1740 and 1635 cm^{-1}; ^{1}H NMR (C_6D_6) δ 4.47 (1 H, d, J = 7 Hz), 3.18 (3 H, s), 2.29–1.40 (4 H, m), 1.34 (1 H, m), 1.20–0.94 (3 H, m), 1.03 (3 H, s), 0.82 (3 H, s); mass spectrum, m/e 206.131 (M^+; calcd for $C_{13}H_{18}O_2$ 206.130).

1,3-Dimethyl-5-isopropenyl-9-methoxytricyclo[4.3.1.0^{3,7}]-dec-8-en-5-ol (29). To a solution of isopropenyllithium[22] (1 mL, 1 M in ether) at 0 °C was added dropwise 18 mg (0.09 mmol) of **21**. The reaction mixture was maintained at 0 °C for 30 min and then was allowed to come to room temperature. After an additional 30 min, the reaction was quenched with water, and the mixture was partitioned between ether and water. The organic extract was dried over magnesium sulfate and the solvent was removed in vacuo. The crude product was subjected to column chromatography on alumina (benzene as eluant) to give 15.3 mg (69%) of **29**: ^{1}H NMR (C_6D_6) δ 5.04 (1 H, br s), 4.95 (1 H, s), 4.79 (1 H, q, J = 2 Hz), 4.59 (1 H, d, J = 7 Hz), 3.28 (3 H, s), 2.47 (1 H, m), 2.14 (3 H, m), 1.78 (3 H, s), 1.86–0.92 (4 H, m), 1.26 (3 H, s), 0.89 (3 H, s); mass spectrum, m/e 248 (M^+).

1,3-Dimethyl-5-isopropenyltricyclo[4.3.1.0^{3,7}]dec-4-en-9-one (31). A solution of 52 mg (0.2 mmol) of **29** in 0.3 mL of dimethyl sulfoxide was heated in an oil bath at 150–160 °C. The course of the reaction was followed by NMR and after 11 h the reaction mixture was diluted with water and extracted with ether. The combined ethereal extracts were washed with water and brine and dried over magnesium sulfate. Removal of the solvent in vacuo gave 43 mg (94%) of virtually pure **31**. A portion of the material which was subjected to column chromatography on alumina [benzene–hexane (9:1) as eluant] afforded a sample of **31**: IR (film) 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.80 (1 H, s), 4.94 (1 H, br d, J = 6 Hz), 2.78 (1 H, m), 2.48 (2 H, d, J = 3 Hz), 1.92 (3 H, s), 1.78–1.01 (4 H, m), 1.12 (3 H, s), and 0.88 (3 H, s); mass spectrum, m/e 216 (M^+).

1,3-Dimethyl-5-isopropyl-9-oxotricyclo[4.3.1.0^{3,7}]decan-9-one (9-Pupukeanone, 3). To a prereduced suspension of 50 mg of platinum oxide in 3 mL of methanol under a hydrogen atmosphere was added 27 mg (0.13 mmol) of **31**. After 46 h, the reaction mixture was diluted with ether and filtered through Celite to give 24 mg of a mixture of **3** and **32** in a 7:3 ratio (as determined by ^{1}H NMR). Preparative chromatography of this mixture on silver nitrate impregnated silica gel provided a sample of pure **3**: ^{1}H NMR ($CDCl_3$) δ 2.34 (2 H, d, J = 3 Hz), 1.71, 1.63, 1.56, 1.49 (br s), 1.04 (3 H, s), 0.91 (3 H, s), 0.90 (6 H, m); mass spectrum, m/e 220 (M^+).

Acknowledgment. We are indebted to Dr. Richard Wielesek, Department of Chemistry, University of Oregon, for the high-resolution mass spectra and to Professor Hisashi Yamamoto, University of Hawaii, for providing spectra of authentic 9-pupukeanone. This research was assisted financially by a fellowship (to G.A.S.) from the Nicholas L. Tartar Foundation and by a grant from the National Science Foundation (CHE77-04379). Funds for the purchase of the Varian FT-80A NMR spectrometer were provided by the National Science Foundation.

Registry No. **3**, 70329-89-4; **5**, 69697-76-3; **6**, 73193-90-5; **7**, 73193-91-6; **8**, 20023-36-3; **9**, 73193-92-7; **10**, 73193-93-8; **12** (isomer 1), 73193-94-9; **12** (isomer 2), 73193-95-0; **14**, 73193-96-1; **16**, 73193-97-2; **17**, 73193-98-3; **18**, 73193-99-4; **19**, 73194-00-0; **20**, 73194-01-1; **21**, 73194-02-2; **29**, 73194-03-3; **31**, 70329-74-7; **32**, 73194-04-4; 2,4-dimethylanisole, 6738-23-4; *p*-cresol methyl ether, 104-93-8; diiodomethane, 75-11-6; ethyl diazoacetate, 623-73-4; vinyl bromide, 593-60-2; isopropenyllithium, 6386-71-6.

(22) E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 3333 (1956).

Macrocyclic Lactone Formation through Sulfide Contraction. Synthesis of (±)-Diplodialide A[1]

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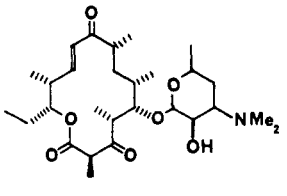
A methodology for the synthesis of macrocyclic β-keto lactones from ω-hydroxy thioamides is described. The hydroxy thioamides were esterified with chloroacetyl chloride, and the resulting chloro esters underwent Eschenmoser sulfide contraction when treated with sodium iodide, diisopropylethylamine, and triethyl phosphite in acetonitrile. The β-keto lactones were obtained in 25–58% yield. The utility of the method was demonstrated by synthesis of diplodialide A.

Recently, several procedures for macrocyclic lactone formation have appeared.[3] Although a few alternate routes have been used, most of the procedures rely on the formation of the lactone bond as the ring-forming step. Existence of natural products such as narbomycin (**1**)[4] and diplodialide A (**2**)[5] which contain the β-keto lactone system suggested that such macrocycles might be synthesized through formation of this grouping by some modification of the Claisen condensation. The Eschenmoser sulfide contraction,[6] in which thioamide **3** was converted into



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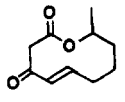
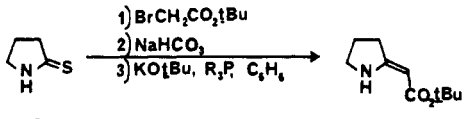


2



3 4

(1) Contribution No. 6088. This investigation was supported by Grant CHE 74-19858 awarded by the National Science Foundation.

(2) Institute fellow, 1975–76. Predoctoral fellow of the National Science Foundation, 1976–79.

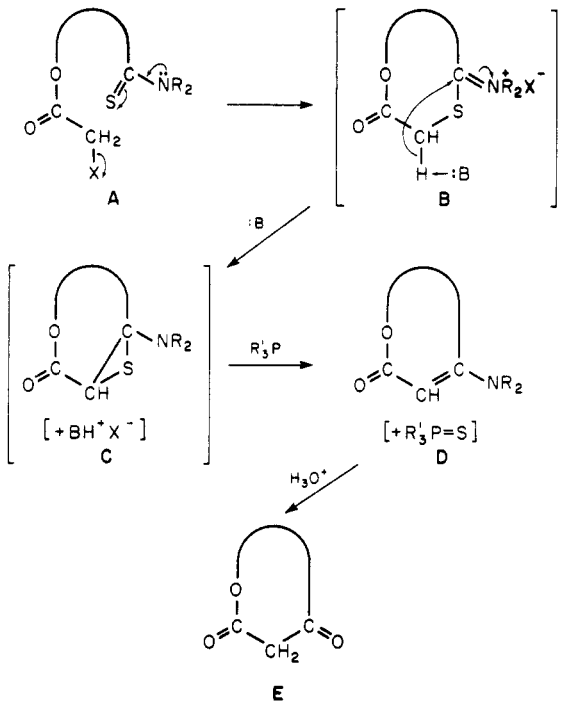
(3) Ishida, T.; Wada, K. *J. Chem. Soc., Perkin Trans. 1* **1979**, 323–7, and references cited therein.

(4) Corbaz, R.; Ettlinger, L.; Gäumann, E.; Keller, W.; Kradolfer, F.; Kyburz, E.; Neipp, L.; Prelog, V.; Reusser, P.; Zähner, H. *Helv. Chim. Acta* **1955**, *38*, 935–42.

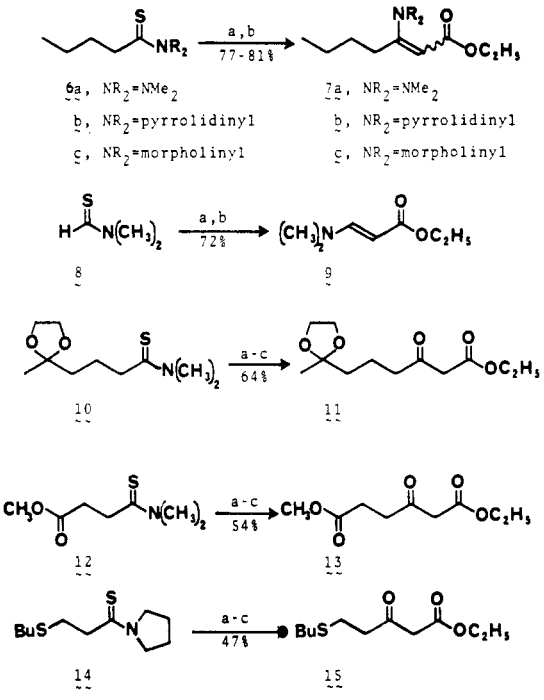
(5) Ishida, T.; Wada K. *J. Chem. Soc., Chem. Commun.* **1975**, 209–10.

0022-3263/80/1945-1868$01.00/0

Chart I. Schematic Presentation of Synthesis of β-Keto Esters through Sulfide Contraction



Scheme I. Intermolecular Sulfide Contraction[a]



[a] a, $ICH_2CO_2C_2H_5$, CH_3CN; b, $C_6H_5P[(CH_2)_3NMe_2]_2$, CH_3CN, Δ; c, silica gel.

enamino ester **4** in 75% yield, seemed to be a viable method. Macrocycle formation would be through initial carbon–sulfur bond formation rather than through more difficult carbon–carbon bond formation as in the Claisen condensation. The sulfide would then be readily converted intramolecularly into a β-keto lactone. Here we report the development of alternate conditions for the Eschenmoser sulfide contraction of thioamides, the adaptation of these conditions to macrocyclic lactone formation, and the synthesis of diplodialide A (**2**) through intramolecular sulfide contraction.

After initial experiments with *N*-monoalkylthioamides proved unsatisfactory, the *N,N*-dialkylthioamides[7] shown were substituted (see Chart I). It was discovered that the intermediate thioimmonium salts B could be induced to undergo the sulfide contraction by treatment of the salt B with a phosphine (R_3P) and an amine base (:B). A strong base such as potassium *tert*-butoxide[6] is not necessary. Phosphine **5**, developed by Eschenmoser and co-

$$PhP[(CH_2)_3NMe_2]_2$$
5

workers,[6] proved especially convenient since it contains both phosphine and amine. Interestingly, in some cases the resulting product of sulfur extrusion with the aid of the phosphine, namely, the enamino lactone D, was isolated directly and hydrolyzed to the β-keto ester E on acid treatment. In other instances, only the end product β-keto ester E could be obtained.

The facility of the reaction as compared to that of the corresponding *N*-alkylthioamides can be explained by the enhanced acidity of the acetate protons due to the presence of the positive charge in the thioimmonium salts B. Also, the proposed intermediate episulfide C, which is a neutral species, would provide a good intramolecular pathway for charge neutralization once deprotonation of salt B occurred.

The necessary *N,N*-dialkylthioamides A were prepared in two general ways. Thioacylation[8] of secondary amines with dithioesters was an especially convenient method when the dithioesters were readily available.[9] The more standard way, phosphorus pentasulfide treatment of the corresponding amide, provided a complementary route to the thioamides when the thioacylation method was inapplicable. The procedure of Rao and co-workers[10] was the method of choice for sulfurization of amides.

Scheme I summarizes the results obtained in the modification sulfide contraction. A particularly interesting case is thioamide **14**. Alkylation occurs preferentially on the thioamide sulfur rather than on the sulfide sulfur. Thus β-keto ester **15** was obtained in 47% yield.

Mechanistic investigations (Scheme II) revealed two important facts about the sulfide contraction. Two crossover experiments showed that alkylation of the thioamides with ethyl iodoacetate (**17a**) is reversible. Heating of thioammonium salt **16a** with ester **17b** in acetonitrile led to a 1:1 mixture of salts **16a** and **16b**. Likewise, salts **18** and **16b**, when heated in acetonitrile and then subjected to sulfide contraction, provided all four possible keto esters (**19a**, **19b**, **20a**, and **20b**). Second, the deprotonation step appears to be irreversible and dependent on the relative acidities of the acetate and α-thioamide protons. Salt **21** has been reported[11] to give thiophene **22** when heated with triethylamine in methanol. Attempted sulfide contraction of this salt led only to the same thiophene. In contrast, thioamide **6a** could not be transformed into thiophene **24** but readily underwent sulfide contraction. The phenyl ring apparently increases[12]

(6) (a) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710–34. (b) Löliger, P.; Flückiger, E. *Org. Synth.* **1976**, *55*, 127–33, and references cited therein.

(7) Use of *N,N*-dialkylthioamides was first suggested to us by G. C. Gerrans, University of the Witwatersrand, Johannesburg, South Africa.

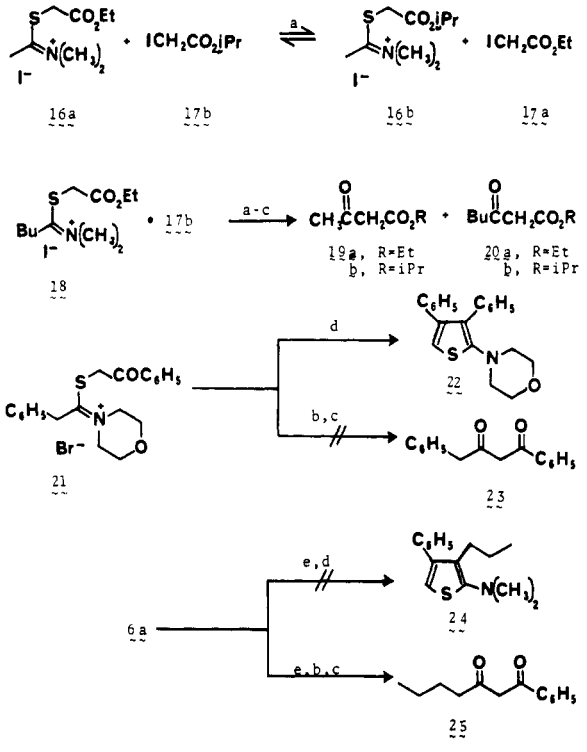
(8) Doyle, K. M.; Kurzer, F. *Chem. Ind. (London)* **1974**, 803–9.

(9) Meijer, J.; Vermeer, P.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 601–4.

(10) Rao, C. S.; Dave, M. P.; Mody, P. N.; Pandya, A. D. *Indian J. Chem.* **1976**, *14*, 999–1000.

