MACROCYCLIC LACTONE FORMATION THROUGH SULFIDE CONTRACTION: SYNTHESIS OF (±)-DIPLODIALIDE A

Thesis by

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In Partial Fulfillment of the Requirements

for the Degree of

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to my Parents

and my Sisters

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ABSTRACT

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

TABLE OF CONTENTS

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

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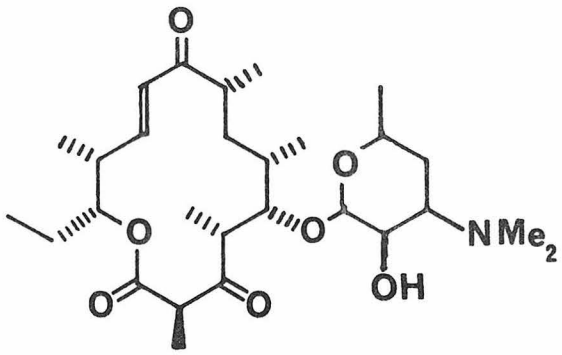
ABSTRACT

A methodology for the synthesis of macrocyclic β-ketolactones from ω-hydroxythioamides is described. The hydroxythioamides were esterified with chloroacetyl chloride, and the resulting chloroesters underwent Eschenmoser sulfide contraction when treated with sodium iodide, diisopropylethylamine, and triethyl phosphite in acetonitrile. The β-ketolactones were obtained in 25-58% yield. The utility of the method was demonstrated by the 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]



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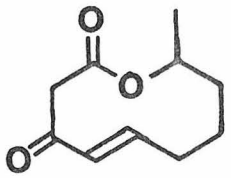

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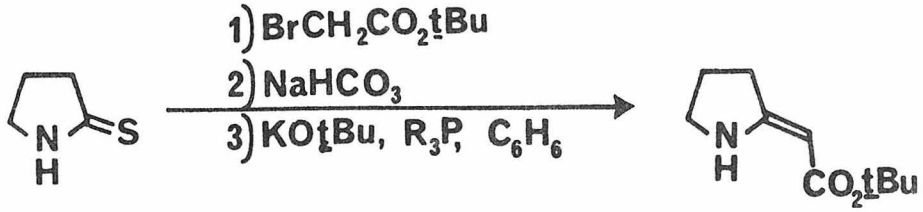
which contain the β-ketolactone system suggested that such macrocycles might be synthesized through formation of this grouping by some modification of the Claisen condensation. The Eschenmoser sulfide contraction,[6] in which thioamide 3 was converted into enaminoester 4 in 75% yield, seemed a



3 4

viable method. Macrocycle formation would be through carbon-sulfur bond formation rather than through more difficult carbon-carbon bond formation as in the Claisen

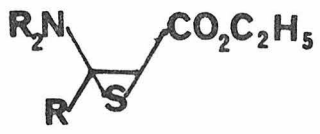
condensation. The sulfide could then be readily converted into a β-ketolactone. Here we report the development of alternate conditions for the Eschenmoser sulfide contraction of thioamides, the adaptation of these conditions to macrocyclic lactone formation, and the synthesis of diplodialide A (2) through intramolecular sulfide contraction.

After initial experiments with N-alkylthioamides provided discouraging results, N,N-dialkylthioamides[7] were substituted. It was discovered that the intermediate thioimmonium salts could be induced to undergo the sulfide contraction by treatment of the salt with a phosphine and an amine base. Strong base such as potassium tert-butoxide[6] is not necessary. Phosphine 5, developed by Eschenmoser and co-workers,[6]

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

5

proved especially convenient since it contains both phosphine and amine. The facility of the reaction as compared to the corresponding N-alkylthioamides can be explained by the enhanced acidity of the acetate protons due to the presence of the positive charge. Also, the proposed intermediate episulfide 6



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which is a neutral species would provide a good intramolecular

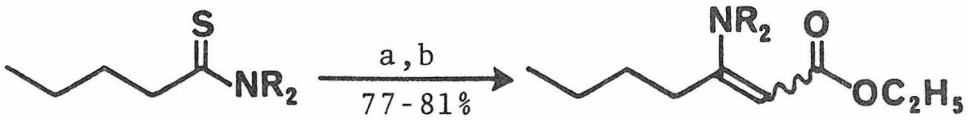
pathway for charge neutralization once deprotonation occurred.

The necessary N,N-dialkylthioamides were prepared in two general ways. Thioacylation[8] of secondary amines with dithioesters was an especially convenient method when the dithioesters were readily obtained.[9] The standard method, 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 modified sulfide contraction. A particularly interesting case is thioamide 15. Alkylation occurs preferentially on the thioamide sulfur rather than on the sulfide sulfur. Thus β-ketoester 16 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 (18a) is reversible. Heating of thioimmonium salt 17a with ester 18b in acetonitrile led to a 1:1 mixture of salts 17a and 17b. Likewise, salts 19 and 17b, when heated in acetonitrile and then subjected to sulfide contraction, provided all four possible ketoesters (20a, 20b, 21a, and 21b). Second, the deprotonation step appears to be irreversible and dependent on the relative acidities of the acetate and α-thioamide protons. Salt 22

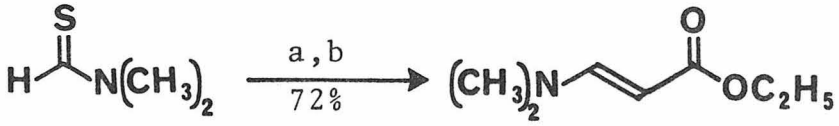
Scheme I. Intermolecular Sulfide Contraction[a]



7a, NR_2=NMe_2 8a, NR_2=NMe_2

b, NR_2=pyrrolidinyl b, NR_2=pyrrolidinyl

c, NR_2=morpholinyl c, NR_2=morpholinyl



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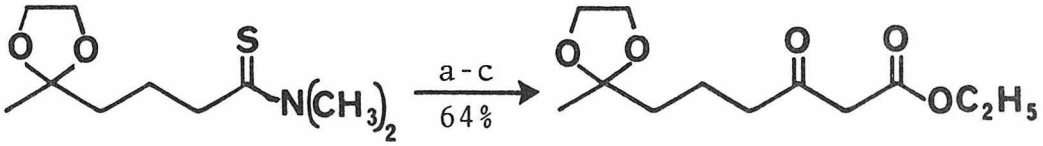

