a solution of **8a** (0.54 g, 2.07 mmol), ethanethiol (1.50 mL, 20.32 mmol), and dichloromethane (20 mL) at 0 °C. The resulting solution was stirred at 0 °C for 10 min and then was quenched with saturated aqueous sodium bicarbonate (5 mL). The mixture was extracted with dichloromethane, and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica gel, ethyl acetate/petroleum ether 1/1) of the crude reaction mixture gave 0.42 g (67%) of **17** and 0.14 g (22%) of **18** as oils.

17: ^1H NMR ($CDCl_3$) δ 4.18 (q, J = 7.3 Hz, 1 H), 3.58 (M, 1 H), 3.30 (m, 2 H), 3.02 (m, 1 H), 2.00–2.65 (m, 11 H), 1.85 (m, 2 H), 1.18 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.2, 63.7, 62.2, 40.0, 39.6, 30.0, 27.5, 26.9, 25.1, 23.2, 22.1, 14.8, 14.0; MS (CI), m/e (relative intensity) 204 (M + 1, 100).

18: ^1H NMR ($CDCl_3$) δ 4.70 (m, 1 H), 3.69 (m, 1 H), 3.26 (m, 2 H), 3.13 (m, 1 H), 1.70–2.70 (m, 13 H), 1.20 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.8, 64.4, 62.2, 55.8, 40.4, 34.9, 29.7, 29.5, 27.1, 27.0, 27.0, 24.9, 13.6; MS (CI), m/e (relative intensity) 204 (M + 1, 100).

Conversion of 18 into 14. Mercuric chloride (0.48 g, 1.76 mmol) was added to a mixture of **18** (0.11 g, 0.35 mmol), calcium carbonate (0.35 g, 3.50 mmol), and 80% aqueous ethanol (3.6 mL). The resulting mixture was stirred at 25 °C for 0.5 h, filtered, and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4), treated with solid Na_2S, filtered, and then concentrated. Flash chromatography (silica gel, ethyl acetate) of the residue gave 22 mg (26%) of **10a** and 20 mg (29%) of an ethyl ether identical with the one derived from **13** (see synthesis of **14**). This ester also gave **14** upon $LiAlH_4$ reduction.

The analogous treatment of **17** produced a number of different products by TLC, none of which corresponded with **15**.

1-Aza-4-(1,3-dithian-2-yl)bicyclo[3.3.0]octan-8-one (19). Trifluoromethane sulfonic acid (28 μL, 0.36 mmol) was added to a solution of **10a** (18 mg, 0.08 mmol) and triethylsilane (25 μL, 0.16 mmol) in dichloromethane (1 mL) at −20 °C. The resulting solution was stirred at 25 °C overnight. The reaction mixture was neutralized with saturated aqueous solution bicarbonate and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (silica gel, ethyl acetate) of the crude mixture gave 13 mg (71%) of **19** as an oil: ^1H NMR ($CDCl_3$) δ 4.06 (d, J = 7.9 H, 1 H), 3.87 (q, J = 7.5 Hz, 1 H), 3.58 (m, 1 H), 3.15 (m, 1 H), 2.86 (m, 4 H), 2.3–2.8 (m, 4 H), 1.8–2.2 (m, 5 H); MS (EI, 70 eV), m/e (relative intensity) 243 (M^+, 46), 168 (M - 75, 10), 137 (M - 106, 23), 136 (M - 107, 100).

1-Aza-4-formylbicyclo[3.3.0]octan-8-one (20). Mercuric chloride (1.20 g, 4.41 mmol) was added to a mixture of **19** (100 mg, 0.41 mmol), calcium carbonate (0.40 g, 4.0 mmol), and 80% aqueous acetonitrile (5 mL) at 25 °C. The resulting mixture was stirred overnight, filtered, and extracted with dichloromethane. The combined organic extracts were dried (Na_2SO_4), treated with solid Na_2S, filtered, and concentrated. Flash chromatography (silica gel, 10% methanol in ethyl acetate) of the residue gave 42 mg (67%) of **20** as an oil: ^1H NMR ($CDCl_3$) δ 9.75 (d, J = 3.1 Hz, 1 H), 4.15 (q, J = 8 Hz, 1 H), 3.74 (m, 1 H), 3.15 (m, 1 H), 2.71 (m, 2 H), 2.2–2.4 (m, 3 H), 1.85 (m, 2 H); MS (EI, 70 eV), m/e (relative intensity) 153 (M^+, 33), 152 (M - 1, 12), 136 (M - 16, 100), 97 (M - 56, 52).