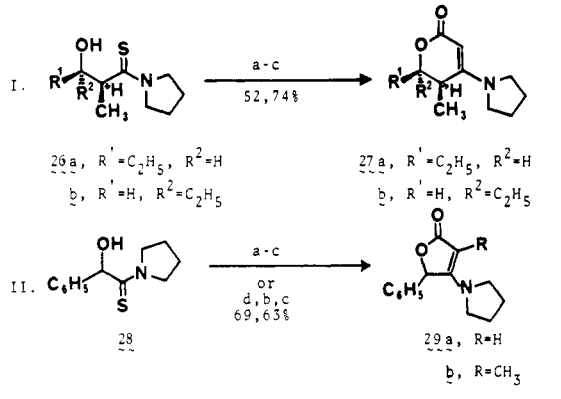
(11) Hartmann, H.; Mayer, R. *Z. Chem.* **1966**, *6*, 28.

Scheme II. Reactions Relating to the Mechanism[a]



[a] a, Δ, CH_3CN; b, $PhP[(CH_2)_3NMe_2]_2$, CH_3CN; c, silica gel; d, Et_3N, MeOH; e, $BrCH_2COC_6H_5$.

Scheme III. Formation of 5- and 6-Membered Lactones[a]



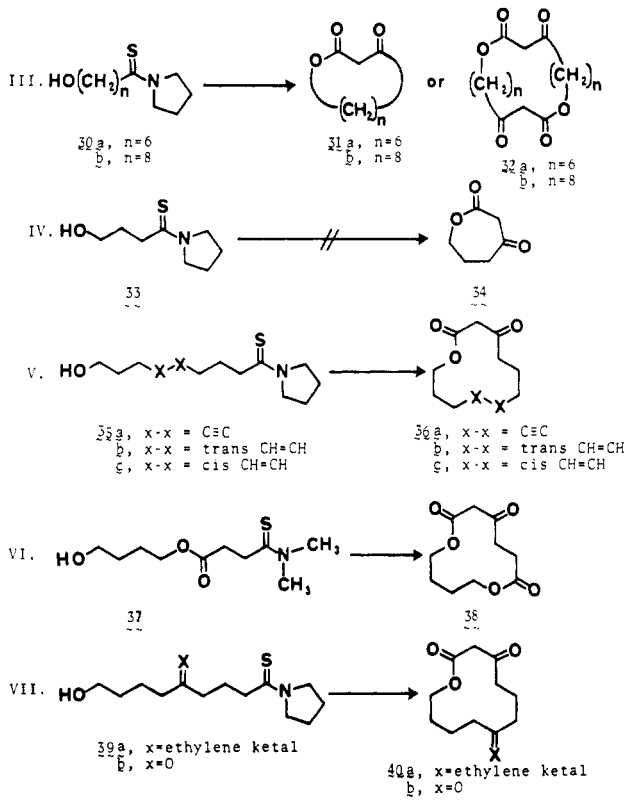
[a] a, $ClCH_2COCl$, CH_2Cl_2; b, NaI, CH_3CN; c, $C_6H_5P[(CH_2)_3NMe_2]_2$, CH_3CN, Δ; d, $CH_3CHClCOCl$, CH_2Cl_2.

the acidity of the β-thioamide protons enough so that deprotonation occurs there in preference to the acetate methyl group.

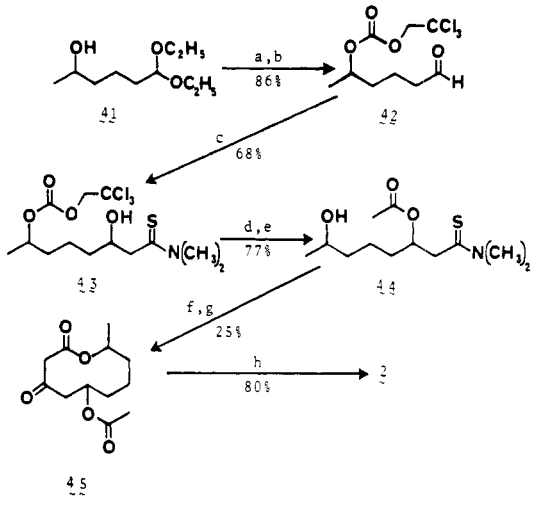
Modification of the sulfide contraction procedure afforded a practical way to form five- and six-membered lactones **27** and **29** (Scheme III). The hydroxy thioamides were esterified with the acid chloride, and the chloro ester was treated with sodium iodide in acetonitrile. Addition of phosphine **5** afforded the chromatographically stable enamino lactones in high yield. Further evidence for an irreversible deprotonation step was provided by the fact that thioamides **26a** and **26b** each afforded the corresponding lactone with no sign of epimerization.

Application of the procedure thus developed to the formation of macrocycles (Scheme IV) led to disappointing results. Thioamides **30a** and **30b** afforded no identifiable products. Since it appeared that the reversible alkylation

Scheme IV. Macrocyclic Lactone Formation



Scheme V. Synthesis of (±)-Diplodialide A[a]



[a] a, Cl_3CCH_2OCOCl, C_5H_5N, CH_2Cl_2; b, HCl, THF, H_2O; c, $ZnCH_2CSNMe_2$, THF-Et_2O; d, CH_3COCl, C_5H_5N, CH_2Cl_2; e, Zn, HOAc; f, $ClCH_2COCl$, C_5H_5N, CH_2Cl_2; g, NaI, $P(OEt)_3$, *i*-Pr_2NEt, CH_3CN, Δ; h, *i*-Pr_2NEt, CH_3CN, Δ.

step was causing the problem, a way was sought to trap the intermediate thioimmonium salt as it was formed. This was accomplished by slowly adding the chloro ester to a solution of sodium iodide, Hunig's base,[13] and triethyl phosphite in acetonitrile heated at reflux. Indeed, this modification led to the desired monomeric macroketones **36**, **38**, and **40** in acceptable yields, but again the seven-membered lactone **34** could not be realized. While high-dilution techniques were necessary in order to accomplish these cyclizations, the reaction conditions were found to be compatible with a useful variety of ancillary functionality, such as acetylenic (**36a**) and olefinic (**36b** and **36c**)

(12) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; pp 492–4.

(13) Hunig, S.; Kiessel, M. *Chem. Ber.* **1958**, *91*, 380–92.

linkages, esters (**38**), ketals (**40a**), or ketones (**40b**). As such, this cyclization procedure has potential for use in the synthesis of the polyfunctional macrolide antibiotics.

The sulfide contraction procedure was first applied to the synthesis of diplodialide A (**2**).[14] Since initial experiments with the corresponding α,β-unsaturated thioamide[15] were unsuccessful, the β-acetoxy thioamide **44** was prepared as a substitute (Scheme V). Reaction of aldehyde **42** with the zinc enolate[16] of *N,N*-dimethylthioacetamide provided alcohol **43** in 68% yield, a substantial improvement over the results with the lithium enolate (41% yield). Alcohol **43** was converted into alcohol **44** and when the sulfide contraction sequence was applied to this alcohol, the acetoxy lactone **45** was formed in 25% yield. Although this yield is low, the fact that macrolactone formation takes place this well with a β-acyloxy thioamide, such as **44**, is rewarding and portends success in the macrolide antibiotic synthesis.

Elimination of the acetate afforded (±)-diplodialide A in 80% yield. Since diplodialides B and C have been synthesized from diplodialide A,[3] this represents a formal synthesis of all three lactones.

Experimental Section

Boiling points are uncorrected. Melting points were determined by using a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on Perkin-Elmer 237B or 737B or Beckman 4210 spectrometers. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian T-60, A-60, or EM-390 spectrometers, and chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as internal standard.

Gas–liquid chromatographic (VPC) analyses were performed on a Hewlett-Packard 5750 gas chromatograph with helium carrier gas at a flow rate of 60 mL/min. All analytical VPC were conducted on a 5 ft × 0.125 in. column packed with 4% SE-30 on 60–80 mesh Chromosorb WAW DMCS.

Thin-layer chromatography (TLC) was performed on E. Merck TLC plates 60F-254, 0.25 mm. "Alumina" refers to the grade I neutral variety manufactured by M. Woelm, Eschwege, Germany, which was neutralized to grade III by addition of 6% water. All silca gel was E. Merck "Silica Gel 60", 70–230 mesh ASTM. "Flash Chromatography (*X*-mm column, solvent system)" refers to the procedure of Still and co-workers[17] where *X* specifies the column diameter.

"Dry" solvents were distilled shortly before use from an appropriate drying reagent. Ether, tetrahydrofuran (THF), dimethoxyethane (DME), and dioxane were distilled under dry argon from sodium metal with benzophenone ketyl as an indicator. Benzene, toluene, and acetonitrile were distilled from calcium hydride. Chloroform, dichloromethane, and carbon disulfide were distilled from phosphorus pentoxide. Acetone was distilled from boric anhydride.[18]

"Dry" amines were distilled as follows: triethylamine and diisopropylamine from sodium metal; pyridine and pyrrolidine from calcium hydride; ammonia from sodium metal.

Other reagents were purified as follows: phosphorus pentasulfide by extraction from a Soxhlet extractor by using dry carbon disulfide under dry argon; dimethyl sulfoxide (Me_2SO) by distillation from CaH_2; aluminum isopropoxide by distillation; anhydrous zinc chloride by fusing three times under vacuum (<0.5 mm).

All other reactants and solvents were "reagent grade" unless otherwise described. "Anhydrous ether" refers to anhydrous ethyl ether which is supplied by Mallinckrodt and Baker. "Petroleum ether" refers to the "Analyzed Reagent" grade hydrocarbon fraction, bp 35–60 °C, which is suppied by J. T. Baker Co., Phillipsburg, NJ, and was not further purified. All reactions except those employing amines or ammonia as solvent or thionyl chloride as a reagent were run under argon which had been dried by passage through indicating Drierite (anhydrous calcium sulfate) which is supplied by Hammond Drierite Co., Xenia, OH. The exceptions were protected from water by drying tubes filled with potassium hydroxide pellets (liquid ammonia) or with anhydrous calcium sulfate (thionyl chloride).

In cases where reaction intermediates or products were isolated by "solvent extraction including washes (drying agent)", the procedure followed was to dilute the reaction mixture with the indicated solvent or to extract the aqueous solution several times with the indicated solvent. The combined organic layers were washed with the indicated solution, described as follows: acid refers to a 2 N aqueous hydrochloric acid solution, base refers to a 10% aqueous sodium hydroxide solution, bicarbonate refers to a saturated aqueous sodium bicarbonate solution, carbonate refers to a saturated aqueous potassium carbonate solution, and $CuSO_4$ refers to a saturated aqueous cupric sulfate solution. Finally, the organic solution was washed with a saturated aqueous sodium chloride solution and dried over anhydrous reagent-grade magnesium sulfate ($MgSO_4$) or sodium sulfate (Na_2SO_4), and solvents were removed under reduced pressure.

Mass spectral analyses were run by Jan Mitchell, California Institute of Technology, on a Du Pont type 21-492 mass spectrometer. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI.

***N,N*-Dimethylpentanethioamide (6a).** A procedure similar to that of P. Reynaud and co-workers[19] was used. To 16.85 g (10.114 mol) of methyl pentanedithioate[9] was added 100 mL of a 25% aqueous dimethylamine solution,[20] and the resulting solution was stirred at room temperature for 2.5 h. Ether extraction ($MgSO_4$) followed by distillation gave 14.2 g (86%) of the thioamide **6a** as a clear liquid: bp 70–75 °C (0.25 mm) [lit.[19] bp 89 °C (0.1 mm)]; IR (neat) 1510 cm^{-1} (NC=S); ^{1}H NMR ($CDCl_3$) δ 3.45 and 3.28 (2 s, 2 × 3 H, NCH_3).

1-(Pentanethioyl)azacyclopentane (6b). A solution of 11.9 g (80 mmol) of methyl pentanedithioate[9] and 8.0 mL of pyrrolidine in 100 mL of dry benzene was heated at reflux for 2 h. The solution was cooled to room temperature, solvents were removed under reduced pressure, and distillation of the residue afforded 12.2 g (89%) of thioamide **6b:** bp 110–113 °C (0.15 mm); IR (neat) 1470 cm^{-1} (NC=S); ^{1}H NMR ($CDCl_3$) δ 3.5–4.0 (m, 4 H, NCH_2), 2.6–2.9 (m, 2 H, CH_2C=S).

Anal. Calcd for $C_9H_{17}NS$: C, 63.10; H, 10.01; N, 8.18. Found: C, 63.10; H, 10.12; N, 8.04.

4-(Pentanethioyl)-1,4-oxaazacyclohexane (6c). By the procedure described above for the preparation of thioamide **6b**, 11.9 g (80 mmol) of the above dithioester with 8.4 mL (96 mmol) of morpholine and 100 mL of dry benzene provided, after distillation, 13.4 g (89%) of the thioamide **6c**: bp 106–114 °C (0.15 mm) [lit.[19] bp 131 °C (0.05 mm)]; IR (neat) 1470 cm^{-1} (NC=S); ^{1}H NMR ($CDCl_3$) δ 4.2–4.4 (m, 2 H, NCH_2), 3.7–3.9 (m, 6 H, NCH_2, OCH_2).

Methyl 5,5-(Ethylenedioxy)hexanedithioate. The procedure of Brandsma and co-workers[9] was used to prepare this dithioester from the ethylene ketal of 5-chloro-2-pentanone:[21] yield 80%; bp 91–95 °C (0.1 mm); IR ($CHCl_3$) was uninformative; ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 4 H, OCH_2), 2.92 (t, 2 H, J = 7 Hz, CH_2C=S), 2.54 (s, 3 H, SCH_3), 1.30 (s, 3 H, CCH_3).

Anal. Calcd for $C_9H_{16}O_2S_2$: C, 49.05; H, 7.32; S, 29.10. Found: C, 49.18; H, 7.31; S, 29.17.

***N,N*-Dimethyl-5,5-(ethylenedioxy)hexanethioamide (10).** By the procedure described above for the preparation of thioamide **6a**, 34.6 g (0.157 mol) of the above dithioester with 125 mL of a 25% aqueous dimethylamine solution[20] provided, after distillation,

(14) For reported syntheses of diplodialide A see: (a) Wakamatsu, T.; Akasaka, K.; Ban, Y. *J. Org. Chem.* **1979**, *44*, 2008–12. (b) Reference 3.
(15) For details see Appendix A of Brown, F. R. Ph.D. Thesis, California Institute of Technology, June 1980.
(16) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310–24.
(17) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–5.
(18) Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 3966–8.
(19) Reynaud, P.; Moreau, R. C.; Samama, J.-P. *Bull. Soc. Chim. Fr.* **1965**, 3623–8.
(20) Purchased from Eastman Organic Chemicals, Rochester, NY.
(21) Purchased from Aldrich Chemical Co., Milwaukee, WI, and used without purification.
(22) Cason, J. "Organic Syntheses"; Wiley: New York, **1955**; Collect. Vol. 3, 169–71.

25.6 g (75%) of the thioamide **10**: bp 115–124 °C (0.05 mm); IR ($CHCl_3$) 1525 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 3.91 (s, 4 H, OCH_2), 3.44 and 3.30 (2 s, 6 H, NCH_3), 1.31 (s, 3 H, CCH_3).