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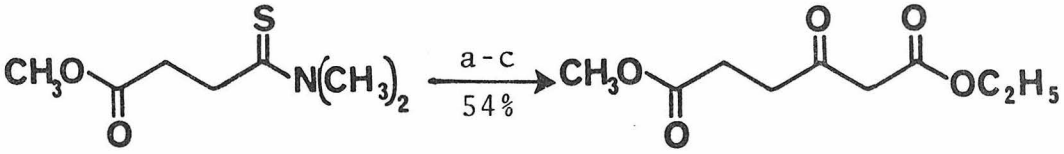

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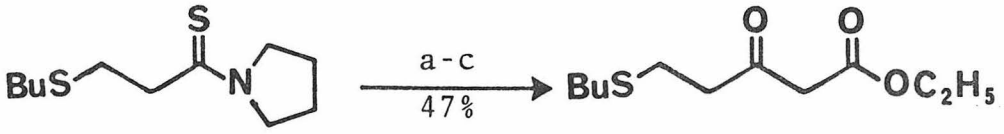
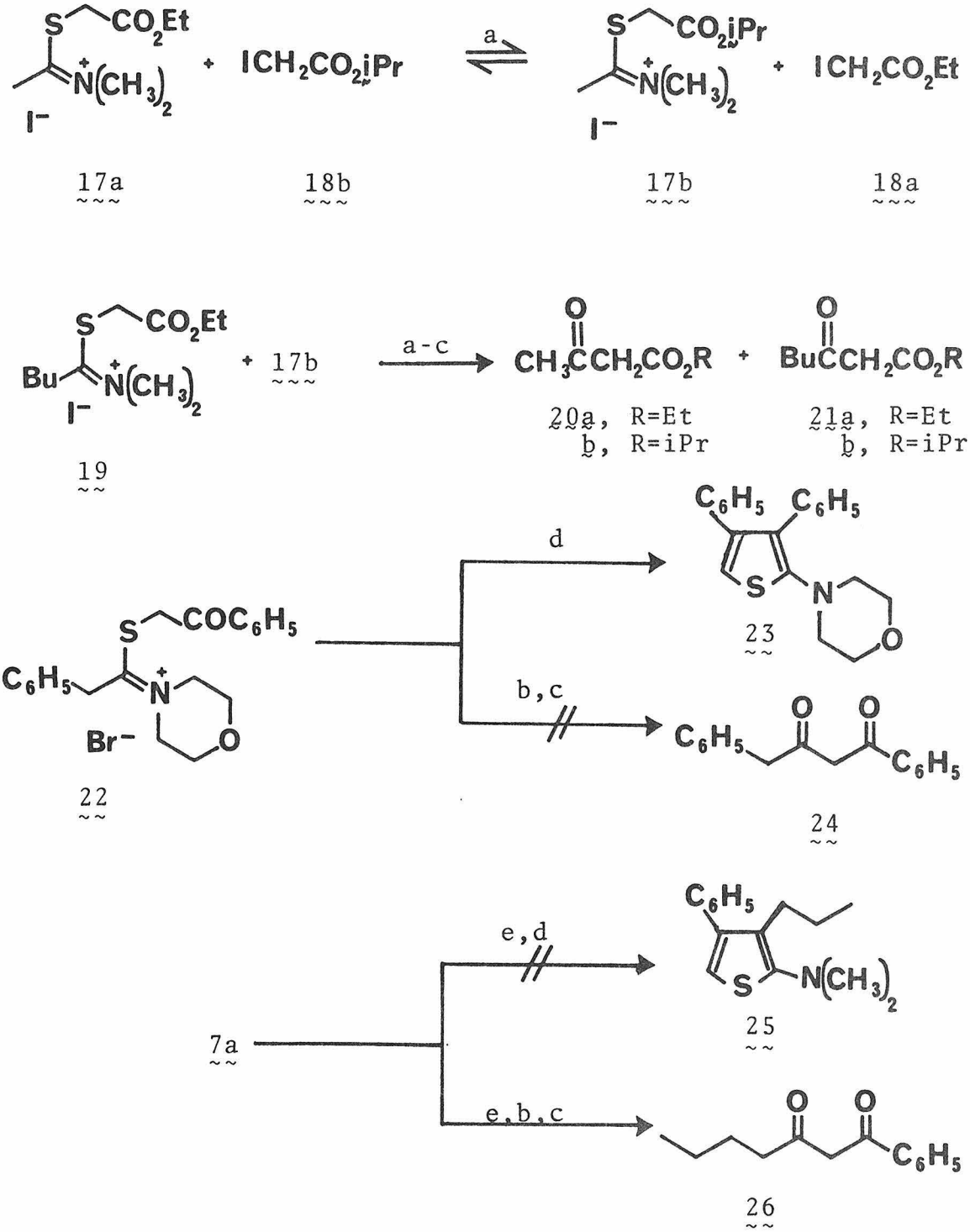


15 16

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

Scheme II. Reactions Relating to the Mechanism[a]



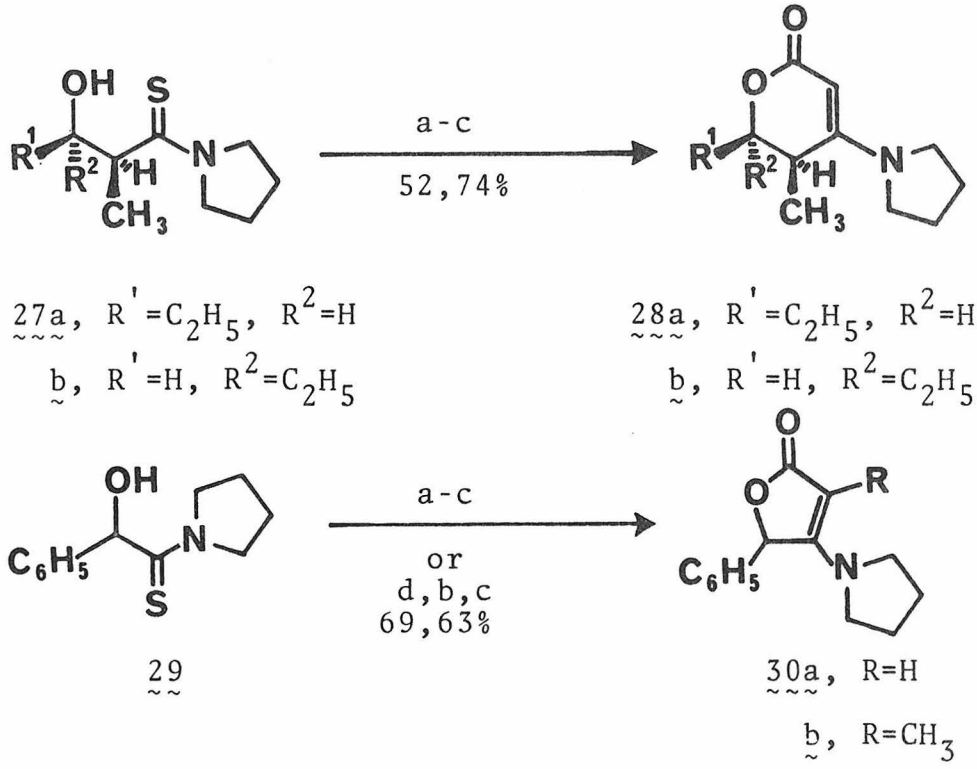
[a] a, Δ, CH_3CN; b, $PhP[(CH_2)_3NMe_2]_2$, CH_3CN; c, silica gel; d, Et_3N, MeOH; e, $BrCH_2COC_6H_5$.