Conversion of 20 to 19. Boron trifluoride etherate (1.5 μL, 0.01 mmol) was added to a solution of **20** (12 mg, 0.08 mmol), 1,3-propanedithiol (8.6 μL, 0.09 mmol) and dichloromethane. The resulting solution was stirred at 25 °C overnight, neutralized with aqueous $NaHCO_3$, and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The product was identical with **19** spectrally and chromatographically.

Reduction of 20 to 14. To a solution of lithium aluminum hydride (146 mg, 3.84 mmol) in THF (5 mL) was added a solution of **20** (98 mg, 0.63 mmol) in THF (5 mL). The resulting mixture was heated at reflux overnight. The cool solution was treated with 0.15 mL of H_2O, 0.15 mL of 15% aqueous NaOH, and 0.30 mL of H_2O. The mixture was filtered and the solid was washed four times with 10% triethylamine in THF solution. The combined filtrates were dried ($MgSO_4$) and concentrated in vacuo to give 56 mg (63%) of an oil with spectral and chromatographic properties identical with **14**.

Synthesis of Supinidine (21). 1-Aza-4-(1,3-dithian-2-yl)-bicyclo[3.3.0]octan-8-one. To a solution of the ketene dithioacetal **10a** (85 mg, 0.374 mmol) in THF (1 mL) containing hexamethylphosphoramide (0.26 mL, 1.5 mmol) was added lithium diisopropylamide (3.54 mL of a 0.57 M solution, 2.0 mmol) at −78 °C under argon. The reaction mixture was allowed to warm to −20 °C over 3 h and stirred for additional 1 h at −20 °C. The dark red solution was cooled to −78 °C and an excess of methanol (0.2 mL) was added. After 15 min, the solution was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Flash chromatography (ethyl acetate/hexane = 4/1) gave 76 mg (89%) of **21** as an oil: IR ($CDCl_3$) 1690, 1630 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.92 (br s, 1 H), 4.75 (m, 1 H), 4.67 (br s, 1 H), 4.39 (d of apparent quintets, J = 16.2, ~1.9 Hz, 1 H), 3.70 (d of apparent quintets, J = 16.2, ~1.8 Hz, 1 H), 1.6–3.0 (m, 1 H). NMR also shows ~5% of the ketene dithioacetal **10a** which does not separate from the product chromatographically; otherwise >99% pure by HPLC (μ-porasil, EtOAC/hexane = 4/1, 254 nm).

1-Aza-4-formylbicyclo[3.3.0]oct-3-en-8-one. To a vigorously stirred mixture of red mercury(II) oxide (542 mg, 2.5 mmol), and boron trifloride etherate (355 mg, 2.5 mmol) in aqueous THF (1 mL, 15% H_2O) was added dropwise at 20 °C a solution of the ketene dithioacetal from the previous reaction 240 mg, 1.0 mmol) dissolved in a minimum amount of THF.[23] After stirring for 3 h, the reaction mixture was diluted with ether (10 mL), the precipitated salts were filtered off, the ethereal filtrate was washed with saturated aqueous K_2CO_3 (10 × 5 mL), dried ($MgSO_4$), and concentrated to give 132 mg (87%) of the crude α,β-unsaturated aldehyde as a crystalline solid: ^1H NMR ($CDCl_3$) δ 9.81 (s, 1 H), 6.89 (d, J = 2.0 Hz, 1 H), 4.87 (m, 1 H), 4.68 (dm, J = 18.8, ~2.1 Hz, 1 H), 3.93 (dm, J = 18.8, ~3 Hz, 1H), 2.6–2.8 (m, 2 H), 2.32 (m, 1 H), 1.94 (m, 1 H). R_f 0.14 (100% EtOAc).