Methyl 3-(Dimethylthiocarbamoyl)propanoate (12). A modified procedure of Rao and co-workers[10] was used. A solution of 31.8 g (0.20 mol) of methyl 3-(dimethylcarbamoyl)-propanoate,[22,23] 18.0 g (0.081 mol) of purified phosphorus pentasulfide, and 12.0 mL (0.086 mol) of dry triethylamine in 200 mL of dry dichloromethane was heated at reflux for 24 h. The crude thioamide was isolated by dichloromethane extraction including base and acid washes ($MgSO_4$) and was filtered through a 1-in. pad of silica gel on a 150-mL coarse fritted funnel (350 mL of 50% ethyl acetate–toluene as eluting solvent). Removal of solvents under reduced pressure followed by distillation afforded 29.1 g (83%) of the thioamide **12** as a yellow oil: bp 85–100 °C (0.09 mm); IR (neat) 1720 (C=O), 1500 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 3.70 (s, 3 H, OCH_3), 3.50 and 3.37 (2 s, 6 H, NCH_3), 2.93 (s, 4 H, CH_2).

Anal. Calcd for $C_7H_{13}NO_2S$: C, 47.97; H, 7.48; N, 7.99; S, 18.27. Found: C, 47.98; H, 7.61; N, 7.99; S, 18.34.

1-[3-(Butylthio)propanoyl]azacyclopentane. A solution of 26.0 g (0.160 mol) of 3-(butylthio)propionic acid,[24] 12.0 mL (164 mmol) of thionyl chloride, and four drops of dimethylformamide[25] was allowed to stand at room temperature for 16 h. The resulting solution was dissolved in 25 mL of dry dichloromethane and was added dropwise over 30 min to an ice-cold solution of 30 mL (0.36 mol) of pyrrolidine in 150 mL of dry dichloromethane. The deep red solution was stirred at room temperature for 1 h, and the amide was isolated by dichloromethane extraction including an acid wash ($MgSO_4$) and then distillation: 31.2 g (90%); bp 132–137 °C (0.3 mm); IR (neat) 1625 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.2–3.6 (m, 4 H, NCH_2).

Anal. Calcd for $C_{11}H_{21}NOS$: C, 61.35; H, 9.83; N, 6.50; S, 14.89. Found: C, 61.46; H, 9.82; N, 6.52; S, 14.90.

1-[3-(Butylthio)propanethioyl]azacyclopentane (14). A solution of 31.2 g (0.145 mol) of the above amide and 7.0 g (0.032 mol) of purified phosphorus pentasulfide in 100 mL of xylenes was heated at reflux for 1 h. The solution was filterd while still hot through a coarse fritted funnel, and the residue was washed with 20 mL of toluene. Solvents were removed under reduced pressure, and the crude material was purified by chromatography of 150 g of silica gel (10% ethyl acetate–toluene). Distillation of the residue after removal of the solvents from the eluant afforded 21.2 g (63%) of the thioamide **14** as a yellow liquid: bp 160–165 °C (0.2 mm); IR (neat) 1465 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 3.5–4.0 (m, 4 H, NCH_2).

Anal. Calcd for $C_{11}H_{21}NS_2$: C, 57.09; H, 9.15; N, 6.05. Found: C, 57.05; H, 9.06; N, 6.07.

Intermolecular Sulfide Contraction. General Procedure. A solution of the requisite thioamide (50 mmol) and 6.5 mL (55 mmol) of ethyl iodoacetate[26] in 100 mL of dry acetonitrile was stirred in the dark for 24 h. A solution of 16.0 g (57 mmol) of the phosphine 5[6] in 10 mL of dry acetonitrile was added, and the resulting solution was heated under reflux for 2 h. The reaction mixture was allowed to cool to room temperature, and most of the acetonitrile was removed under reduced pressure. The residue was dissolved in 150 mL of dichloromethane and in 75 mL of a 1 M aqueous sodium dihydrogen phosphate solution. The layers were separated, and the aqueous phase was extracted once with a 25-mL portion of dichloromethane. The combined organic layers were washed with 50 mL of a saturated aqueous sodium chloride solution and dried over anhydrous $MgSO_4$. Removal of solvents under reduced pressure followed by distillation of the residue provided the β-enamino ester.

Alternatively, the β-keto ester was prepared by passing a crude enamino ester through 50 g of silica gel (25 to 50% ethyl acetate–cyclohexane). Solvents were removed under reduced pressure, the residue was slurried with 50 g of silica gel and 100 mL of cyclohexane, and the slurry was allowed to stand with occasional shaking for 2 h. The β-keto ester was isolated by filtration through a 150-mL coarse fritted funnel followed by washing of the silica gel with 200 mL of ethyl acetate and removal of solvents under reduced pressure. The slurry procedure was repeated if hydrolysis (as shown by ^1H NMR) was not complete. Distillation provided the ketone.

Ethyl 3-(*N*,*N*-Dimethylamino)-2-heptenoate (7a): yield 83%; bp 75–80 °C (0.12 mm); IR (neat) 1675 (C=O), 1530 (C=C), 790 cm^{-1} (C=CH); ^1H NMR ($CDCl_3$) δ 4.48 (s, 1 H, vinylic H), 4.04 (q, 2 H, J = 7 Hz, OCH_2), 2.92 (s, 6 H, NCH_3), 1.23 (t, 3 H, J = 7 Hz, OCH_2CH_3). A portion of the enamine was chromatographed on silica gel (5% ethyl acetate–toluene) to give the corresponding ketone, ethyl 3-oxoheptanoate, identical (IR, ^1H NMR, TLC, VPC) with an authentic sample:[27] IR (neat) 1735 (C=O), 1705 (C=O), 1635 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 4.18 (q, 2 H, J = 7 Hz, OCH_2), 3.40 (s, 2 H, C-2 H), 1.27 (t, 3 H, J = 7 Hz, OCH_2CH_3).

Ethyl 3-(1-Azacyclopentyl)-2-heptenoate (7b): yield 81%; bp 110–124 °C (0.45 mm); IR (neat) 1675 (C=O), 1570 (C=C), 790 cm^{-1} (C=CH); ^1H NMR ($CDCl_3$) δ 4.40 (s, 1 H, vinylic H), 4.08 (q, 2 H, J = 7 Hz, OCH_2), 1.40 (t, 3 H, J = 7 Hz, OCH_2CH_3). A portion of the enamine was chromatographed on silica gel (5% ethyl acetate–toluene) to afford the corresponding ketone which was identical (IR, ^1H NMR, TLC, VPC) with an authentic sample.

Ethyl 3-[4-(1,4-Oxaazacyclohexyl)]-2-heptenoate (7c): yield 77%; bp 105–120 °C (0.35 mm); IR (neat) 1675 (C=O), 1570 (C=C), 795 cm^{-1} (C=CH); ^1H NMR ($CDCl_3$) δ 4.67 (s, 1 H, vinylic H), 4.05 (q, 2 H, J = 7 Hz, OCH_2), 1.23 (t, 3 H, J = 7 Hz, OCH_2CH_3). A portion of the enamine was chromatographed on silica gel (5% ethyl acetate–toluene) to give the corresponding ketone which was identical (IR, ^1H NMR, TLC, VPC) with an authentic sample.

Ethyl (*E*)-3-(*N*,*N*-Dimethylamino)propenoate (9): yield 72%; bp 74–76 °C (2 mm) [lit.[28] bp 68–70 °C (1.5 mm), 90–91 °C (2.3 mm)]; ^1H NMR ($CDCl_3$) shifts for the vinylic protons were identical with those previously reported.[28b]

Ethyl 7,7-(Ethylenedioxy)-3-oxooctanoate (11): yield 64% bp 95–105 °C (0.03 mm); IR ($CHCl_3$) 1735 (C=O), 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.17 (q, 2 H, J = 7 Hz, OCH_2), 3.59 (s, 4 H, ketal), 3.40 (s, 2 H, C-2 H), 1.32 (s, 3 H, CH_3), 1.27 (t, 3 H, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.05; H, 8.23.

Ethyl Methyl 3-Oxohexanedioate (13): yield 54%; bp 89–95 °C (0.15 mm); IR (neat) 1735 (C=O), 1705 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.19 (q, 2 H, J = 7 Hz, OCH_2), 3.67 (s, 3 H, OCH_3), 3.47 (s, 2 H, C-2 H), 1.43 (t, 3 H, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.53; H, 6.98.

Ethyl 5-(Butylthio)-3-oxopentanoate (15): yield 47%; bp 94–102 °C (0.05 mm); IR ($CHCl_3$) 1740 (C=O), 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.12 (q, 2 H, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{11}H_{20}O_3S$: C, 56.86; H, 8.68; S, 13.80. Found: C, 56.84; H, 8.69; S, 13.86.

1-[(Carboethoxy)methylthio]ethylidenyldimethylammonium Iodide (16a). A solution of 0.520 g (5.0 mmol) of *N*,*N*-dimethylethanethioamide[20] and 0.65 mL (5.50 mmol) of ethyl iodoacetate[26] in 10 mL of anhydrous ether was stirred at room temperature for 12 h. The white precipitated salt was filtered by using a 15-mL medium fritted funnel and washed with 30 mL of anhydrous ether. After being dried under vacuum, the salt formed amounted to 1.07 g (67%): mp 115–116 °C; IR ($CHCl_3$) 1740 (C=O), 1615 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 4.38 (s, 2 H, SCH_2), 4.24 (q, 2 H, J = 7 Hz, OCH_2), 3.51 and 3.37 (2 s, 6 H, NCH_3), 2.93 (s, 3 H, $>CCH_3$), 1.30 (t, 3 H, J = 7 Hz, OCH_2CH_3).

1-[(Carboisopropoxy)methylthio]ethylidenyldimethylammonium Iodide 16b. By the procedure described above for the preparation of salt **16a**, 2.03 g (20 mmol) of *N*,*N*-dimethylethanethioamide[20] with 4.8 g (21 mmol) of isopropyl iodoacetate (**17b**)[29] and 20 mL of dry acetonitrile provided 6.3 g (97%) of

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the salt **16b** as a pale yellow solid: IR ($CHCl_3$) 1725 (C=O), 1600 cm^{-1} (C=C); ^1H (NMR ($CDCl_3$) δ 5.06 (septet, 1 H, J = 6 H, OCH), 4.40 (s, 2 H, SCH_2), 3.87 and 3.73 (2 s, 6 H, NCH_3), 2.76 (s, 3 H, CH_3), 1.48 (d, 6 H, $CHCH_3$).

1-[(Carboethoxy)methylthio]pentylidenyldimethylammonium Iodide 18. A solution of 1.48 g (10 mmol) of thioamide **6a** and 1.30 mL (11 mmol) of ethyl iodoacetate in 20 mL of dry acetonitrile was stirred for 18 h at room temperature. Solvents were removed under reduced pressure, and the red oil solidified after standing over anhydrous ether for several hours at 0 °C. Filtration and desiccation of the solid as described for iodide **16a** afforded 3.36 g (92%) of the salt **18** as an off-white solid: IR ($CHCl_3$) 1735 (C=O), 1615 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 4.33 (s, 2 H, SCH_2), 4.28 (q, 2 H, J = 7.5 Hz, OCH_2), 3.87 and 3.73 (2 s, 6 H, NCH_3), 1.33 (t, 3 H, J = 7.5 Hz, OCH_2CH_3).

Isopropyl 3-Oxoheptanoate (20b). By the general procedure for intermolecular sulfide contractions described above, 0.465 g (3.2 mmol) of thioamide **18** with 0.85 g (3.7 mmol) of iodoacetate **17b**, 0.90 g (3.2 mmol) of bis[(dimethylamino)propyl]phenylphosphine, and 10 mL of dry acetonitrile provided after chromatography on 40 g of silica gel (2% ethyl acetate–toluene) and Kugelrohr distillation at 100 °C (0.2 mm) 0.425 g (71 %) of β-keto ester **20b**: IR ($CHCl_3$) 1735 (C=O), 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 5.04 (septet, 1 H, J = 6 Hz, OCH), 3.38 (s, 2 H, C-2 H), 2.19 (t, 2 H, J = 7 Hz, C-4 H), 1.24 (d, 6 H, $CHCH_3$).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.54; H, 9.74.

Crossover Experiment I. A solution of iodide salt **16a** and 1.15 g (5.0 mmol) of isopropyl iodoacetate[29] in 10 mL of dry acetonitrile was heated under reflux for 1 h and cooled to room temperature. Solvents were removed under reduced pressure, and the red oil was dried under high vacuum until the residue solidified. The solid mass was broken apart and washed with 30 mL of anhydrous ether. Desiccation of the brown solid under vacuum provided 0.943 g; ^1H NMR ($CDCl_3$) showed that this solid was a 1:1 mixture of salts **16a** and **16b**.

Crossover Experiment II. A solution of 1.65 g (5.0 mmol) of salt **16b** and 1.80 g (5.0 mmol) of salt **18** in 10 mL of dry acetonitrile was heated under reflux for 1 h. The reddish solution was stirred at room temperature for 2 h, 3.0 g (11 mmol) of bis((dimethylamino)propyl)phenylphosphine[6] was added, and the clear solution was heated under reflux for 2 h. Workup as described above in the general procedure for intermolecular sulfide contraction provided after filtration through 20 g of silica gel (ethyl acetate) 1.79 g of a yellowish liquid. VPC analysis at 85 °C showed the presence of all four possible β-keto esters: **19a** (retention time 1.1 min), **19b** (retention time 1.3 min), **20a** (retention time 5.4 min), and **20b** (retention time 7.0 min). All esters were identified by coinjection with authentic samples. Heptanoates **20a** and **20b** were present in a 1:1 ratio.

Attempted Synthesis of 1,4-Diphenyl-1,3-butanedione (23). A solution of 0.507 g (1.21 mmol) of bromide **21**[11] in 5.0 mL of dry acetonitrile was treated with 0.70 g (2.5 mmol) of bis((dimethylamino)propyl)phenylphosphine as described above for intermolecular sulfide contractions. Workup afforded 0.352 g (81%) of thiophene **22**[11] as the sole product.

Attempted Synthesis of 2-(Dimethylamino)-3-propyl-4-phenylthiophene (24). A modified procedure of Hartmann and Mayer[11] was used. A solution of 0.293 g (2.0 mmol) of thioamide **6a** and 0.43 g (2.2 mmol) of phenacyl bromide in 5.0 mL of dry dichloromethane was stirred at room temperature for 17 h. Solvents were removed under reduced pressure, the residue was dissolved in 5.0 mL of methanol, and 0.10 mL (0.7 mmol) of triethylamine was added. The resulting solution was heated under reflux for 1.5 h, and solvents were removed under reduced pressure. TLC analysis (10% ethyl acetate–cyclohexane) showed at least ten spots, all of approximately equal intensity.

1-Phenyl-1,3-heptanedione (25). By the general procedure for intermolecular sulfide contraction described above, 0.730 g (5.0 mmol) of the thioamide **6a** with 1.01 g (5.1 mmol) of phenacyl bromide, 1.40 g (5.0 mmol) of bis[(dimethylamino)propyl]-phenylphosphine, and 10 mL of dry acetonitrile provided after chromatography on 90 g of silica gel (20% ethyl acetate–cyclohexane) and Kugelrohr distillation at 110 °C (0.1 mm) 0.681 g (66%) of dione **25**: IR ($CHCl_3$) 1600 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 7.8–8.1 (m, 2 H, m-Ar H), 7.3–7.6 (m, 3 H, o,p-Ar H), 6.34 (s, 2 H, CH_2).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.29; H, 7.86.