has been reported[11] to give thiophene 23 when heated with triethylamine in methanol. Attempted sulfide contraction of this salt led only to the same thiophene. In contrast, thioamide 7a could not be transformed into thiophene 25, but readily underwent sulfide contraction. The phenyl ring apparently increases[12] 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. The hydroxythioamides were esterified with the acid chloride, and the chloroester was treated with sodium iodide in acetonitrile. Addition of phosphine 5 afforded the chromatographically stable enaminolactones in high yield (Scheme III). Further evidence for an irreversible deprotonation step was provided by the fact that thioamides 27a and 27b each afforded the corresponding lactone with no sign of epimerization.

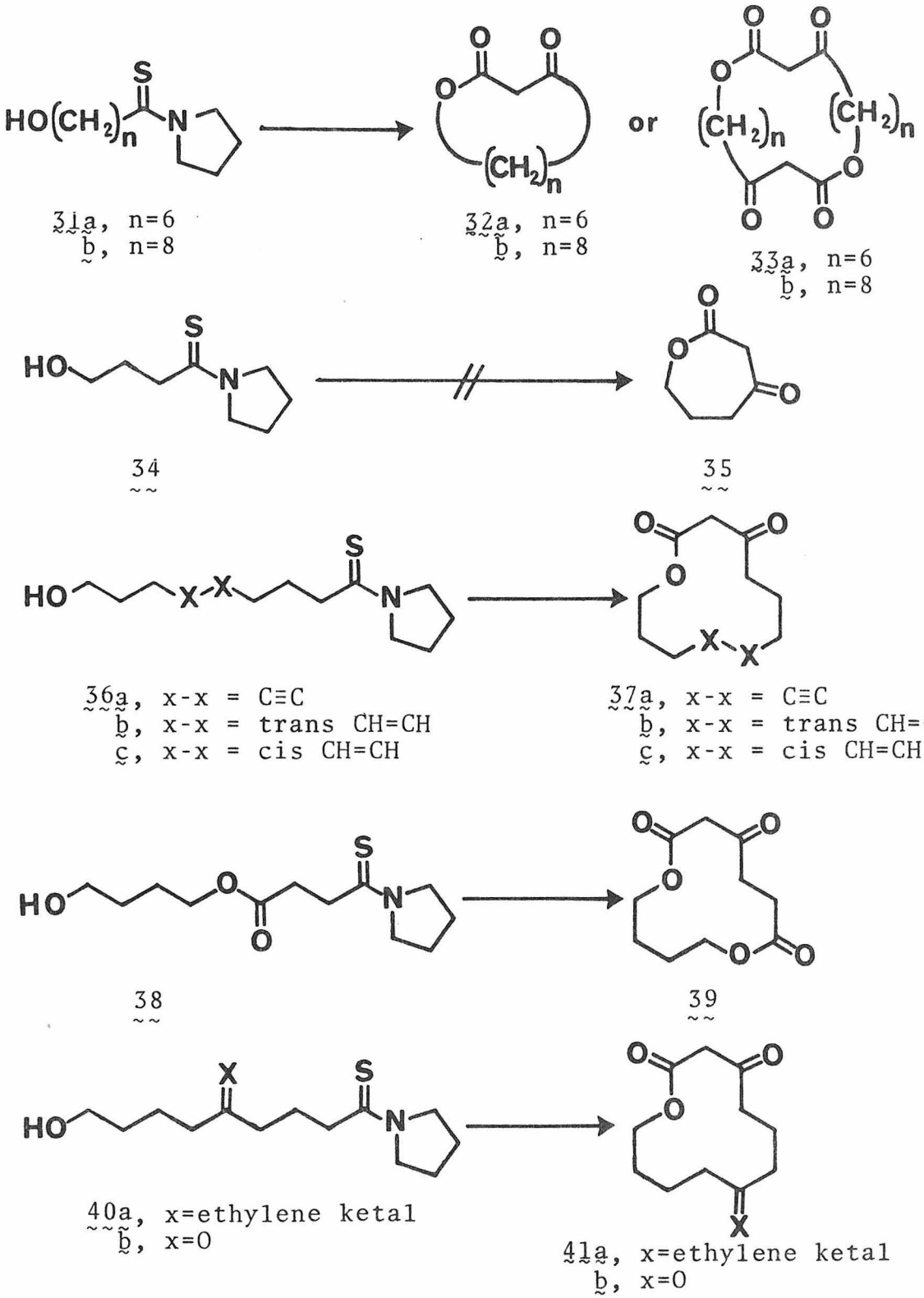
Application of the procedure thus developed to the formation of macrocycles (Scheme IV) led to disappointing results. Thioamides 31a and 31b afforded the dimers 33a and 33b, while thioamide 34 afforded no identifiable products. Since it appeared that the reversible alkylation step was causing the problem, a way was sought to trap the intermediate thioimmonium salt as it was formed. This was accomplished by slowly adding the chloroester to a solution of sodium iodide, Hunig's base,[13] and triethyl phosphite in

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.