(±)-Supinidine (21). To a suspension of $LiAlH_4$ (40.2 mg, 1.06 mmol) in THF (5 mL) was added a solution of the amide aldehyde from the previous reaction (20 mg, 0.13 mmol) in a minimum amount of THF dropwise at room temperature under argon. After heating at reflux for 2 h, the reaction mixture was worked up by the successive addition of 40 μL of H_2O, 80 μL of 15% NaOH solution, and 40 μL of H_2O. Evaporation of volatiles left a residue which was triturated with ether. Filtration through K_2CO_3/Celite and concentration gave 15 mg of crude product. Flash chromatography ($CHCl_3$/MeOH/ NH_4OH = 10/4/1) gave 11 mg (60%) of (±)-supinidine as a colorless oil. The 250-MHz ^1H NMR, ^{13}C NMR, IR, and MS (EI) were identical with those of an authentic sample.[24] IR ($CDCl_3$) 3330, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.51 (m, 1H), 4.1–4.3 (m, 2 H) 3.92 (dm, 1 H), 3.35 (dm, 1 H), 3.15 (dt, 1 H), 2.55 (dt, 1 H), 2.0–1.4 (m, 2 H); MS (EI), m/e 139 (M^+, 31%), 138 (9%), 122 (26%), 120 (12%), 111 (13%), 110 (14%), 108 (28%), 94 (0%), 80 (100%); ^{13}C NMR ($CDCl_3$) δ 144.1, 120.7, 71.7, 61.9, 60.0, 56.8, 30.4, 26.0. The samples also co-

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(23) This is the method of Vedejs and Fuchs. For references to it and many other alternatives, see: Seebach, D.; Gröbel, B. T. *Synthesis* **1977**, 357.

(24) Authentic supinidine was obtained by the hydrolysis of supinine (3 N H_2SO_4 reflux, 24 h), which was kindly provided by Dr. Mathew Suffness of the National Institutes of Health.

chromatographed by TLC (R_f 0.27, SiO_2, $CHCl_3$/MeOH/concentrated NH_4OH = 10/4/1).

Synthesis of Elaeokanine A (22). 1-Aza-5-[2-(1,3-dithianylidene)]bicyclo[4.3.0]nonane. To a solution of lithium aluminum hydride (0.12 g, 3.21 mmol) in THF (11 mL) was added a solution of **10b** (0.55 g, 2.15 mmol) in THF (11 mL). The resulting solution was stirred for 1 h and quenched with a mixture of H_2O–THF. The solution was basified with saturated aqueous Na_2CO_2 and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give 0.49 g (95%) of the amine as a yellowish solid: IR ($CDCl_3$) 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.17 (dd, J = 10.6 Hz, J = 7.0 Hz, 1 H) 2.70–3.10 (m, 7 H), 2.59 (m, 1 H), 2.48 (m, 1 H), 2.14 (m, 2 H), 1.50–2.00 (m, 7 H); MS (EI, 70 eV), m/e (relative intensity) 241 (M^+, 64), 167 (M - C_3H_7S, 69), 123 (M - $C_4H_6S_2$, 100), 122 (M - $C_4H_7S_2$, 85).

1-Aza-5-[2-(2-propyl-1,3-dithianyl)]bicyclo[4.3.0]nonene. *n*-Butyllithium (2.42 mL of a 2.15 M solution in hexane, 5.20 mmol) was added to a solution of diisopropylamine (0.73 mL, 5.21 mmol) in THF (4 mL). The resulting solution was stirred for 20 min at 0 °C and then was added to a solution of the product from the previous reaction (0.25 g, 1.04 mmol), hexamethylphosphoramide (0.90 mL, 5.17 mmol), and THF (7 mL) at -78 °C. After warming to -20 °C over 2 h, the dark red solution was cooled to -78 °C and *n*-propyl iodide (1 mL, 10.25 mmol) was added. This resulting solution was stirred at -78 °C for 1 h, quenched with 2 mL of methanol, diluted with 10 mL of ethyl acetate, and washed with water. The organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, 8% triethylamine in ethyl acetate) of the crude product gave 0.13 g of the dithiane and 0.09 g of starting material (43% yield, or 68% yield based on recovery of starting material): ^1H NMR ($CDCl_3$) δ 6.30 (br s, 1 H), 3.19 (m, 1 H), 2.95 (m, 1 H), 2.80 (m, 1 H), 2.74 (m, 2 H), 2.62 (m, 4 H), 2.38 (m, 2 H), 2.22 (m, 2 H), 1.85 (m, 4 H), 1.50 (m, 2 H), 1.25 (m, 2 H), 0.83 (t, J = 6.8 Hz, 3 H); MS (EI, 70 eV), m/e (relative intensity) 283 (M^+, 3), 250 (M - 33, 4), 240 (M - 43, 3), 223 (M - 60, 3), 208 (M - 75, 100), 177 (M - 106, 47), 149 (M - 134, 64).