I. Six-Step Synthesis of the β-Hydroxy Thioamides 26a and 26b. A. 1-[3-(4-Oxothiacyclohexyl)carbonyl]azacyclopentane. Tripyrrolidinylborane was prepared by the procedure of Skinner and Smith[30] and was used without isolation according to the procedure of Nelson and Pelter.[31] To a mechanically stirred and ice–salt bath cooled solution of 68.2 g (0.96 mol) of dry pyrrolidine in 100 mL of dry dichloromethane under an argon atmosphere was added 80 mL of a 1.85 M solution of boron trichloride in dichloromethane at a rate such that the temperature of the reaction mixture remained below 20 °C. The resulting solution was stirred with cooling for 1 h, and a solution of 25.0 g (0.144 mol) of 3-(carbomethoxy)thian-4-one[32] in 50 mL of dry dichloromethane was added over 5 min. The reaction mixture was stirred at room temperature for 1 h and quenched with 50 mL of methanol. The solvents were removed under reduced pressure, and the residue was dissolved in 200 mL of ether. To this solution was carefully added 250 mL of 2 N aqueous hydrochloric acid. Ether extraction ($MgSO_4$) gave 5.15 g of a yellow solid. The aqueous phase was diluted with 50 mL of methanol and was briefly refluxed. Dichloromethane extraction ($MgSO_4$) afforded an additional 14.0 g of crude amide. The combined crude solids gave 16.9 g (55%) of slightly beige crystals upon recrystallization from benzene–petroleum ether: mp 121–123 °C; IR ($CHCl_3$) 1705 (C=O), 1620 cm^{-1} (C=O); ^1H NMR was uninformative.

Anal. Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57. Found: C, 56.29; H, 7.10; N, 6.45.

B. 1-[3-(*cis*- and *trans*-4-Hydroxythiacyclohexyl)carbonyl]azacyclopentane. A solution of 16.50 g (77.4 mmol) of the above β-keto amide in 250 mL of dry THF was added dropwise over 10 min to an ice-bath cooled, stirred slurry of 24.5 g (96 mmol) of lithium tri(*tert*-butoxy)aluminum hydride[33] in 100 mL of dry THF. After 45 min at 0 °C, this mixture was hydrolyzed,[34] and the resulting white precipitate was removed by filtration and washed with 50 mL of ether. The filtrates were combined, and the solvents were removed under reduced pressure. Chromatography of the residue on 300 g of silica gel (2 L of ethyl acetate followed by acetone) provided first the cis alcohol: 6.43 g (39%); mp 77–78 °C (benzene–petroleum ether); R_f 0.31 (ethyl acetate); IR ($CHCl_3$) 3400 (OH), 1615 (C=O), 935 cm^{-1} (axial[35] R–OH) (the OH stretch was concentration independent in CCl_4); ^1H NMR ($CDCl_3$) δ 5.21 (br s, 1 H, OH), 4.18 (br s, 1 H, >CHO–).

Anal. Calcd for $C_{10}H_{17}NO_2S$: C, 55.78; H, 7.96; N, 6.51. Found: C, 55.73; H, 8.01; N, 6.52.

The trans alcohol eluted second: 6.28 g (38%); mp 130–133 °C (ethyl acetate); R_f 0.09 (ethyl acetate); IR ($CHCl_3$) 3420 (OH), 1620 (C=O), 1070 cm^{-1} (equatorial[35] R–OH) (the OH stretch was concentration independent in CCl_4); ^1H NMR was not informative.

Anal. Calcd for $C_{10}H_{17}NO_2S$: C, 55.78; H, 7.96; N, 6.51. Found: C, 55.89; H, 8.00; N, 6.42.

C. 1-[(2*R,3*S**)-3-Hydroxy-2-methylpentanoyl]azacyclopentane.** A solution of 6.97 g (32.4 mmol) of the cis thioether in 150 mL of absolute ethanol was heated under reflux in the presence of 50 mL of W-4 Raney nickel[36] for 1 h. The hot solution was filtered through Celite, and the resulting cake was washed with 350 mL of absolute ethanol. Removal of solvents under reduced pressure afforded 5.42 g (90%) of the desulfurized amide as a white solid: mp 62–63 °C (petroleum ether); IR ($CHCl_3$) 3390

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(OH), 1600 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.77 (br s, 1 H, CHOH), 1.14 (d, 3 H, J = 7 Hz, $CHCH_3$), 0.94 (t, 3 H, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.70; H, 10.36, N, 7.46.

D. 1-[(2*R,3*S**)-3-Acetoxy-2-methylpentanoyl]azacyclopentane.** To a solution of 5.42 g (29.3 mmol) of the corresponding alcohol and 2.8 mL (34.6 mmol) of dry pyridine in 40 mL of dry dichloromethane cooled in an ice bath was added 2.4 mL (33.8 mmol) of acetyl chloride. The solution was stirred at room temperature for 3 h and poured into 25 mL of 2 N aqueous hydrochloric acid. Dichloromethane extraction including bicarbonate wash ($MgSO_4$) followed by distillation gave 5.82 g (88%): bp 98–102 °C (0.05 mmHg); IR ($CHCl_3$) 1725 (C=O), 1615 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 5.13 (dt, 1 H, J = 5 Hz, J' = 8 Hz, CHOH), 2.05 (s, 3 H, CH_3C=O), 1.10 (d, 3 H, J = 7, $CHCH_3$), 0.89 (t, 3 H, J = 7 Hz, CH_2CH_3). An analytical sample was prepared by Kugelrohr distillation at 90 °C (0.03 mm).

Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.44; H, 9.33; N, 6.30.

E. 1-[(2*R,3*S**)-3-Acetoxy-2-methylpentanethioyl]azacyclopentane.** A solution of 5.82 g (25.6 mmol) of the corresponding amide in 125 mL of dry dioxane was heated at reflux with 6.0 g (26.9 mmol) of purified phosphorus pentasulfide for 1 h. The supernatant liquid was decanted from the black precipitate, and the precipitate was washed with 100 mL of ether. Isolation by ether extraction including base wash gave a black residue. Chromatography on 180 g of silica gel (10% ethyl acetate–benzene) afforded 2.16 g (35%) of the thioamide as a clear oil: IR ($CHCl_3$) 1715 (C=O), 1475 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 5.30 (dt, 1 H, J = 4 Hz, J' = 5 Hz, >CHO–), 2.08 (s, 3 H, CH_3C=O), 1.20 (d, 3 H, J = 7 Hz, $CHCH_3$), 0.83 (t, 3 H, J = 9 Hz, CH_2CH_3). An analytical sample was prepared by Kugelrohr distillation at 125 °C (0.01 mm).

Anal. Calcd for $C_{12}H_{21}NO_2S$: C, 59.22; H, 8.70; N, 5.76. Found: C, 59.35; H, 8.70; N, 5.90.

F. 1-[(2*R,3*S**)-3-Hydroxy-2-methylpentanethioyl]azacyclopentane (26a).** A solution of 2.16 g (8.9 mmol) of the acetate in 26 mL of a 0.5 M solution of lithium hydroxide in 80% aqueous methanol was stirred at room temperature for 1 H. The solution was diluted with 50 mL of water. Isolation by ether extraction ($MgSO_4$) provided after chromatography on 175 g of silica gel (25% ethyl acetate–benzene) 1.60 g (89%) of an oil: IR ($CHCl_3$) 3300 (OH), 1475 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 2.93 (dq, 1 H, J = 7 Hz, J' = 2 Hz, $CHCH_3$), 1.20 (d, 3 H, J = 7 Hz, $CHCH_3$). An analytical sample was prepared by Kugelrohr distillation at 100 °C (0.03 mm).

Anal. Calcd for $C_{10}H_{19}NOS$: C, 59.66; H, 9.51; N, 6.96. Found: C, 59.58; H, 9.58; N, 7.01.

1-[(2*R,3*R**)-3-Hydroxy-2-methylpentanoyl]azacyclopentane.** By method I.C, 6.73 g (31.3 mmol) of the *trans*-thioether in 70 mL of absolute ethanol was treated with 70 mL of W-4 Raney nickel. Workup as described above gave 5 g of yellowish liquid. Chromatography on 190 g of silica gel (5% acetone–ethyl acetate) yielded 2.75 g (47%) of the hydroxy amide as a clear oil: IR (neat) 3390 (OH), 1605 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.13 (br s, 1 H, CHOH), 1.52 (d, 3 H, J = 8 Hz, $CHCH_3$). An analytical sample was prepared by Kugelrohr distillation at 70 °C (0.2 mm).

Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.74; H, 10.27; N, 7.49.

1-[(2*R,3*R**)-3-methylpentanoyl]azacyclopentane.** By method I.D for the preparation of the epimeric acetate, 2.68 g (14.5 mmol) of the corresponding alcohol with 1.50 mL (18.5 mmol) of dry pyridine, 1.25 mL (17.6 mmol) of acetyl chloride, and 20 mL of dry dichloromethane provided after Kugelrohr distillation at 140 °C (0.1 mm) 2.99 g (91%) of the acetate as a clear oil: IR ($CHCl_3$) 1735 (C=O), 1650 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.98 (dt, 1 H, J = 4 Hz, J' = 8 Hz, >CHO–), 2.02 (s, 3 H, CH_3C=O), 1.15 (d, 3 H, J = 7 Hz, $CHCH_3$), 0.85 (t, 3 H, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.45; H, 9.53; N, 6.31.

1-[(2*R,3*R**)-3-Acetoxy-2-methylpentanethioyl]azacyclopentane.** A solution of 2.05 g (9.04 mmol) of the amide in 100 mL of dry dioxane was heated under reflux with 1.00 g (4.50 mmol) of purified phosphorus pentasulfide for 1 h. The reaction mixture was cooled to room temperature, 50 mL of a 2 N aqueous hydrochloric acid solution was added, and the resulting solution was stirred for 10 min. Then 50 mL of a saturated aqueous sodium chloride solution was added, and ether extraction including bicarbonate wash ($MgSO_4$) gave 1.95 g of a reddish oil. Chromatography on 175 g of silica gel (10% ethyl acetate–benzene) provided 1.45 g (66%) of a pale yellow oil: IR (neat) 1720 (C=O), 1470 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 5.10 (dt, 1 H, J = 4 Hz, J' = 7 Hz, >CHO–), 3.6–4.0 (m, 4 H, NCH_2), 1.95 (s, 3 H, CH_3C=O), 1.25 (d, 3 H, J = 7 Hz, $CHCH_3$), 0.88 (t, 3 H, J = 7 Hz, CH_2CH_3). An analytical sample was prepared by Kugelrohr distillation at 120 °C (0.01 mm).

Anal. Calcd for $C_{12}H_{21}NO_2S$: C, 59.22; H, 8.70; N, 5.76. Found: C, 59.19; H, 8.75; N, 5.88.

1-[(2*R,3*R**)-3-Hydroxy-2-methylpentanethioyl]azacyclopentane (26b).** By metnod I.F for the preparation of alcohol **26a**, 1.45 g (5.96 mmol) of the acetate with 20 mL of a 0.5 M solution of lithium hydroxide in 80% aqueous methanol provided after chromatography on 45 g of silica gel (20% ethyl acetate–benzene) 1.07 g (89%) of alcohol **26b** as an oil: IR ($CHCl_3$) 3310 (OH), 1475 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 1.21 (d, 3 H, J = 7 Hz, $CHCH_3$), 0.98 (t, 3 H, J = 7 Hz, CH_2CH_3). An analytical sample was prepared by Kugelrohr distillation at 70 °C (0.01 mm).

Anal. Calcd for $C_{10}H_{19}NOS$: C, 59.66; H, 9.51; N, 6.96. Found: C, 59.66; H, 9.49; N, 6.95.

II. Preparation of α-Hydroxy Thioamide 28. A. 1-(2-Acetoxy-2-phenylacetyl)azacyclopentane. A solution of 14.56 g (68.5 mmol) of acetylmandelyl chloride[37] in 30 mL of dry dichloromethane was added dropwise over 30 min to an ice-bath cooled solution of 17.0 mL (204 mmol) of pyrrolidine in 150 mL of dry dichloromethane. The resulting solution was stirred at room temperature for 30 min, and the crude product was isolated by dichloromethane extraction including acid and bicarbonate washes ($MgSO_4$). The crude product was filtered through 25 g of silica gel with 300 mL of 50% ethyl acetate–toluene, the solvent was removed, and recrystallization of the residue from ether–pentane afforded 10.86 g (64%) of the amide as white crystals: mp 105–106 °C; IR ($CHCl_3$) 1735 (C=O), 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 5.95 (s, 1 H, >CHO–), 2.13 (s, 3 H, CH_3C=O).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.00; H, 6.95; N, 5.69.

B. 1-(2-Acetoxy-2-phenylethanethioyl)azacyclopentane. A modified procedure of Klingsberg and Papa[38] was used. A solution of 9.51 g (38.5 mmol) of the amide and 8.70 g (39.1 mmol) of purified phosphorus pentasulfide in 200 mL of dry pyridine was heated under reflux for 2.5 h and poured without cooling into 200 mL of hot water. The resulting solution was diluted with 200 mL of water and 200 mL of saturated aqueous sodium chloride solution, and the thioamide was isolated by ether extraction including carbonate wash ($MgSO_4$). The crude thioamide was taken up in dichloromethane and filtered through 50 g of silica gel with 275 mL of 25% ethyl acetate–toluene. Recrystallization of the yellowish crystals from ethanol provided 8.81 g (87%) of the thioamide as white crystals: mp 105.5–106.5 °C with reddening (ether–pentane); IR ($CHCl_3$) 1735 (C=O), 1485 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 6.37 (s, 1 H, >CHO–), 2.17 (s, 3 H, CH_3C=O).

Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.85, H, 6.51; N, 5.32; S, 12.18. Found: C, 63.80; H, 6.54; N, 5.31; S, 12.13.

C. 1-(2-Hydroxy-2-phenylethanethioyl)azacyclopentane (28). By the procedure above for the preparation of alcohol **26a**, 8.43 g (32.0 mmol) of the acetate with 96 mL of a 0.5 M solution of lithium hydroxide in 80% aqueous methanol provided after dichloromethane extraction ($MgSO_4$) and recrystallization from ethanol 6.59 g (93%) of alcohol **28** as a white solid: mp 91–92 °C; IR ($CHCl_3$) 3250 (OH), 1490 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 7.2–7.5 (m, 5 H, Ar H), 5.29 (d, 1 H, J = 8 Hz, OH), 5.11 (d, 1 H, J = 8 Hz; CHOH).

Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33; S, 14.49. Found: C, 65.06; H, 6.76; N, 6.40; S, 14.57.

Formation of 5- and 6-Membered Ring Lactones. General Procedure. A solution of the requisite alcohol (1.0 mmol) and 0.10 mL (1.26 mmol) of chloroacetyl chloride (or 0.11 mL (1.13 mmol) of chloropropionyl chloride) in 10 mL of dry dichloro-

(37) Thayer, F. K. "Organic Syntheses"; Wiley, New York, 1932; Collect. Vol. 1, 12–3.

(38) Klingsberg. E.; Papa, D. *J. Am. Chem. Soc.* **1951**, *73*, 4988–9.

methane was stirred at room temperature for 3 h. Solvents were removed under reduced pressure, and the residue was placed under vacuum (<0.5 mm) for 30 min.