Scheme IV. Macrocyclic Lactone Formation



31a, n=6
b, n=8

32a, n=6
b, n=8

33a, n=6
b, n=8

34

35

36a, x-x = C≡C
b, x-x = trans CH=CH
c, x-x = cis CH=CH

37a, x-x = C≡C
b, x-x = trans CH=CH
c, x-x = cis CH=CH

38

39

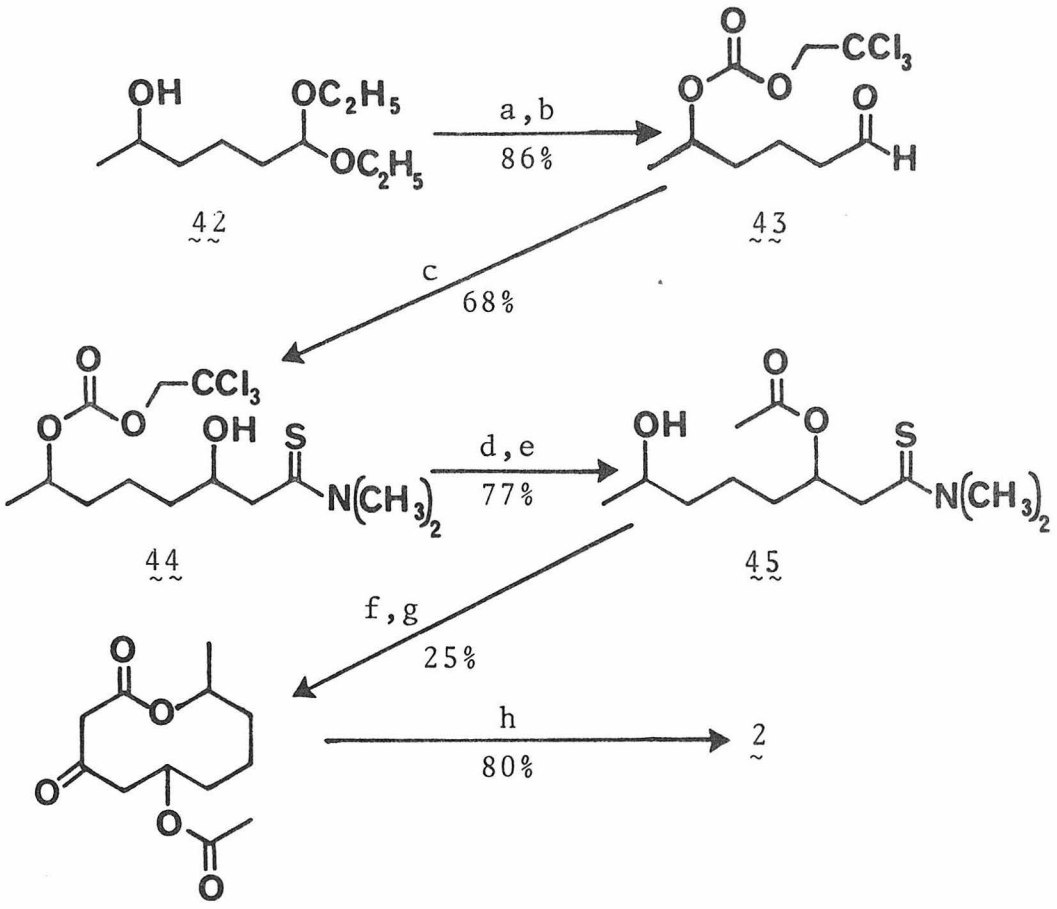
40a, x=ethylene ketal
b, x=O

41a, x=ethylene ketal
b, x=O

acetonitrile heated at reflux. Indeed, this modification led to the desired monomeric lactones in acceptable yields (Table I).

The sulfide contraction procedure was applied to the synthesis of diplodialide A (2).[14] Initial experiments using the corresponding α,β-unsaturated thioamide[15] were unsuccessful so β-acetoxythioamide 45 was synthesized (Scheme V). Reaction of aldehyde 43 with the zinc enolate[16] of N,N-dimethylthioacetamide provided alcohol 44 in 68% yield which represents a substantial improvement over the lithium enolate (41% yield). Alcohol 44 was converted into alcohol 45, and sulfide contraction of alcohol 45 afforded acetoxylactone 46 in 25% yield. 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.

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, $P(OEt)_3$, iPr_2NEt, CH_3CN, Δ; h, iPr_2NEt, CH_3CN, Δ.

Experimental Section

Boiling points are uncorrected. Melting points were determined using a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on Perkin-Elmer 237B or 737B or Beckmann 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 using helium carrier gas at a flow rate of 60 mL/min. All analytic 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, 0.25mm. "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 silica gel was E. Merck "Silica Gel 60", 70-230 mesh ASTM. "Flash chromatography (Xmm 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 using 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 using dry carbon disulfide under dry argon, dimethyl sulfoxide (DMSO) by distillation from CaH_2; aluminum isopropoxide by distillation; anhydrous zinc chloride by fusing three times under vacuum (<0.5mm).

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^{o}C, which is supplied by J. T. Baker Co., Phillipsburg, N.J., 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, Ohio. 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 2N 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, Pasadena, Ca., on a Du Pont type 21-492 mass spectrometer. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Mich..

N,N-Dimethylpentanethioamide (7a). A procedure similar to that of P. Reynaud and co-workers[19] was used. To 16.85g (0.114 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 a clear liquid: bp 70-75°C (0.25 mm), Lit.[19] 89°C (0.1 mm); IR (neat) 1510 cm^{-1} (>NC=S); ^{1}H-NMR ($CDCl_3$) δ 3.45, 3.28 (2 s, 2 × 3 H, $>NCH_3$).

1-Pentanethioylazacyclopentane (7b). 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 7b: 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, 2 × 2 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-oxazacyclohexane (7c). By the procedure described above for the preparation of thioamide 7b, 11.9 g (80 mmol) of the dithioester with 8.4 mL (96 mmol) of morpholine and 100 mL of dry benzene provided after distillation 13.4 g (89%): bp 106-114°C (0.15 mm), Lit.[19] 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, 3 × 2 H, $>NCH_2$-, $-OCH_2$-).

Methyl 5,5-Ethylenedioxyhexanedithioate. The procedure of Brandsma and co-workers[9] was used to prepare the 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, 2 × 2 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-ethylenedioxyhexanethioamide (11). By the procedure described above for the preparation of thioamide 7a, 34.6 g (0.157 mol) of dithioester with 125 mL of a 25% aqueous dimethylamine solution[20] provided after distillation 25.6 g (75%) of thioamide 11: bp 115-124°C (0.05 mm); IR ($CHCl_3$) 1525 cm^{-1} (>NC=S); ^{1}H-NMR ($CDCl_3$) δ 3.91 (s, 2 × 2 H, $-OCH_2-$), 3.44, 3.30 (2 s, 2 × 3 H, $>NCH_3$), 1.31 (s, 3 H, $>CCH_3$).