Elaeokanine A (22). A mixture of the dithiane from the previous reaction (162 mg, 0.57 mmol), mercuric chloride (0.31 g, 1.14 mmol), calcium carbonate (0.23 g, 2.30 mmol), and 80% aqueous acetonitrile (12 mL) was heated at 50 °C for 1 H. The cooled mixture was filtered, and the solid was washed with acetonitrile. The combined solutions were concentrated, diluted with dichloromethane (20 mL), and washed with saturated aqueous Na_2CO_3. The organic extract was treated with solid Na_2S, filtered, and then dried (Na_2SO_4). Flash chromatography (silica gel, 2% triethylamine in ethyl acetate) of the crude product gave 78 mg (70%) of **22** as an oil: IR ($CDCl_3$) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.88 (br s, 1 H), 3.50 (m, 1 H), 2.20–3.00 (m, 10 H), 1.20–1.90 (m, 4 H), 0.93 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 200.8, 141.9, 136.9, 58.9, 52.9, 45.3, 39.4, 29.6, 25.6, 22.5, 18.3, 14.0; MS (EI, 70 eV), m/e (relative intensity) 193 (M^+, 15), 192 (M - 1, 11), 128 (M - 15, 9), 165 (M - 18, 8), 164 (M - 19, 14), 151 (M - 42, 11), 150 (M - 43, 100), 149 (M - 44, 12), 124 (M - 70, 23), 122 (M - 71, 42), 120 (M - 73, 16). Spectral data and chromatographic mobility (R_f 0.27, 8% Et_3N in ethyl acetate) are identical with an authentic sample of elaeokanine A.[18b]

Acknowledgment. This research was supported by the National Institutes of Health (GM 30073), to which we express our gratitude. We also thank the National Science Foundation for providing instrumentation funds.

Registry No. **7a**, 83177-75-7; **7b**, 89556-85-4; **7c**, 89556-86-5; **7d**, 89556-87-6; **7e**, 89556-88-7; (±)-**10a**, 83177-77-9; (±)-**10b**, 89556-89-8; (±)-**10c**, 89556-90-1; (±)-**10d**, 89556-91-2; (±)-**10e**, 89556-92-3; (±)-**11**, 85588-63-2; (±)-**12**, 486-72-6; (±)-**13**, 89556-93-4; (±)-**13** ethyl ester derivative, 77513-73-6; (±)-**14**, 18929-91-4; (±)-**17**, 89556-94-5; (±)-**18**, 89556-95-6; (±)-**19**, 89556-96-7; (±)-**20**, 89556-97-8; (±)-**21**, 23185-51-5; (±)-**22**, 73971-21-8; succinimide, 123-56-8; glutarimide, 1121-89-7; (±)-1-aza-4-formylbicyclo[3.3.0]oct-3-en-8-one, 83177-79-1; (±)-1-aza-5-[2-(2-propyl-1,3-dithianyl)]bicyclo[4.3.0]nonene, 89556-98-9; 1,3-propanedithiol, 109-80-8; butyrolactone, 96-48-0; valerolactone, 108-29-2; caprolactone, 502-44-3.

Total Synthesis of (±)-Nitramine. Development of a Ketene Equivalent in the Ene Reaction

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Received November 30, 1983

(±)-Nitramine (**1a**) was synthesized in seven steps from methylenecyclohexane in 33% overall yield. A three-step sequence was developed from methylenecyclohexane to aldehyde **4** in which methyl α-chloroacrylate was used as a ketene equivalent in the ene reaction. Aldehyde **4** was converted to nitrone **3** which cyclized to a 2.5:1 mixture of **2** and **9**. Hydrogenolysis of **2** gave **1a**. Lewis acid catalyzed cyclization of **4** gave a 3.5:1 mixture of hydrindanones **13** and **14** at 25 °C and a 12:1 mixture of **13** and **14** at -20 °C.

(+)-Nitramine (**1a**), isolated from *Nitraria schoberi*, is the first alkaloid to possess a 2-azaspiro[5.5]undecane skeleton.[2] More recently, the diastereomers of **1a** and **1b**, isonitramine[2a,b,3a] and sibirene,[3b] and (±)-nitramine[3c] (**1a**), have been isolated from *Nitraria sibirica*. The structures of nitramine and isonitramine were determined by X-ray crystallography.[2b] These alcohols are related to the neurotoxins histrionicotoxin and congeners, which are 2,7-disubstituted 1-azaspiro[5.5]undecan-8-ols.[4] The unusual carbon skeleton of **1a** and the potential for biological activity in this class of γ-amino alcohols made it an intriguing synthetic problem.

Our approach to nitramine was based on the intramolecular cycloaddition[5] of the nitrone **3** to give **2**, which can be converted to nitramine by hydrogenolysis. The relative

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