The crude chloroacetate was dissolved in 20 mL of dry acetonitrile, and 0.18 g (1.2 mmol) of sodium iodide was added. The resulting solution was heated under reflux for 1 h, and 0.40 g (1.4 mmol) of the phosphine **5**[6] in 2.0 mL of dry acetonitrile was added at once. The reaction mixture was heated under reflux for 4 h and then diluted with 25 mL of dichloromethane. The resulting solution was washed once with 25 mL of a 2 M aqueous NaH_2PO_4 solution, and the aqueous phase was extracted with two 25-mL portions of dichloromethane. The combined organic phases were then washed with a saturated aqueous sodium chloride solution and dried ($MgSO_4$). After removal of solvents, chromatography of the residue of 10 g of silica gel afforded corresponding cyclic enamino lactone.

4-(1-Azacyclopentyl)-*cis*-5-methyl-6-ethyloxacyclohex-3-en-2-one (27a): yield 52%; R_f 0.19 (1% methanol–ethyl acetate); IR ($CHCl_3$) 1645 (C=O), 1580 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 4.51 (s, 1 H, vinylic H), 4.1–4.4 (m, 1 H, >CHO–), 1.10 (d, 3 H, J = 7 Hz, $CHCH_3$). An analytical sample was prepared by Kugelrohr distillation at 120 °C (0.1 mm).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.89; H, 9.08; N, 6.61.

4-(1-Azacyclopentyl)-*trans*-5-methyl-6-ethyloxacyclohex-3-en-2-one (27b): yield 74%; mp 80–81 °C (ether); R_f 0.25 (5% methanol–ethyl acetate); IR ($CHCl_3$) 1650 (C=O), 1580 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 4.43 (s, 1 H, vinylic H), 3.9–4.2 (m, 1 H, >CHO–), 1.33 (d, 3 H, J = 7 Hz, $CHCH_3$).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.93; H, 9.15; N, 6.78.

4-(1-Azacyclopentyl)-5-phenyloxacyclopent-3-en-2-one (29a): yield 69%; mp 137–138 °C (ethyl acetate); R_f 0.35 (ethyl acetate); IR ($CHCl_3$) 1725 (C=O), 1615 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 7.33 (s, 5 H, Ar H), 5.70 (s, 1 H, >CHO–), 4.67 (s, 1 H, vinylic H).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.40; H, 6.56; N, 6.14.

4-(1-Azacyclopentyl)-2-methyl-5-phenyloxacyclopent-3-en-2-one (29b): yield 63%; mp 119–120 °C (ethyl acetate); R_f 0.33 (50% ethyl acetate–toluene); IR ($CHCl_3$) 1710 (C=O), 1600 cm^{-1} (C=C); 1H NMR ($CDCl_3$) δ 7.25 (s, 5 H, Ar H), 5.52 (s, 1 H, >CHO–), 2.06 (s, 3 H, CH_3).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.76. Found: C, 73.97; H, 7.08; N, 5.80.

III. Preparation of ω-Hydroxy Thioamides 30a and 30b. A. Methyl 7-[(2-Oxacyclohexyl)oxy]heptanedithioate. According to the procedure of Brandsma and co-workers,[9] 11.05 g (50.1 mmol) of the corresponding chloride[39] in 50 mL of dry THF with 1.41 g (58 mmol) of magnesium turnings, 3.2 mL (53 mmol) of dry carbon disulfide in 10 mL of dry THF, and 3.3 mL (53 mmol) of iodomethane provided 12.7 g (92%) of a golden-yellow oil which was carried on to the next step without further purification: IR was uninformative; ^1H NMR δ 4.53 (br s, 1 H, >CHO–), 2.60 (s, 3 H, SCH_3). An analytical sample was prepared by chromatography on silica gel (benzene) followed by Kugelrohr distillation at 140 °C (0.15 mm).

Anal. Calcd for $C_{13}H_{24}O_2S_2$: C, 56.48; H, 8.75; S, 23.20. Found: C, 56.58; H, 8.84; S, 23.22.

B. 1-(7-Hydroxyheptanethioyl)azacyclopentane (30a). A solution of the above crude dithioester and 8.4 mL (101 mmol) of pyrrolidine in 50 mL of benzene was heated under reflux for 2 h. The solvents were removed under reduced pressure, the resulting yellow oil was dissolved in 100 mL of absolute methanol, and 1.5 mL of concentrated hydrochloric acid was added to acidify the solution. The resulting solution was stirred for 1 h, and 10 mL of a saturated aqueous potassium carbonate solution and 40 mL of water were added. Then most of the methanol was removed under reduced pressure, and the thioamide was isolated by ethyl acetate extraction. Chromatography on 250 g of silica gel (50% ethyl acetate–benzene) yielded 9.21 g (85% from the corresponding chloride) of the hydroxy thioamide **30a** as a slowly crystallizing oil: mp 30–32 °C; IR ($CHCl_3$) 3610 (OH), 1490 cm^{-1} (NC=S); ^1H NMR was uninformative. An analytical sample was prepared by Kugelrohr distillation at 140 °C (0.01 mm).

Anal. Calcd for $C_{11}H_{21}NOS$: C, 61.35; H, 9.83; N, 6.50; S, 14.89. Found: C, 61.41; H, 9.86; N, 6.51; S, 14.75.

2-(8-Chlorooctyloxy)oxacyclohexane. To a solution of 19.1 g (0.116 mol) of 8-chloro-1-octanol[40] in 13.0 mL (0.142 mol) of dihydropyran was added 0.5 mL of concentrated hydrochloric acid. The solution was stirred for 3 h, and then solid potassium carbonate was added. After fractional distillation of this solution through a 15-cm Vigreux column, there was obtained 22.5 g (78%) of the chloride as a clear liquid: bp 116–120 °C (0.4 mm); IR was uninformative; ^1H NMR ($CDCl_3$) δ 4.53 (br s, 1 H, >CHO–).

Anal. Calcd for $C_{13}H_{25}ClO_2$: C, 62.76; H, 10.13. Found: C, 62.72; H, 10.21.

Methyl 9-[(2-Oxacyclohexyl)oxy]nonanedithioate. According to the procedure of Brandsma and co-workers,[9] 12.46 g (50.1 mmol) of the chloride in 50 mL of dry THF with 1.41 g (58 mmol) of magnesium turnings, 3.2 mL (53 mmol) of dry carbon disulfide in 10 mL of dry THF, and 3.3 mL (53 mmol) of iodomethane gave the crude dithioester as a golden-yellow oil which was used without further purification: IR was uninformative; ^1H NMR ($CDCl_3$) δ 4.50 (br s, 1 H, >CHO–), 2.58 (s, 3 H, SCH_3). An analytical sample was prepared by chromatography on silica gel (5% ethyl acetate–benzene) followed by Kugelrohr distillation at 140 °C (0.05 mm).

Anal. Calcd for $C_{15}H_{28}O_2S_2$: C, 59.16; H, 9.27; S, 21.06. Found: C, 59.10; H, 9.27; S, 20.97.

1-(9-Hydroxynonanethioyl)azacyclopentane (30b). By method IIIC for the preparation of thioamide **30a**, the crude dithioester with 8.4 mL (101 mmol) of pyrrolidine and 50 mL of benzene followed by 2.0 mL of concentrated hydrochloric acid and 50 mL of methanol gave a yellowish oil which slowly crystallized. Chromatography on 250 g of silica gel (600 mL of 25% ethyl acetate–benzene followed by 50% ethyl acetate–benzene) yielded 9.83 g (81% from the chloride) of thioamide **30b** as a white solid: mp 57–57.5 °C (ether); IR ($CHCl_3$) 3640 (OH), 1490 cm^{-1} (NC=S); ^1H NMR was uninformative.

Anal. Calcd for $C_{13}H_{25}NOS$: C, 64.15; H, 10.35; N, 5.85; S, 13.17. Found: C, 64.14; H, 10.13; N, 5.85; S,

IV. Preparation of γ-Hydroxy Thioamide 33. A. 1-(4-Hydroxybutanoyl)azacyclopentane. A solution of 17.2 g (0.20 mol) of γ-butyrolactone and 25 mL (0.30 mol) of dry pyrrolidine in 150 mL of dry benzene was heated at reflux for 3 h. Solvents were removed under reduced pressure, and the residue was distilled to yield 28.2 g (90%) of the hydroxy amide as a viscous liquid: bp 135–145 °C (0.01 mm); IR (neat) 3350 (OH), 1620 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.3–3.8 (m, 4 H, NCH_2), 2.4 (t, 2 H, J = 7 Hz, CH_2C=O).

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.17; H, 9.60; N, 8.90.

B. 1-(4-Acetoxybutanoyl)azacyclopentane. By the esterification procedure described above, 27.0 g (0.172 mol) of the alcohol with 16.0 mL (0.198 mol) of dry pyridine and 13.5 mL (0.190 mol) of acetyl chloride in 170 mL of dry dichloromethane provided after distillation 25.8 g (75%) of the acetate as a clear oil: bp 118–122 °C (0.15 mm); IR (neat) 1715 (C=O), 1620 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.07 (t, 2 H, J = 6 Hz, OCH_2), 2.02 (s, 3 H, CH_3C=O).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.30; H, 8.63; N, 7.05.

C. 1-(4-Acetoxybutanethioyl)azacyclopentane. By the procedure described above, 8.06 g (40.5 mmol) of the amide with 4.55 g (20.5 mmol) of purified phosphorus pentasulfide and 200 mL of dry dioxane provided 6.7 g of a red oil. Chromatography on 300 g of silica gel (25% ethyl acetate–benzene) gave a yellow solid (5.74 g, 66%) which was crystallized from absolute ethanol to yield 4.87 g (56%) of the thioamide as white needles: mp 36–37 °C; IR ($CHCl_3$) 1730 (C=O), 1490 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 4.12 (t, 2 H, J = 6 Hz, OCH_2), 2.03 (s, 3 H, CH_3C=O).

Anal. Calcd for $C_{10}H_{17}NO_2S$: C, 55.78; H, 7.96; N, 6.51. Found: C, 55.75; H, 7.92; N, 6.53.

D. 1-(4-Hydroxybutanethioyl)azacyclopentane (33). A solution of 3.23 g (15.0 mmol) of the corresponding acetate in 40

(39) Fournet, A.; Achard, R.; Morel, J. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1965**, *260*, 5054–5.

(40) (a) Coleman, W. R.; Bywater, W. G. *J. Am. Chem. Soc.* **1944**, *66*, 1821–3. (b) Bennett, G. M.; Mosses, A. N. *J. Chem. Soc.* **1931**, 1697–1701.

mL of a 0.5 M solution of lithium hydroxide in 80% aqueous methanol was stirred at room temperature for 4 h. The solution was diluted with 25 mL of water and 50 mL of a saturated aqueous sodium chloride solution, and the thioamide was isolated by chloroform extraction ($MgSO_4$) as a red oil. Kugelrohr distillation at 160 °C (0.1 mm) yielded 2.10 g (81%) of thioamide **33** as a yellow oil: IR (neat) 3390 (OH), 1460 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) was uninformative. An analytical sample was prepared by chromatography on silica gel (50% ethyl acetate–toluene) followed by Kugelrohr distillation at 100 °C (0.1 mm).

Anal. Calcd for $C_8H_{15}NOS$: C, 55.45; H, 8.73; N, 8.08; S, 18.51. Found: C, 55.43; H, 8.64, N, 8.17; S, 18.41.

V. Preparation of Acetylenic ω-Hydroxy Thioamide 35a. A. 8-[(2-Oxacyclohexyl)oxy]oct-4-yn-1-ol. Lithium wire (5.60 g, 0.81 mol) was slowly added to an anhydrous ammonia solution containing 0.50 g of ferric nitrate decahydrate.[41] After formation of the amide was complete, a solution of 33.6 g (0.40 mol) of 4-pentyn-1-ol[42] in 200 mL of dry THF was added over 15 min, and the resulting solution was stirred for 1 h. A solution of 75.7 g (0.34 mol) of 2-(3-bromopropoxy)oxacyclohexane[43] in 200 mL of dry THF was added over 5 min, and the solution was stirred at reflux for 9 h. The ammonia was allowed to evaporate overnight, and 500 mL of water was added. Isolation by ether extraction followed by distillation afforded 67.3 g (88%) of the alkylated acetylene: bp 125–135 °C (0.1 mm); IR (neat) 3400 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 4.57 (br s, 1 H, >CH–), 3.3–4.0 (m, 6 H, OCH_2).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.91; H, 9.72.

B. 2-(8-Chloro-4-octynyloxy)oxacyclohexane. A modified procedure of I. M. Downie and co-workers[44] was used. To a solution of 22.6 g (0.100 mol) of the alcohol and 12.0 mL (0.124 mol) of carbon tetrachloride in 200 mL of dry THF cooled with a dry ice–acetone bath was added 19.0 mL (0.105 mol) of hexamethylphosphorus triamide. The solution was allowed to warm to room temperature by stirring for 4.5 h. The solvents were removed under reduced pressure, and the residue was taken up in 500 mL of hexane. The hexane solution was washed with two 100-mL portions of water and dried over anhydrous Na_2SO_4. The solution was filtered, solvents were removed under reduced pressure, and then distillation of the residue afforded 17.5 g (71%) of the chloride as a clear liquid: bp 110–120 °C (0.2 mm); IR (neat) lacked hydroxyl stretch; ^1H NMR ($CDCl_3$) δ 4.53 (br s, 1 H, >CH–), 3.60 (t, 2 H, J = 6 Hz, CH_2Cl).

Anal. Calcd for $C_{13}H_{21}ClO_2$: C, 63.79; H, 8.65. Found: C, 63.72; H, 8.76.

C. Methyl (*E*)-9-[(2-Oxacyclohexyl)oxy]non-5-enedithioate. According to the procedure of Brandsma and co-workers,[9] 12.48 g (51 mmol) of the above chloride in 50 mL of dry THF with 1.42 g (59 mmol) of magnesium turnings, 3.2 mL (53 mmol) of dry carbon disulfide in 10 mL of dry THF, and 3.3 mL (53 mmol) of iodomethane afforded the corresponding crude dithioester as a golden-yellow oil which was used without further purification: IR was uninformative; ^1H NMR ($CDCl_3$) δ 4.58 (br s, 1 H, >CH–), 2.62 (s, 3 H, SCH_3). An analytical sample was prepared by chromatography on silica gel (5% ethyl acetate–toluene) followed by Kugelrohr distillation at 120 °C (0.005 mm).

Anal. Calcd for $C_{15}H_{24}O_2S_2$: C, 59.96; H, 8.05; S, 21.34. Found: C, 59.97; H, 8.03; S, 21.30.

D. 1-(9-Hydroxy-5-nonynethioyl)azacyclopentane (35a). By the procedure described above for the preparation of thioamide **30a**, the above crude dithioester with 8.4 mL (101 mmol) of pyrrolidine and 50 mL of toluene followed by 1.0 mL of concentrated hydrochloric acid and 50 mL of methanol gave a dark red oil. Chromatography on 175 g of silica gel (50% ethyl acetate–toluene) afforded 4.99 g (41% of the thioamide **35a** as a reddish oil, one spot by TLC (R_f 0.30, 50% ethyl acetate–toluene): IR ($CHCl_3$) 3640, 3450 (OH), 1490 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 3.5–3.9 (m, 6 H, NCH_2, OCH_2), 2.7–2.9 (m, 2 H, CH_2C=S). An analytical sample was prepared by Kugelrohr distillation at 175 °C (0.05 mm).