Methyl 3-(Dimethylcarbamoyl)propanoate. To a stirred solution of 100 g (2.22 mol) of dimethylamine in 1000 mL of dichloromethane maintained at a temperature of -20 to -25°C with a dry ice-acetone bath was added 150.6 g (1.00 mol) of 3-carbomethoxypropionyl chloride[22] over 30 min. The solution was then stirred for 30 min at 0°C (ice-water bath) and then at room temperature for 15 min. Then 200 mL of anhydrous ether was added, and the resulting solution was filtered through a 350 mL coarse fritted funnel. The salts were washed with 200 mL of anhydrous ether, and the filtrate was concentrated under reduced pressure. The residue was taken up in 150 mL of anhydrous ether and was refiltered. Solvents were removed under reduced pressure, and distillation of the residue gave 142 g (89%):

bp 90-95°C (0.8 mm), Lit.[23] 151°C (24 mm).

Methyl 3-(Dimethylthiocarbamoyl)propanoate (13). A modified procedure of Rao and co-workers[10] was used. A solution of 31.8 g (0.20 mol) of the corresponding amide, 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 one inch 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 a yellow oil: bp 85-100°C (0.09 mm); IR (neat) 1720 (C=O), 1500 cm^{-1} (>NC=S); ^{1}H-NMR ($CDCl_3$) δ 3.70 (s, 3 H, $-OCH_3$), 3.50, 3.37 (2 s, 2 × 3 H, $>NCH_3$), 2.93 (s, 2 × 2 H, $-CH_2-$).

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

1-(3-Butylthiopropanoyl)azacyclopentane. A solution of 26.0 g (0.160 mol) of 3-butylthiopropionic 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 acid wash ($MgSO_4$) followed by distillation: 31.2 g (90%); bp 132-137°C (0.3 mm); IR (neat) 1625 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 3.2-3.6 (m, 2 × 2 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-Butylthiopropanethioyl)azacyclopentane (15). 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 filtered 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 chromatographed on 150 g of silica gel (10% ethyl acetate-toluene) and was then distilled to afford 21.2 g (63%) of a yellow liquid: bp 160-165°C (0.2 mm); IR (neat) 1465 cm^{-1} (>NC=S); ^{1}H-NMR ($CDCl_3$) δ 3.5-4.0 (m, 2 × 2 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 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 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 were dried over anhydrous $MgSO_4$. Removal of solvents under reduced pressure followed by distillation provided the β-enaminoester.

Alternatively, the ketone was prepared by passing the crude enaminoester 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 ketone 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 by removal of solvents under reduced pressure. The slurry procedure was repeated if hydrolysis (as shown by ^{1}H-NMR) was not complete. Distillation provided the ketone.

Ethyl 3-(N,N-Dimethylamino)-2-heptenoate (8a). Yield 83%; bp 75-80°C (0.12 mm); IR (neat) 1675 (C=O), 1530 (C=C), 790 cm^{-1} (>C=CH-); ^{1}H-NMR ($CDCl_3$) δ 4.48 (s, 1 H, vinylic H), 4.04 (q, 2 H, J = 7 Hz, $-OCH_2-$), 2.92 (s, 2 × 3 H, $>NCH_3$),

1.23 (t, 3 H, J = 7 Hz, $-OCH_2\underset{\sim}{CH_3}$). A portion of the enamine was chromatographed on silica gel (5% ethyl acetate-toluene) to give the corresponding ketone, ethyl 3-oxoheptanoate, identical (IR, ^{1}H-NMR, TLC, VPC) with an authentic sample:[27] IR (neat) 1735 (C=O), 1705 (C=O), 1635 cm^{-1} (C=C); ^{1}H-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, $-OCH_2\underset{\sim}{CH_3}$).

Ethyl 3-(1-azacyclopentyl)-2-heptenoate (8b). Yield 81%; bp 110-124°C (0.45 mm); IR (neat) 1675 (C=O), 1570 (C=C), 790 cm^{-1} (>C=CH-); ^{1}H-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, $-OCH_2\underset{\sim}{CH_3}$). A portion of the enamine was chromatographed on silica gel (5% ethyl acetate-toluene) to afford the corresponding ketone which was identical (IR; ^{1}H-NMR, TLC, VPC) with an authentic sample.

Ethyl 3-[4-(1,4-oxazacyclohexyl)]-2-heptenoate (8c). Yield 77%, bp 105-120°C (0.35 mm); IR (neat) 1675 (C=O), 1570 (C=C), 795 cm^{-1} (C=CH-); ^{1}H-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, $-OCH_2\underset{\sim}{CH_3}$). A portion of the enamine was chromatographed on silica gel (5% ethyl acetate-toluene) to give the corresponding ketone which was identical (IR, ^{1}H-NMR, TLC, VPC) with an authentic sample.

Ethyl (E)-3-(N,N-Dimethyl)propenoate (10). Yield 72%; bp 74-76°C (2 mm), Lit.[28] 68-70°C (1.5 mm), 90-91°C (2.3 mm); ^{1}H-NMR ($CDCl_3$) shifts for the vinylic protons were identical to those previously reported.[28b]

Ethyl 7,7-Ethylenedioxy-3-oxooctanoate (12). Yield 64%; bp 95-105°C (0.03 mm); IR ($CHCl_3$) 1735 (C=O), 1715 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 4.17 (q, 2 H, J = 7 Hz, $-OCH_2-$), 3.59 (s, 2 × 2 H, ketal), 3.40 (s, 2 H, C-2 H), 1.32 (s, 3 H, $\rightarrow CH_3$), 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 (14). Yield 54%; bp 89-95°C (0.15 mm); IR (neat) 1735 (C=O), 1705 cm^{-1} (C=O); ^{1}H-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 (16). Yield 47%; bp 94-102°C (0.05 mm); IR ($CHCl_3$) 1740 (C=O), 1715 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 4.12 (q, 2 H, J = 7 Hz, $-OCH_2-$), 3.47 (s, 2 H, C-2 H), 1.29 (t, 3 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.

N,N-Dimethylethanethioamide. By the procedure described above for the preparation of thioamide 13, 17.5 g (0.20 mol) of N,N-dimethylacetamide, 18.0 g (0.081 mol) of purified phosphorus pentasulfide, 12.0 mL (0.086 mol) of dry triethylamine, and 200 mL of dry dichloromethane provided after chromatography on 290 g of silica gel (45% ethyl acetate-toluene) 14.5 g (70%) of a white solid: mp

73-74°C; Lit.[20] 73-74°C.

1-(Carboethoxymethylthio)ethylidenyldimethylammonium Iodide (17a). A solution of 0.520 g (5.0 mmol) of N,N-dimethylethanethioamide 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 using a 15 mL medium fritted funnel and was washed with 30 mL of anhydrous ether. The salt was dried under vacuum to obtain 1.07 g (67%): mp 115-116°C; IR ($CHCl_3$) 1740 (C=O), 1615 cm^{-1} (C=C) ^{1}H-NMR ($CDCl_3$) δ 4.38 (s, 2 H, $-SCH_2-$), 4.24 (q, 2 H, J = 7 Hz, $-OCH_2-$), 3.51, 3.37 (2 s, 2 × 3 H, $>NCH_3$) 2.93 (s, 3 H, $\rightarrow CCH_3$), 1.30 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$).

1-(Carboisopropoxymethylthio)ethylidenyldimethylammonium Iodide (17b). By the procedure described above for the preparation of salt 19, 2.03 g (20 mmol) of N,N-dimethylethanethioamide with 4.8 g (21 mmol) of isopropyl iodoacetate (18b)[29] and 20 mL of dry acetonitrile provided 6.3 g (97%) of a pale yellow solid: IR ($CHCl_3$) 1725 (C=O) 1600 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$) δ 5.06 (septet, 1 H, J = 6 H, -OCH<), 4.40 (s, 2 H, $-SCH_2-$), 3.87, 3.73 (2 s, 2 × 3 H, $>NCH_3$), 2.76 (s, 3 H, $-CH_3$), 1.48 (d, 2 × 3 H, $>CHCH_3$).

1-(Carboethoxymethylthio)pentylidenyldimethylammonium Iodide (19). A solution of 1.48 g (10 mmol) of thioamide 7a 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. Filtering and drying of the solid as described for iodide 17a afforded 3.36 g (92%) of an off-white solid: IR ($CHCl_3$) 1735 (C=O), 1615 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$) δ 4.33 (s, 2 H, $-SCH_2-$), 4.28 (q, 2 H, J = 7.5 Hz, $-OCH_2-$) 3.87, 3.73 (2 s, 2 × 3 H, $>NCH_3$), 1.33 (t, 3H, J = 7.5 Hz, $-OCH_2CH_3$).

Isopropyl 3-Oxoheptanoate (21b). By the general procedure for intermolecular sulfide contractions described above, 0.465 g (3.2 mmol) of thioamide 2a with 0.85 g (3.7 mmol) of iodoacetate 18b, 0.90 g (3.2 mmol) of bis(dimethylaminopropyl)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-ketoester 21b: IR ($CHCl_3$) 1735 (C=O), 1715 cm^{-1} (C=O); ^{1}H-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, 2 × 3 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.

Cross-over Experiment I. A solution of iodide salt 17a 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 was 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 was washed with 30 mL of anhydrous

ether. Drying of the brown solid under vacuum provided 0.943 g: ^{1}H-NMR ($CDCl_3$) showed that the salt was a 1:1 mixture of salts 17a and 17b.

Cross-over Experiment II. A solution of 1.65 g (5.0 mmol) of salt 17b and 1.80 g (5.0 mmol) of salt 19 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(dimethylaminopropyl)phenylphosphine[6] was added, and the clear solution was heated under reflux for 2 h. Workup as described above for 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-ketoesters: 20a (retention time = 1.1 min), 20b (retention time = 1.3 min), 21a (retention time = 5.4 min), and 21b (retention time = 7.0 min). All esters were identified by coinjection with authentic samples. Heptanoates 21a and 21b were present in a 1:1 ratio.

Attempted Synthesis of 1,4-Diphenyl-1,3-butanedione (24). A solution of 0.507 g (1.21 mmol) of bromide 22[11] in 5.0 mL of dry acetonitrile was treated with 0.70 g (2.5 mmol) of bis(dimethylaminopropyl)phenylphosphine as described above for intermolecular sulfide contractions. Workup afforded 0.352 g (81%) of thiophene 23 as the sole product.

Attempted synthesis of N,N-Dimethyl-3-propyl-4-phenyl-2-thiopheneamine (25). A modified procedure of Hartmann and Mayer[11] was used. A solution of 0.293 g (2.0 mmol) of thioamide 2a 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 (26). By the general procedure for intermolecular sulfide contraction described above, 0.730 g (5.0 mmol) with 1.01 g (5.1 mmol) of phenacyl bromide, 1.40 g (5.0 mmol) of bis(dimethylaminopropyl)-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 22: IR ($CHCl_3$) 1600 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$) δ 7.8-8.1 (m, 2 H, m-ArH), 7.3-7.6 (m, 3 H, o, p-ArH), 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.

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-carbomethoxythian-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 was 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); ^{1}H-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.

1-[3-(cis and trans-4-Hydroxythiacyclohexyl)carbonyl]-azacyclopentane. A solution of 16.50 g (77.4 mmol) of the β-ketoamide 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 hydrolysed,[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 (2000 mL 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; ^{1}H-NMR ($CDCl_3$) δ5.21 (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 dependent in CCl_4; ^{1}H-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.

1-[(2R*,3S*)-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 (-OH), 1600 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ4.77 (br s, 1 H, >C$\underset{\sim}{H}$OH), 1.14 (d, 3 H, J=7 Hz, >CHC$\underset{\sim}{H}_3$), 0.94 (t, 3 H, J=7 Hz, -$CH_2C\underset{\sim}{H}_3$).

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.

1-[(2R*,3S*)-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 was 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); ^{1}H-NMR ($CDCl_3$) δ5.13 (dt, 1 H, J = 5 Hz, J' = 8 Hz, >C$\underset{\sim}{H}$OH), 2.05 (s, 3H, CH_3C=O), 1.10 (d, 3 H, J = 7, >CHC$\underset{\sim}{H}_3$) 0.89 (t, 3 H, J = 7 Hz; -$CH_2C\underset{\sim}{H}_3$). 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.

1-[(2R*,3S*)-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); ^{1}H-NMR ($CDCl_3$) δ5.30 (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.