Anal. Calcd for $C_{13}H_{21}NOS$: C, 65.23; H, 8,84; N, 5.85; S, 13.40. Found: C, 65.19; H, 8.93; N, 5.77; S, 13.46.

VI. Preparation of Isomeric Olefinic ω-Hydroxy Thioamides 35b and 35c. A. (*E*)-8-[(2-Oxacyclohexyl)oxy]oct-4-en-1-ol. According to the procedure of Campbell and Eby,[45] a solution of 34.0 g (0.15 mol) of the acetylene in 10 mL of dry THF with 11.0 g (0.48 mol) of sodium metal in 500 mL of dry ammonia afforded after distillation 31.4 g (91%) of the trans alkene: bp 120–130 °C (0.08 mm); IR (neat) 3400 (OH), 962 cm^{-1} (trans C=C); ^1H NMR ($CDCl_3$) δ 5.3–5.5 (m, 2 H, vinylic H), 4.48 (br s, 1 H, >CH–).

Anal. Calcd for $C_{13}H_{24}O_3$: C, 63.79; H, 8.65. Found: C, 63.72; H, 8.76.

B. 2-[(*E*)-8-Chloro-4-octenyloxy]oxacyclohexane. By the procedure described above for the preparation of the chloroalkyne, 28.5 g (0.125 mol) of the alcohol with 25.0 mL (0.125 mol) of hexamethylphosphorus triamide, 17.0 mL (0.176 mol) of carbon tetrachloride, and 200 mL of dry THF afforded 25.1 g (81%) of the chloride: bp 105–115 °C (0.15 mm); IR (neat) lacked hydroxyl stretch; ^1H NMR ($CDCl_3$) δ 5.3–5.5 (m, 2 H, vinylic H), 4.55 (br s, 1 H, >CH–).

Anal. Calcd for $C_{13}H_{23}ClO_2$: C, 63.27; H, 9.39. Found: C, 63.14; H, 9.35.

C. Methyl (*E*)-9-(2-Cyclohexyloxy)non-5-enedithioate. According to the procedure of Brandsma and co-workers,[9] 12.41 g (50.3 mmol) of the corresponding chloride in 50 mL of dry THF with 1.44 g (59 mmol) of magnesium turnings, 3.2 mL (53 mmol) of dry carbon disulfide in 10 mL of dry THF, and 3.3 mL (53 mmol) of iodomethane afforded the crude dithioester which was used without further purification: IR (neat) 964 cm^{-1} (trans C=C); ^1H NMR δ 5.3–5.5 (m, 2 H, vinylic H), 4.52 (br s, 1 H, >CH–), 2.57 (s, 3 H, SCH_3). An analytical sample was prepared by chromatography on silica gel (2% ethyl acetate–toluene) followed by Kugelrohr distillation at 150 °C (0.07 mm).

Anal. Calcd for $C_{15}H_{26}O_2S_2$: C, 59.56; H, 8.66; S, 21.20. Found: C, 59.50; H, 8.71; S, 21.20.

D. 1-[(*E*)-9-Hydroxy-5-nonenethioyl]azacyclopentane (35b). By the procedure described above for the preparation of thioamide **30a**, the crude dithioester with 8.4 mL (101 mmol) of pyrrolidine and 50 mL of benzene followed by 1.0 mL of concentrated hydrochloric acid and 50 mL of methanol afforded after chromatography on 180 g of silica gel (50% ethyl acetate–toluene) 7.57 g (62%) of thioamide **35b**: IR ($CHCl_3$) 3625, 3425 (OH), 1490 cm^{-1} (NC=S), 980 (trans (C=C); ^1H NMR ($CDCl_3$) δ 5.3–5.5 (m, 2 H, vinylic H), 3.5–4.0 (m, 6 H, NCH_2, OCH_2). An analytical sample was prepared by Kugelrohr distillation at 150 °C (0.001 mm).

Anal. Calcd for $C_{13}H_{23}NOS$: C, 64.68; H, 9.60; N, 5.80; S, 13.28. Found: C, 64.67; H, 9.55; N, 5.78; S, 13.32.

(*Z*)-8-[(2-Oxacyclohexyl)oxy]oct-4-en-1-ol. The procedure of Brown and Brown[46] was used. To 1.25 g (5.0 mmol) of nickel(II) acetate tetrahydrate in 40 mL of 95% ethanol was added dropwise 5 mL of a 1.0 M solution of sodium borohydride in 95% ethanol. A solution of 11.31 g (50.0 mmol) of the corresponding acetylene in 10 mL of 95% ethanol was added and the resulting solution was stirred under a hydrogen atmosphere for 4.5 h, by which time VPC analysis (170 °C, retention times: acetylene, 1.43 min; alkene, 1.25 min) indicated that the reaction was complete. The reaction mixture was filtered through Celite with about 200 mL of ethyl acetate, and the filtrate was concentrated under reduced pressure. The residue was filtered through 40 g of alumina (200 mL of 35% ethyl acetate–toluene), solvents were removed, and the residue was distilled to give 9.59 g (84%) of the cis olefin: bp 105–118 °C (0.1 mm); IR (neat) 3400 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 5.37 (t, 2 H, J = 5 Hz, vinylic H), 4.70 (br s, 1 H, >CH–).

Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.49; H, 10.64.

2-[(*Z*)-8-Chloro-4-octenyloxy]oxacyclohexane. By method VB, 9.54 g (41.8 mmol) of the alcohol with 9.1 mL of hexa-

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methylphosphorus triamide, 6.0 mL of carbon tetrachloride, and 200 mL of dry THF afforded 6.97 g (68%) of the chloride: bp 110–115 °C (0.3 mm); IR (neat) lacked hydroxyl stretch; ^{1}H NMR ($CDCl_3$) δ 5.2–5.6 (m, 2 H, vinylic H), 4.55 (br s, 1 H, >CH–).

Anal. Calcd for $C_{13}H_{23}ClO_2$: C, 63.27; H, 9.39. Found: C, 63.37; H, 9.39.

Methyl (*Z*)-9-[(2-Oxacyclohexyl)oxy]non-5-enedithioate. According to the procedure of Brandsma and co-workers,[9] 6.17 g (25.0 mmol) of the chloride in 25 mL of dry THF with 0.75 g (31 mmol) of magnesium turnings, 1.60 mL (27 mmol) of dry carbon disulfide in 5 mL of dry THF, and 1.80 mL (29 mmol) of iodomethane afforded the crude dithioester which was used without further purification: IR was uninformative; ^{1}H NMR ($CDCl_3$) δ 5.3–5.5 (m, 2 H, vinylic H), 4.53 (br s, 1 H, >CH–), 2.60 (s, 3 H, SCH_3). An analytical sample was prepared by chromatography on alumina (toluene) followed by Kugelrohr distillation at 130 °C (0.005 mm).

Anal. Calcd for $C_{15}H_{26}O_2S_2$: C, 59.56; H, 8.66; S, 21.20. Found: C, 59.52; H, 8.62; S, 21.39.

1-[(*Z*)-9-Hydroxy-5-nonenethioyl]azacyclopentane (35c). By method V.D for the preparation of thioamide **30a**, the crude dithioester with 5.0 mL (60 mmol) of dry pyrrolidine and 30 mL of dry benzene followed by 0.5 mL of concentrated hydrochloric acid and 30 mL of methanol afforded after chromatography on 330 g of alumina (30% ethyl acetate–toluene) 4.51 g (75%) of thioamide **35c** as a viscous oil (one spot by TLC, R_f 0.30, 50% ethyl acetate–toluene): IR ($CHCl_3$) 3450 cm^{-1} (OH), 1495 cm^{-1} (NC=S); ^{1}H NMR ($CDCl_3$) δ 5.2–5.5 (m, 2 H, vinylic H), 3.5–3.9 (m, 6 H, OCH_2, NCH_2). An analytical sample was prepared by Kugelrohr distillation at 150 °C (0.001 mm).

Anal. Calcd for $C_{13}H_{23}NOS$: C, 64.68; H, 9.60; N, 5.80; S, 13.28. Found: C, 64.71; H, 9.68; N, 5.84; S, 13.26.

VII. Preparation of Ester-Linked ω-Hydroxy Thioamide 37. 4-Hydroxybutyl 3-(Dimethylthiocarbamoyl)propanoate (37). A solution of 8.76 g (50.0 mmol) of ester **12**, 0.10 g (2.0 mmol) of sodium methoxide, and 45 mL of 1,4-butanediol was stirred under vacuum (<1 mm) for 1 h. The reaction mixture was diluted with 250 mL of water, and the crude hydroxy ester was isolated by chloroform extraction ($MgSO_4$). Chromatography on 325 g of silica gel (1.0 L of 2% methanol–ethyl acetate, 1.0 L of 5% methanol–ethyl acetate, 1.0 L of 10% methanol–ethyl acetate) yielded 7.17 g (61%) of hydroxy ester **37** as a viscous oil: R_f 0.28 (ethyl acetate); IR ($CHCl_3$) 3400 (OH), 1730 (C=O), 1520 cm^{-1} (NC=S); ^{1}H NMR ($CDCl_3$) δ 3.47 and 3.35 (2 s, 2 6 H, NCH_3), 2.90 (s, 4 H, $O{=}CCH_2CH_2C{=}S$). An analytical sample was prepared by Kugelrohr distillation at 140 °C (0.001 mm).

Anal. Calcd for $C_{10}H_{19}NO_3S$: C, 51.47; H, 8.21; N, 6.00. Found: C, 51.46; H, 8.22; N, 5.91.

VIII. Multistage Preparation of Ketal 39a and Ketone 39b ω-Hydroxy Thioamides. A. 1-(5-Hydroxypentanoyl)azacyclopentane. Treatment of a solution of 50.2 g (0.50 mol) of δ-valerolactone in 350 mL of benzene with 65 mL (0.78 mol) of pyrrolidine provided 70.6 g (82%) of the corresponding hydroxy amide as a yellow viscous oil: bp 135–143 °C (0.005 mm); IR ($CHCl_3$) 3400 (OH), 1625 cm^{-1} (C=O); ^{1}H NMR was uninformative.

B. 1-(5-Oxopentanoyl)azacyclopentane. Oxidation was accomplished by the procedure of Swern and co-workers.[47] A solution of 20.0 mL (0.229 mol) of oxalyl chloride in 600 mL of dichloromethane was maintained at −25 to −50 °C by a dry ice–acetone bath while 33.0 mL (0.465 mol) of dry Me_2SO was added over 15 min. The solution was stirred for 5 min and then the alcohol in 80 mL of dichloromethane was added over 10 min while the temperature of the reaction mixture was kept at −45 to −50 °C. The resulting solution was stirred with cooling for 5 min, and 164 mL (1.18 mol) of triethylamine was added at once. The resulting solution was stirred with cooling for 5 min and then allowed to warm to room temperature. The reaction was quenched with 450 mL of water, and the aldehyde was isolated by dichloromethane extraction ($MgSO_4$) as a red oil. Flash chromatography (50-mm column, 50% acetone–petroleum ether) gave 26.8 g (79%) of the amide aldehyde as a red liquid (one spot by TLC, R_f 0.38, 50% acetone–petroleum ether): IR ($CHCl_3$) 2750 (aldehyde CH), 1725 (C=O), 1640 cm^{-1} (C=O); ^{1}H NMR δ 9.75 (t, 1 H, J = 1 Hz, HC=O), 3.3–3.6 (m, 4 H, NCH_2). An analytical sample was prepared by Kugelrohr distillation at 160 °C (0.005 mm).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.73; H, 8.81; N, 8.26.

C. 1-[5-Hydroxy-9-[(2-oxacyclohexyl)oxy]nonanoyl]azacyclopentane. A solution of the Grignard reagent was prepared from 34.0 g (0.176 mol) of 2-(4-chlorobutyloxy)oxacyclohexane,[48] 5.10 g (0.210 mol) of magnesium turnings, and 100 mL of dry THF. The Grignard reagent was added dropwise over 15 min to a stirred solution of 26.8 g (0.158 mol) of the aldehyde in 160 mL of dry THF maintained at −50 °C by a dry ice–acetone bath. The resulting solution was stirred for 5 min and then warmed to 0 °C by stirring in an ice–water bath for 15 min. The reaction mixture was quenched by the careful addition of 100 mL of saturated aqueous ammonium chloride solution followed by 400 mL of water. The alcohol was isolated by dichloromethane extraction ($MgSO_4$) and purified by flash chromatography (60-mm column, 50% acetone–petroleum ether) to yield 32.1 g (62%) of the alcohol as one spot by TLC (R_f 0.34, 50% acetone–petroleum ether): IR ($CHCl_3$) 3450 (OH), 1630 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 4.62 (br s, 1 H, >CH–). An analytical sample was prepared by Kugelrohr distillation at 200 °C (0.025 mm).

Anal. Calcd for $C_{18}H_{33}NO_4$: C, 66.02; H, 10.16; N, 4.28. Found: C, 65.90; H, 10.18; N, 4.30.

D. 1-[9-[(2-Oxacyclohexyl)oxy]-5-[(2,2,2-trichloroethoxy)formyloxy]nonanoyl]azacyclopentane. To a solution of 27.0 g (82.5 mmol) of the alcohol and 7.1 mL (88 mmol) of dry pyridine in 150 mL of dry dichloromethane cooled with a dry ice–acetone bath was added over 2 min 11.9 mL (86.4 mmol) of trichloroethyl chloroformate. The resulting solution was warmed to 0 °C and stirred for 2.5 h. The carbonate was isolated by ether extraction ($MgSO_4$) as a red oil, and purification by flash chromatography (60-mm column, 35% acetone–petroleum ether) afforded 36.0 g (87%) of a pale liquid: IR ($CHCl_3$) 1750 (C=O), 1625 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 4.73 (s, 2 H, CH_2CCl_3), 4.50 (br S, >CH–); exact mass m/e calcd for $C_{21}H_{34}Cl_3NO_6$ 501.146, found 501.145.

E. 1-[9-Hydroxy-5-[(2,2,2-trichloroethoxy)formyloxy]nonanoyl]azacyclopentane. A solution of 36.0 g (71.6 mmol) of the tetrahydropyranyl ether and 2.0 mL of concentrated hydrochloric acid in 300 mL of methanol was stirred at room temperature for 1.5 h and poured into 600 mL of water. Dichloromethane extraction ($MgSO_4$) followed by flash chromatography (60-mm column, 45% acetone–petroleum ether) afforded 27.7 g (92%) of the corresponding alcohol as a clear oil: IR ($CHCl_3$) 3400 (OH), 1750 (C=O), 1625 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 4.77 (s, 2 H, CH_2CCl_3); exact mass m/e calcd for $C_{16}H_{26}Cl_3NO_5$ 417.088, found 417.089.

F. 1-[9-(Benzoyloxy)-5-[(2,2,2-trichloroethoxy)formyloxy]nonanoyl]azacyclopentane. Treatment of 27.7 g (66.1 mmol) of the above alcohol in 140 mL of dry dichloromethane with 8.4 mL (72 mmol) of benzoyl chloride and 5.9 mL (73 mmol) of dry pyridine provided after flash chromatography (60-mm column, 40% acetone–petroleum ether) 32.9 g (95%) of the benzoate as a clear viscous oil: IR ($CHCl_3$) 1750 (C=O), 1710 (C=O), 1620 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 4.72 (s, 2 H, CH_2CCl_3), 4.28 (t, 2 H, J = 6 Hz, OCH_2), 3.2–3.5 (m, 4 H, NCH_2); exact mass m/e calcd for $C_{23}H_{30}Cl_3NO_6$ 521.115, found 521.113.