1-[(2R*,3S*)-3-Hydroxy-2-methylpentanethioyl]azacyclopentane (27a). 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); ^{1}H=NMR ($CDCl_3$) δ2.93 (dq, 1 H, J = 7 Hz, J' = 2 Hz, >C<u>H</u>CH_3), 1.20 (d, 3 H, J = 7 Hz, >CH$C\underline{H}_3$). 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-[(2R*,3R*)-3-Hydroxy-2-methylpentanoyl]azacyclopentane. By the procedure described above for the preparation of the epimeric alcohol, 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 hydroxyamide as a clear oil: IR (neat) 3390 (-OH), 1605 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ4.13 (br s, 1 H, >C<u>H</u>OH), 1.52 (d, 3 H, J = 8 Hz, >CH$C\underline{H}_3$). 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-[(2R*,3R*)-3-Acetoxy-2-methylpentanoyl]azacyclopentane. By the procedure described above 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); ^{1}H-NMR ($CDCl_3$) δ4.98 (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, >C$\underset{\sim}{H}CH_3$), 0.85 (t, 3 H, J = 7 Hz, -$CH_2\underset{\sim}{CH_3}$).

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-[(2R*,3R*)-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); ^{1}H-NMR ($CDCl_3$) δ5.10 (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, 3H, J = 7 Hz, >CH$\underset{\sim}{CH_3}$), 0.88 (t, 3 H, J = 7 Hz), -$CH_2\underset{\sim}{CH_3}$). 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-[(2R*,3R*)-3-Hydroxy-2-methylpentanethioyl]azacyclopentane (27b). By the procedure described above for the preparation of alcohol 27a, 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 27b as an oil: IR ($CHCl_3$) 3310 (-OH), 1475 cm^{-1} (>NC=S); ^{1}H-NMR ($CDCl_3$) δ1.21 (d, 3H, 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.

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 the aid of 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); ^{1}H-NMR ($CDCl_3$) δ5.95 (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.

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 was 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 was filtered through 50 g of silica gel with the aid of 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); ^{1}H-NMR ($CDCl_3$) δ6.37 (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.

1-(2-Hydroxy-2-phenylethanethioyl)azacyclopentane (29). By the procedure described above for the preparation of alcohol 27a, 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 29 as a white solid: mp: 91-92°C; IR ($CHCl_3$) 3250 (-OH) 1490

cm^{-1} (>NC=S); ^{1}H-NMR ($CDCl_3$) δ 7.2-7.5 (m, 5 H, ArH), δ 5.29 (d, 1 H, J = 8 Hz, -OH), δ 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.

5- and 6-membered Ring Lactones: General Procedure. A solution of the alcohol (1.0 mmol) and 0.10 mL (1.26 mmol) of chloroacetyl chloride (or 0.11 mL (1.13 mmol) of chloropropionyl chloride) on 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.

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 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 was diluted with 25 mL of dichloromethane, and the resulting solution was washed once with 25 mL of a 2 M aqueous NaH_2PO_4 solution. The aqueous phase was extracted twice with 25 mL portions of dichloromethane, and the combined organic phases were washed with a saturated aqueous sodium chloride solution and were dried over $MgSO_4$. Removal of solvent and chromatography on 10 g of silica gel yielded the enaminolactone.

4-(1-Azacyclohexyl)-cis-5-methyl-6-ethyloxacyclohex-3-en-2-one (28a). Yield 52%; R_f = 0.19 (1% methanol-ethyl acetate); IR ($CHCl_3$) 1645 (C=O), 1580 cm^{-1} (C=C) ^{1}H-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-Azacyclohexyl)-trans-5-methyl-6-ethyloxacyclohex-3-en-2-one (28b). 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); ^{1}H-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-Azacyclohexyl)-5-phenyloxacyclopent-3-en-2-one (30a). 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), ^{1}H-NMR ($CDCl_3$) δ 7.33 (s, 5 H, ArH), 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-Azacyclohexyl)-2-methyl-5-phenyloxacyclopent-3-en-2-one (30b). 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); ^{1}H-NMR ($CDCl_3$) δ 7.25 (s, 5 H, ArH), 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.

Methyl 7-(2-Oxacyclohexyloxy)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; ^{1}H-NMR δ 4.53 (br s, 1 H, >CH-), 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.

1-(9-Hydroxyheptanethioyl)azacyclopentane (31a). A solution of the 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 in order 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 hydroxythioamide 31a as a slowly crystallizing oil: mp 30-32°C; IR ($CHCl_3$) 3610 (-OH), 1490 cm^{-1} (>NC=S); ^{1}H-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 turned dark and became very hot. The solution was stirred for 3 h, and solid potassium carbonate was added. The solution was fractionally distilled through a 15 cm Vigreaux column to yield 22.5 g (78%) of the chloride as a clear liquid: bp 116-120°C (0.4 mm); IR was uninformative; ^{1}H-NMR ($CDCl_3$) δ 4.53 (br s, 1 H, >CH-).

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-Oxacyclohexyloxy)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; ^{1}H-NMR ($CDCl_3$) δ 4.50 (br s, 1 H, >CH-),

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 (31b). By the procedure described above for the preparation of thioamide 31a, 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% ethylacetate-benzene followed by 50% ethyl acetate-benzene) yielded 9.83 g (81% from the chloride) of thioamide 31b as a white solid: mp 57-57.5°C (ether); IR ($CHCl_3$) 3640 (-OH), 1490 cm^{-1} (>NC=S); ^{1}H-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, 13.19.

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 hydroxyamide as a viscous liquid: bp 135-145°C (0.01 mm); IR (neat) 3350 (-OH), 1620 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 3.3-3.8 (m, 2 × 2 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.

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); ^{1}H-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.

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); ^{1}H-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.

1-(4-Hydroxybutanethioyl)azacyclopentane (34). A

solution of 3.23 g (15.0 mmol) of the corresponding acetate in 40 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 the thioamide as a yellow oil: IR (neat) 3390 (-OH), 1460 cm^{-1} (>NC=S); ^{1}H-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.

8-(2-Oxacyclohexyloxy)oct-4-yn-1-ol. A modified procedure of Ames and co-workers[41] was used. Lithium wire (5.60 g, 0.81 mol) was slowly added to an anhydrous ammonia solution containing 0.50 g of ferric nitrate decahydrate. After formation of the amide was complete (as evidenced by disappearance of the blue color), 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); ^{1}H-NMR ($CDCl_3$) δ 4.57 (br s, 1 H, >CH-) 3.3-4.0 (m, 3 × 2 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.