G. 1-[9-(Benzoyloxy)-5-[(2,2,2-trichloroethoxy)formyloxy]nonanethioyl]azacyclopentane. By the procedure described above for the preparation of thioamide **12**, 32.9 g (63 mmol) of the above amide with 11.2 g (50 mmol) of purified phosphorus pentasulfide, 7.5 mL (50 mmol) of triethylamine, and 150 mL of dichloromethane provided after flash chromatography (60-mm column, 33% acetone–petroleum ether) 25.4 g (75%) of the thioamide as a viscous yellow oil: IR ($CHCl_3$) 1750 (C=O), 1710 (C=O), 1495 cm^{-1} (NC=S); ^{1}H NMR ($CDCl_3$) δ 4.73 (s, 2 H, CH_2CCl_3), 4.27 (t, 2 H, J = 6 Hz, OCH_2), 3.80 and 3.57 (2 t, 4 H, J = 6 Hz, NCH_2), 2.5–2.8 (m, 2 H, $CH_2C{=}S$); exact mass m/e calcd for $C_{23}H_{30}Cl_3NO_5S$ 537.091, found 537.089.

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H. 1-[9-(Benzoyloxy)-5-hydroxynonanethioyl]azacyclopentane. A slurry of 25.4 g (0.047 mol) of the above carbonate thioamide, 18.5 g (0.28 mol) of zinc dust, and 185 mL of glacial acetic acid was stirred at room temperature for 1.5 h. The solution was filtered through a 60-mL coarse fritted funnel, and the solid was washed with 125 mL of dichloromethane. The clear filtrate was poured into 600 mL of water. The alcohol was isolated by dichloromethane extraction including bicarbonate washes ($MgSO_4$), and purification by chromatography on 300 g of silica gel (70% ethyl acetate–petroleum ether) afforded 16.0 g (93%) of the hydroxy thioamide as a viscous oil: IR ($CHCl_3$) 3625 (OH), 1710 (C=O), 1495 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 4.27 (t, 2 H, J = 6 Hz, OCH_2), 3.4–3.9 (m, 5 H NCH_2, >CHO–), 2.67 (t, 2 H, J = 7 Hz, CH_2C=S). An analytical sample was prepared by Kugelrohr distillation at 150 °C (0.001 mm).

Anal. Calcd for $C_{20}H_{29}NO_3S$: C, 66.08; H, 8.04; N, 3.85; S, 8.82. Found: C, 66.22; H, 8.09; N, 3.74; S, 8.89.

I. 1-[9-(Benzoyloxy)-5-oxononanethioyl]azacyclopentane. Oppenauer oxidation[49] of 16.0 g (44 mmol) of the above hydroxy thioamide with 31.8 g (160 mmol) of aluminum isopropoxide, 265 mL of dry acetone, and 350 mL of dry benzene followed by chromatography on 400 g of silica gel (2.5 L of 50% ethyl acetate–petroleum ether followed by ethyl acetate) provided 4.37 g (27%) of the corresponding ketone: R_f 0.59 (ethyl acetate); IR ($CHCl_3$) 1715 (C=O), 1500 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) 4.15–4.4 (m, 2 H, OCH_2), 3.77 and 3.60 (2 t, 4 H, J = 6 Hz, NCH_2); exact mass m/e calcd for $C_{20}H_{27}NO_3S$ 361.171, found 361.169.

Also recovered were 11.4 g (71%) of the starting alcohol. Yield of the ketone was 95% based on recovered starting alcohol.

J. 1-[9-(Benzoyloxy)-5,5-(ethylenedioxy)nonanethioyl]azacyclopentane. A solution of 2.53 g (7.0 mmol) of the above ketone, 1.95 mL (35 mmol) of distilled ethylene glycol, and 0.011 g (0.6 mmol) of *p*-toluenesulfonic acid monohydrate in 25 mL of benzene was heated under reflux for 1 h with removal of water by means of a Dean–Stark trap filled with Drierite. The solution was poured into a solution composed of 25 mL of water and 25 mL of a saturated aqueous sodium bicarbonate solution. Ether extraction (1:1 Na_2SO_4–K_2CO_3) followed by chromatography on 250 g of alumina (25% ethyl acetate–cyclohexane) afforded 2.56 g (90%) of the ketal thioamide as an oil: IR ($CHCl_3$) 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.26 (t, 2 H, J = 6.5 Hz, $PhCO_2CH_2$), 3.88 (s, 4 H, OCH_2); exact mass m/e calcd for $C_{22}H_{31}NO_4S$ 405.197, found 405.196.

K. 1-[5,5-(Ethylenedioxy)-9-hydroxynonanethioyl]azacyclopentane (39). Treatment of 2.51 g (6.2 mmol) of the *ketal* benzoate in 80% aqueous methanol with 15 mL of a 0.5 M solution of lithium hydroxide afforded after chromatography on 100 g of alumina (30% acetone–petroleum ether) 1.65 g (88%) of the ketal hydroxy thioamide **39a**: IR ($CHCl_3$) 3650 (OH), 1500 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 3.89 (s, 4 H, OCH_2). An analytical sample was prepared by Kugelrohr distillation at 190 °C (0.02 mm).

Anal. Calcd for $C_{15}H_{27}NO_3S$: C, 59.76; H, 9.03; N, 4.65; S, 10.64. Found: C, 59.57; H, 9.09; N, 4.74; S, 10.72.

L. 1-(9-Hydroxy-5-oxononanethioyl)azacyclopentane (39b). Treatment of 1.82 g (5.0 mmol) of the ketone benzoate in 80% aqueous methanol with 12 mL of a 0.5 M solution of lithium hydroxide afforded 0.983 g (76%) of the ketone hydroxy thioamide **39b** after chromatography on 120 g of silica gel (ethyl acetate): IR ($CHCl_3$) 3640 (OH), 1715 (C=O), 1495 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 3.1–3.9 (m, 6 H, NCH_2, OCH_2), 2.3–2.8 (m, 4 H, CH_2C=O). An analytical sample was prepared by Kugelrohr distillation at 180 °C (0.02 mm).

Anal. Calcd for $C_{13}H_{23}NO_2S$: C, 60.66; H, 9.01; N, 5.44; S, 12.46. Found: C, 60.61; H, 9.06; N, 5.40; S, 12.42.

1,11-Dioxacycloeicosane-2,4,12,14-tetrone (32a). A solution of 0.217 g (1.01 mmol) of thioamide **30a** and 0.10 mL (1.25 mmol) of chloroacetyl chloride in 10 mL of dry dichloromethane was stirred at room temperature for 3 h. Solvents were removed under reduced pressure, and the residue was placed under vacuum (<0.5 mm) for 30 min.

A solution of this chloro ester in 10 mL of dry acetonitrile was added over 15 min to a solution of 3.0 g (20 mmol) of sodium iodide in 20 mL of dry acetonitrile heated at reflux. After 15 more min, 0.48 g (1.7 mmol) of phosphine **5** was added, and the resulting solution was heated at reflux for 4.5 h. Workup as described under the general procedure for 5- and 6-membered lactones afforded 0.083 g (48%): mp 118–119 °C (benzene–petroleum ether); IR ($CHCl_3$) 1735 (C=O), 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.13 (t, 4 H, J = 6 Hz, OCH_2), 3.40 (s, 4 H, O=CCH_2C=O), exact mass m/e calcd for $C_{18}H_{28}O_6$ 340.189, found 340.188.

Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.50; H, 8.29.

1,13-Dioxacyclotetracosane-2,4,14,16-tetrone (32b). By the procedure described above for the preparation of dimer **32a**, 0.263 g (1.08 mmol) of thioamide **30b** provided 0.092 g (43%) of the dimer **32b**: mp 122–123 °C (benzene–petroleum ether); IR ($CHCl_3$) 1735 (C=O), 1705 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.0–4.3 (m, 4 H, OCH_2), 3.36 (s, 4 H, O=CCH_2C=O); exact mass m/e calcd for $C_{22}H_{36}O_6$ 396.252, found 396.251.

Anal. Calcd for $C_{22}H_{36}O_6$: C, 66.64; H, 9.15. Found: C, 66.49; H, 9.10.

Macrocyclic Lactones. General Procedure. To a solution of the requisite hydroxy thioamide (1.0 mmol) and 0.12 mL (1.5 mmol) of dry pyridine in 6 mL of dry dichloromethane cooled with a dry ice–acetone bath was added 0.10 mL (1.25 mmol) of chloroacetyl chloride. The solution was stirred at −78 °C for 30 min and at 0 °C for 15 min. The reaction mixture was poured into 15 mL of 50% ethyl acetate–cyclohexane, and the resulting solution was filtered through 5 g of alumina. The ester was eluted with 50 mL of 50% ethyl acetate–cyclohexane. Solvents were removed under reduced pressure, and the residue was placed under vacuum (<0.5 mm) for 30 min.

To a solution of 3.0 g (20 mmol) of sodium iodide, 0.55 mL (3.2 mmol) of diisopropylethylamine, and 0.26 mL (1.5 mmol) of triethyl phosphite in 20 mL of dry acetonitrile heated at reflux was added over 30 min by a syringe pump[50] a solution of the above chloro ester in 10 mL of dry acetonitrile. The resulting solution was heated at reflux for 1 to 2 h after addition was complete, the solution was cooled to room temperature, and solvents were removed under reduced pressure. The residue was dissolved in 50 mL of 1 M aqueous NaH_2PO_4 solution. The lactones were isolated by dichloromethane extraction ($MgSO_4$) followed by chromatography on silica gel. Results are summarized in Table I. .

Diplodialide A Synthesis. 1,1-Diethoxy-5-[(2,2,2-trichloroethoxy)formyloxy]hexane. Treatment of 11.40 g (59.9 mmol) of 6,6-diethoxy-2-hexanol[51] in 100 mL of dry dichloromethane with 8.4 mL (61.0 mmol) of trichloroethyl chloroformate and 5.2 mL (64.3 mmol) of dry pyridine provided after flash chromatography (60-mm column, 9% ethyl acetate–petroleum ether) 21.7 g (99%) of the trichlorocarbonate as a clear oil: IR ($CHCl_3$) 1755 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.76 (s, 2 H, CH_2Cl_3). An analytical sample was prepared by Kugelrohr distillation at 140 °C (0.005 mm).

Anal. Calcd for $C_{13}H_{23}Cl_3O_5$: C, 42.70; H, 6.34. Found: C, 42.61; H, 6.38.

5-[(2,2,2-Trichloroethoxy)formyloxy]hexanal (42). A solution of 21.7 g (59.3 mmol) of the acetal with 10 mL of 2 N aqueous hydrochloric acid and 90 mL of THF was stirred at room temperature for 1.5 h. The reaction was quenched with 200 mL of a saturated aqueous sodium bicarbonate solution, and the aldehyde was isolated by ether extraction ($MgSO_4$). Flash chromatography (60-mm column, 30% ethyl acetate–petroleum ether) yielded 15.05 g (87%) of the aldehyde **42** as a clear oil: IR ($CHCl_3$) 2750 (aldehyde CH), 1750 (C=O), 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 9.81 (t, 1 H, J = 1 Hz, HC=O), 4.74 (s, 2 H, CH_2CCl_3), 1.33 (d, 3 H, J = 6 Hz, $CHCH_3$). An analytical sample was prepared by Kugelrohr distillation at 120 °C (0.005 mm).

Anal. Calcd for $C_9H_{13}Cl_3O_4$: C, 37.07; H, 4.49. Found: C, 36.99; H, 4.32.

IX. *N,N*-Dimethyl-3-hydroxy-7-[(2,2,2-trichloroethoxy)formyloxy]octanethioamide (43). A. Lithium Enolate. To

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Table I. Macrocyclic Lactone Formation

thioamide (mol wt)	macrocyclic lactone	% yield	mp, °C (bp, °C/mm)[a]	IR, cm^{-1}	^1H NMR, δ		m/e		analysis		R_F
					OCH_2 (J)	O=CCH$_2$-C=O	calcd	found	calcd	found	
30a (215.35)	oxacyclododecane-2,4-dione (**31a**)	35	(70/0.8)	1735, 1710	4.32 (5.5)	3.38	170.09	170.095	C, 63.51 H, 8.29	63.54 8.18	0.20[e]
30b (243.40)	oxacyclododecane-2,4-dione (**31b**)	35	(70/0.005)	1730, 1710	4.1–4.3 (m)	3.40	198.12	198.127	C, 66.64 H, 9.15	66.68 9.19	0.28[g]
35a (239.37)	oxacyclodec-8-yne-2,4-dione (**36a**)	58	81–82[b]	1745, 1715	4.2–4.4 (m)	3.43	194.09	194.094	C, 68.02 H, 7.26	67.97 7.15	0.22[e]
35b (241.38)	(*E*)-oxacyclododec-8-ene-2,4-dione (**36b**)	49	35–36[b]	1740, 1710	4.1–4.4 (m)	3.28	196.11	196.109	C, 67.32 H, 8.22	67.33 8.17	0.27[g]
35c (241.38)	(*Z*)-oxacyclododec-8-ene-2,4-dione (**36c**)	55	(100/0.15)	1745, 1710	4.08 (7)	3.35	196.11	196.112	C, 67.32 H, 8.22	67.34 8.26	0.37[g]
37 (233.32)	1,6-dioxacyclododecane-7,9,12-trione (**38**)	37	91–92[b]	1715 (br)	3.9–4.3 (m)	3.48	214.08	214.087	C, 56.07 H, 6.59	55.97 6.47	0.27[f]
39a (301.44)	1,4,10-trioxaspiro[4.11]hexadecane-11,13-dione (**40a**)	50	68–69[c]	1740, 1715	4.15 (6)	3.41	256.13	256.132	C, 60.92 H, 7.87	60.73 7.79	0.39[f]
39b (257.38)	oxacyclododecane-2,4,8-trione (**40b**)	28	78–79[d]	1740, 1715	4.1–4.3 (m)	3.37	212.10	212.106	C, 62.25 H, 7.60	62.01 7.60	0.28[f]

[a] Kugelrohr distilled at indicated temperature/pressure (mm). [b] Hexane. [c] Ethyl acetate–hexane. [d] Ether–hexane. [e] 25% ethyl acetate–cyclohexane. [f] 50% ethyl acetate–cyclohexane. [g] 10% ethyl acetate–toluene.

a solution of 1.60 mL (11.4 mmol) of dry diisopropylamine in 10 mL of dry THF cooled with an ice–water bath was added 4.4 mL of a 2.32 M solution of butyllithium in hexane. The resulting solution was stirred for 10 min at 0 °C and cooled to −78 °C with a dry ice–acetone bath. A solution of 1.03 g (10 mmol) of *N,N*-dimethylethanethioamide in 5 mL of dry THF was added over 5 min, and the resulting solution was stirred for 10 min. A solution of 2.92 g (10 mmol) of aldehyde **42** in 5 mL of dry THF was added over 10 min, and the resulting solution was stirred for 30 min at −78 °C. The reaction was quenched with 50 mL of 2 N aqueous hydrochloric acid, and the hydroxy thioamide **43** was isolated by ether extraction ($MgSO_4$) followed by chromatography on 350 g of silica gel (1.8 L of 40% ethyl acetate–petroleum ether, 1.0 L of 50% ethyl acetate–petroleum ether, and ethyl acetate): 1.63 g (41%); IR ($CHCl_3$) 3520 (OH), 1750 (C=O), 1520 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 4.67 (s, 2 H, CH_2CCl_3), 3.41 and 3.23 (2 s, 6 H, NCH_3), 1.26 (d, 3 H, J = 6 Hz, $CHCH_3$). An analytical sample was prepared by Kugelrohr distillation at 165 °C (0.005 mm).

Anal. Calcd for $C_{13}H_{22}Cl_3NO_4S$: C, 39.55; H, 5.62; N, 3.55; S, 8.12. Found: C, 39.57; H, 5.61; N, 3.58; S, 8.20.

B. Zinc Enolate. A solution of the lithium enolate was prepared as above from 1.315 g (12.7 mmol) of the thioamide, 2.0 mL (14 mmol) of dry diisopropylamine, 5.7 mL of a 2.32 M solution of butyllithium in hexane, and 15 mL of dry THF. This solution was warmed to 0 °C and 1.84 g (14 mmol) of anhydrous zinc chloride[16] in 20 mL of dry ether was added. Immediately a flocculent pink precipitate formed. After 1 min, 3.73 g (12.8 mmol) of aldehyde **42** in 5 mL of dry THF was added over 0.5 min with shaking of the flask. The precipitate dissolved to form a bright yellow solution. After 5 min at 0 °C, the reaction mixture was poured into 50 mL of 2 N aqueous hydrochloric acid. Ether extraction ($MgSO_4$) followed by flash chromatography (50-mm column, 70% ethyl acetate–petroleum ether) provided 3.41 g (68%) of the hydroxy thioamide **43**.

***N,N*-Dimethyl-3-acetoxy-7-[(2,2,2-trichloroethoxy)-formyloxy]octanethioamide.** Treatment of 4.01 g (10.2 mmol) of hydroxy thioamide **44** in 20 mL of dry dichloromethane with 0.75 mL (10.5 mmol) of acetyl chloride and 0.85 mL (10.5 mmol) of dry pyridine provided after flash chromatography (60-mm column, 40% ethyl acetate–petroleum ether) the acetate as a yellowish oil: 3.78 g (85%); IR ($CHCl_3$) 1750 (carbonate C=O), 1730 (acetate C=O), 1520 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 5.23 (br q, 1 H, J = 6 Hz, CHOAc), 4.71 (s, 2 H, CH_2CCl_3), 3.41 and 3.34 (2 s, 6 H, NCH_3), 3.12 (dd, 1 H, J = 14 Hz, J' = 7 Hz, CHC=S), 2.93 (dd, 1 H, J = 14 Hz, J' = 6 Hz, CHC=S), 2.01 (s, 3 H, CH_3C=O), 1.29 (d, 3 H, J = 6 Hz, $CHCH_3$). An analytical sample was prepared by Kugelrohr distillation at 160 °C (0.0005 mm).

Anal. Calcd for $C_{15}H_{24}Cl_3NO_5S$: C, 41.24; H, 5.54; N, 3.21; S, 7.34. Found: C, 41.14; H, 5.57; N, 3.19; S, 7.45.

***N,N*-Dimethyl-3-acetoxy-7-hydroxyoctanethioamide (44).** Treatment of 3.78 g (8.65 mmol) of the trichloro carbonate above with 3.60 g (55.1 mmol) of zinc powder and 36 mL of glacial acetic acid provided after flash chromatography (25-mm column, ethyl acetate) 2.06 g (91%) of alcohol **44** as an oil: IR ($CHCl_3$) 3625 (OH), 1735 (C=O), 1520 cm^{-1} (NC=S); ^1H NMR ($CDCl_3$) δ 5.28 (q, 1 H, J = 6Hz, CHOAc), 3.41 and 3.34 (2 s, 6 H, NCH_3), 3.12 (dd, 1 H, J = 14 Hz, J' = 7 Hz, CHC=S), 2.93 (dd, 1 H, J = 14 Hz, J' = 6 Hz, CHC=S), 2.01 (s, 3 H, CH_3C=O), 1.16 (d, 3 H, J = 7 Hz, $CHCH_3$). An analytical sample was prepared by Kugelrohr distillation at 140 °C (0.005 mm).

Anal. Calcd for $C_{12}H_{23}NO_3S$: C, 55.14; H, 8.87; N, 5.36; S, 12.27. Found: C, 55.07; H, 8986; N, 5.26; S, 12.17.

6-Acetoxy-10-methyloxacyclodecane-2,4-dione (45). According to the general procedure for macrocyclic lactone formation, 0.279 g (1.07 mmol) of alcohol **44** provided 0.062 mg (24%) of acetate **45** as a mixture of two isomers: R_f 0.17, 0.19 (25% ethyl acetate–cyclohexane); IR ($CHCl_3$) 1730 (C=O), 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.00 and 1.97 (2 s, 3 H, 2 CH_3C=O), 1.26 (d, 3 H, J = 7 Hz, $CHCH_3$); exact mass m/e calcd for $C_{12}H_{18}O_5$ 242.115, found 242.116.

(±)-Diplodialide A (2). A solution of 0.062 mg (0.26 mmol) of acetate **45** and 0.4 mL (2.3 mmol) of diisopropylethylamine in 5 mL of dry acetonitrile was heated under reflux for 5 h. The reaction mixture was cooled to room temperature and diluted with 75 mL of ether. The resulting solution was washed with 15-mL

portions of water and a saturated aqueous sodium chloride solution and dried over $MgSO_4$. Removal of solvents under reduced pressure and chromatography on 10 g of silica gel impregnated with 10% silver nitrate (30% ethyl acetate–cyclohexane) afforded 0.037 g (80%) of diplodialide A (**2**) whose characteristics (IR, ^1H NMR, and mass spectra) were identical with those previously reported.[14a]

Registry No. 2, 68296-70-8; **5**, 32357-32-7; **6a**, 5309-98-8; **6b**, 73199-91-4; **6c**, 2832-99-7; **7a**, 73199-92-5; **7b**, 73199-93-6; **7c**, 73199-94-7; **8**, 758-16-7; **9**, 1117-37-9; **10**, 73199-95-8; **11**, 27428-41-7; **12**, 73199-96-9; **13**, 56294-09-8; **14**, 73199-97-0; **15**, 73199-98-1; **16a**, 73199-99-2; **16b**, 73200-00-7; **17a**, 623-48-3; **17b**, 64987-88-8; **18**, 73200-01-8; **19a**, 141-97-9; **19b**, 542-08-5; **20a**, 7737-62-4; **20b**, 73200-02-9; **21**, 73200-03-0; **22**, 5892-65-9; **25**, 40568-55-6; **26a**, 73200-04-1; **26a** acetate (ester), 73200-05-2; **26b**, 73200-06-3; **26b** acetate (ester), 73200-07-4; **27a**, 73200-08-5; **27b**, 73200-09-6; **28**, 73200-10-9; **28** acetate (ester), 73200-11-0; **29a**, 73200-12-1; **29b**, 73200-13-2; **30a**, 73200-14-3; **30b**, 73200-15-4; **31a**, 73200-16-5; **31b**, 73200-17-6; **32a**, 73199-63-0; **32b**, 73199-64-1; **33**, 73199-65-2; **33** acetate (ester), 73199-66-3; **35a**, 73199-67-4; **35b**, 73199-68-5; **35c**, 73199-69-6; **36a**, 73199-70-9; **36b**, 73199-71-0; **36c**, 73199-72-1; **37**, 73199-73-2; **38**, 73199-74-3; **39a**, 73199-75-4; **39a** benzoate (ester), 73199-76-5; **39b**, 73199-77-6; **39b** benzoate (ester), 73199-78-7; **40a**, 73199-79-8; **40b**, 73199-80-1; **41**, 73199-81-2; **42**, 73210-24-9; **43**, 73199-82-3; **43** acetate (ester), 73199-83-4; **44**, 73199-84-5; **45**, isomer I, 73199-85-6; **45**, isomer II, 73245-88-2; methyl pentanedithioate, 55130-99-9; pyrrolidine, 123-75-1; morpholine, 110-91-8; methyl 5,5-(ethylenedioxy)hexanedithioate, 73199-86-7; 5-chloro-2-pentanone ethylene ketal, 5978-08-5; methyl 3-(dimethylcarbamoyl)propanoate, 30891-34-0; 1-[3-(butylthio)propanoyl]azacyclopentane, 73199-87-8; 3-(butylthio)propionic acid, 22002-73-9; ethyl 3-oxoheptanoate, 7737-62-4; *N,N*-dimethylethanethioamide, 631-67-4; phenacyl bromide, 70-11-1; 1-[3-(4-oxothiacyclohexyl)carbonyl]azacyclopentane, 73199-88-9; 3-(carbomethoxy)thian-4-one, 4160-61-6; 1-[3-(*cis*-4-hydroxythiacyclohexyl)carbonyl]azacyclopentane, 73199-89-0; 1-[3-(*trans*-4-hydroxythiacyclohexyl)carbonyl]azacyclopentane, 73199-90-3; 1-[(2*R**,3*S**)-3-hydroxy-2-methylpentanoyl]azacyclopentane, 73200-18-7; 1-[(2*R**,3*S**)-3-acetoxy-2-methylpentanoyl]-azacyclopentane, 73230-62-3; 1-[(2*R**,3*R**)-3-hydroxy-2-methylpentanoyl]azacyclopentane, 73200-19-8; 1-[(2*R**,3*R**)-3-acetoxy-2-methylpentanoyl]azacyclopentane, 73200-20-1; 1-(2-acetoxy-2-phenylacetyl)azacyclopentane, 73200-21-2; acetylmandelyl chloride, 49845-72-9; methyl 7-[(2-oxacyclohexyl)oxy]heptanedithioate, 73200-22-3; 2-[(6-chlorohexyl)oxy]oxacyclohexane, 2009-84-9; 2-[(8-chlorooctyl)oxy]oxacyclohexane, 19754-57-5; 8-chloro-1-octanol, 23144-52-7; methyl 9-[(2-oxacyclohexyl)oxy]nonanedithioate, 73200-23-4; 1-(4-hydroxybutanoyl)azacyclopentane, 73200-24-5; γ-butyrolactone, 96-48-0; 1-(4-acetoxybutanoyl)azacyclopentane, 73200-25-6; 8-[(2-oxacyclohexyl)oxy]oct-4-yn-1-ol, 73200-26-7; 4-pentyn-1-ol, 5390-04-5; 2-(3-bromopropoxy)oxacyclohexane, 33821-94-2; 2-[(8-chloro-4-octynyl)oxy]oxacyclohexane, 73200-27-8; methyl 9-[(2-oxacyclohexyl)oxy]non-5-ynedithioate, 73200-28-9; (*E*)-8-[(2-oxacyclohexyl)oxy]oct-4-en-1-ol, 73200-29-0; 2-[[(*E*)-8-chloro-4-octenyl]oxy]-oxacyclohexane, 73200-30-3; methyl (*E*)-9-[(2-oxacyclohexyl)oxy]-non-5-enedithioate, 73200-31-4; (*Z*)-8-[(2-oxacyclohexyl)oxy]oct-4-en-1-ol, 62422-46-2; 2-[[(*Z*)-8-chloro-4-octenyl]oxy]oxacyclohexane, 73200-32-5; methyl (*Z*)-9-[(2-oxacyclohexyl)oxy]non-5-enedithioate, 73200-33-6; 1-(5-hydroxypentanoyl)azacyclopentane, 1938-53-0; δ-valerolactone, 542-28-9; 1-(5-oxopentanoyl)azacyclopentane, 73200-34-7; 5-chloro-5-oxopentanal, 73200-35-8; 1-[5-hydroxy-9-[(2-oxacyclohexyl)oxy]nonanoyl]azacyclopentane, 73200-36-9; 2-[(4-chlorobutyl)oxy]oxacyclohexane, 41302-05-0; 1-[9-[(2-oxacyclohexyl)-oxy]-5-[(2,2,2-trichloroethoxy)formyloxy]nonanoyl]azacyclopentane, 73200-37-0; trichloroethyl chloroformate, 17341-93-4; 1-[9-hydroxy-5-[(2,2,2-trichloroethoxy)formyloxy]nonanoyl]azacyclopentane, 73200-38-1; 1-[9-(benzoyloxy)-5-[(2,2,2-trichloroethoxy)formyloxy]-nonanoyl]azacyclopentane, 73200-39-2; 1-[9-(benzoyloxy)-5-[(2,2,2-trichloroethoxy)formyloxy]nonanethioyl]azacyclopentane, 73200-40-5; 1-[9-(benzoyloxy)-5-hydroxynonanethioyl]azacyclopentane, 73200-41-6; 1,1-diethoxy-5-[(2,2,2-trichloroethoxy)formyloxy]hexane, 73200-42-7.

α-Functionalized Amino Acid Derivatives. A Synthetic Approach of Possible Biogenetic Importance

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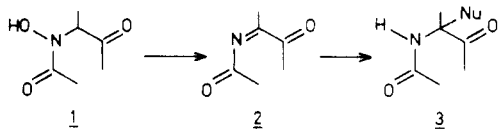
A new and efficient approach of general applicability to the synthesis of α-functionalized α-amino acid derivatives **3** is described. It is based upon the proposal that the biosynthesis of such compounds might occur via oxidation of an N-acylated amino acid to hydroxamic acid **1**, which might then be converted into compound **3** through acylimine **2** (Scheme I). The procedures reported are efficient and can be used for the synthesis of α-oxygenated α-amino acids having an oxidizable function in the side chain. In addition, the method is also applicable for the preparation of peptide analogues with the title compound in their sequence. Starting from the α-oximino acid derivatives **5** and **6**, the O-protected *N*-hydroxy-*N*-acetyl-α-amino esters **9** and **10** were prepared, which could be converted into the *N*-acetyl-α-amino-α-methoxy esters **12** in fair to good overall yields (Scheme II). To extend the scope of this reaction, *N*-hydroxy cyclodipeptides **19** were prepared by reaction of the *N*-benzyloxy-α-amino acid amides **15** with pyruvoyl chloride (**16**) in 54–71% yield (Scheme III). Tosylation of **19a** and subsequent treatment with $(CH_3)_3COK$ in CH_3OH afforded the corresponding *C*(3)-methoxy cyclodipeptide **24a**, whereas **19b** gave a mixture of the *C*(3)- and *C*(6)-methoxy cyclodipeptides **24b** and **25**, respectively (Scheme IV). A mechanism for this isomerization is discussed. It is suggested that **25** arises from the α-lactam intermediate **23b**. This intermediate might also explain the formation of the hydantoin **32**, which is formed when **19b** is tosylated and treated with CH_3SNa in 2-propanol. Under these reaction conditions **19a** gives the reduced cyclodipeptide **30** (Scheme V).

α-Functionalized α-amino acids are known as structural elements in naturally occurring compounds. They are found in the cephamycins,[1] which are of considerable therapeutic significance, and in other physiologically active compounds such as the ergot peptides.[2] In addition, α-hydroxylysine has been mentioned[3] to occur as a free amino acid in plants, whereas ureidoglycine is an example

Scheme I



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