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 twice with 100 mL portions of water and was dried over anhydrous Na_2SO_4. The solution was filtered, solvents were removed under reduced pressure, and the residue was distilled to yield 17.5 g (71%) of a clear liquid: bp 110-120°C (0.2 mm); IR (neat) lacked hydroxyl stretch; ^{1}H-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.

Methyl 9-(2-Oxacyclohexyloxy)non-5-ynedithioate. According to the procedure of Brandsma and co-workers,[9] 12.48 g (51 mmol) of the 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 crude dithioester as a golden-yellow oil which was used without further purification: IR was uninformative; ^{1}H-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 $C_{15}H_{26}O_2S_2$: C, 59.96; H, 8.05; S, 21.34. Found: C, 59.97; H, 8.03; S, 21.30.

1-(9-Hydroxy-5-nonynethioyl)azacyclopentane (36a). By the procedure described above for the preparation of thioamide 31a, the 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) yielded 4.99 g (41%) of 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); ^{1}H-NMR ($CDCl_3$) δ 3.5-3.9 (m, 3 × 2 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.

(E)-8-(2-Oxacyclohexyloxy)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); ^{1}H-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.

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; ^{1}H-NMR ($CDCl_3$) δ 5.3-5.5 (m, 2 H, vinylic H), δ 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.

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), ^{1}H-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.

1-[(E)-9-Hydroxy-5-nonenethioyl]azacyclopentane (36b). By the procedure described above for the preparation of thioamide 31a, 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 36b: IR ($CHCl_3$) 3625, 3425 (-OH), 1490 cm^{-1} (>NC=S), 980 (trans C=C); ^{1}H-NMR ($CDCl_3$) δ 5.3-5.5 (m, 2 H, vinylic H), 3.5-4.0 (m, 3 × 2 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-Oxacyclohexyloxy)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 the aid of 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); ^{1}H-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 the procedure described above, 9.54 g (41.8 mmol) of the alcohol with 9.1 mL of hexamethylphosphorus tramide, 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-Cyclohexyloxy)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 (36c). By the procedure described above for the preparation of thioamide 31a, 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 36c 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, 3 × 2 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.

4-Hydroxybutyl 3-(Dimethylthiocarbamoyl)propanoate (38). A solution of 8.76 g (50.0 mmol) of ester 12, 0.10 g (0.02 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 hydroxyester was isolated by chloroform extraction ($MgSO_4$). Chromatography on 325 g of silica gel (1000 mL of 2% methanol-ethyl acetate, 1000 mL of 5% methanol-ethyl acetate, 1000 mL of 10% methanol-ethyl acetate) yielded 7.17 g (61%) of hydroxyester 38 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, 3.35 (2 s, 2 × 3 H, $>NCH_3$), 2.90 (s, 2 × 2 H, O=C-CH_2CH_2-C=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.

1-(5-Hydroxybutanoyl)azacyclopentane. By the procedure described above for the preparation of the hydroxybutyramide, 50.2 g (0.50 mol) of δ-valerolactone with 65 mL (0.78 mol) of pyrrolidine and 350 mL of benzene provided 70.6 g (82%) of the hydroxyamide 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.

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.12; H, 10.01; N, 8.18. Found: C, 63.23; H, 9.93; N, 8.11.

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 means of a dry ice-acetone bath while 33.0 mL (0.465 mol) of dry DMSO 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 was 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 aldehyde as a red liquid, one spot by TLC (R_f = 0.38, 50% acetone-petroleum ether): IR ($CHCl_3$) 2750 (aldehyde C-H), 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, 2 × 2 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.

1-[5-Hydroxy-9-(2-oxacyclohexyloxy)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 a temperature of -50°C by means of a dry ice-acetone bath. The resulting solution was stirred for 5 min and was 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 was 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.

1-[9-(2-Oxacyclohexyloxy)-5-(2,2,2-trichloroethoxyformyloxy)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-).

m/e. Calcd for $C_{21}H_{34}Cl_3NO_6$: 501.146. Found: 501.145.

1-[9-Hydroxy-5-(2,2,2-trichloroethoxyformyloxy)nonanoyl]azacyclopentane. A solution of 36.0 g (71.6 mmol) of the tetrahydropyranylether and 2.0 mL of concentrated hydrochloric acid in 300 mL of methanol was stirred at room temperature for 1.5 h and was 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 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, $-CH_2CCl_3$).

m/e. Calcd for $C_{16}H_{26}Cl_3NO_5$: 417.088. Found: 417.089.

1-[9-Benzoyloxy-5-(2,2,2-trichloroethoxyformyloxy)-nonanoyl]azacyclopentane. By the procedure described above for the preparation of the acetoxyamides, 27.7 g (66.1 mmol) of the alcohol with 8.4 mL (72 mmol) of benzoyl chloride, 5.9 mL (73 mmol) of dry pyridine, and 140 mL of dry dichloromethane provided after flash chromatography (60 mm column, 40% acetone-petroleum ether) 32.9 g (95%) of 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, 2 × 2 H, $>NCH_2-$).

m/e. Calcd for $C_{23}H_{30}Cl_3NO_6$: 521.115. Found: 521.113.

1-[9-Benzoyloxy-5-(2,2,2-trichloroethoxyformyloxy)-nonanethioyl]azacyclopentane. By the procedure described above for the preparation of thioamide 13, 32.9 g (63 mmol) of the 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 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, 3.57 (2 t, 2 × 2 H, J = 6 Hz, $>NCH_2-$), 2.5-2.8 (m, 2 H, $-CH_2C=S$).

m/e. Calcd for $C_{23}H_{30}Cl_3NO_5S$: 537.091. Found: 537.089.

1-(9-Benzoyloxy-5-hydroxynonanethioyl)azacyclopentane. A slurry of 25.4 g (0.047 mol) of the carbonate, 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 a viscous oil: IR ($CHCl_3$) 3625 (-OH), 1710 (C=O), 1495 cm^{-1} (>NC=S); ^{1}H-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.

1-(9-Benzoyloxy-5-oxononanethioyl)azacyclopentane. Oppenauer oxidation[49] of 16.0 g (44 mmol) of the alcohol 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 (2500 mL of 50% ethyl acetate-petroleum ether followed by ethyl acetate) provided 4.37 g (27%) of the ketone: R_f = 0.59 (ethyl acetate); IR ($CHCl_3$) 1715 (C=O), 1500 cm^{-1} (>NC=S); ^{1}H-NMR ($CDCl_3$) δ 4.15-4.4 (m, 2 H, $-OCH_2-$), 3.77, 3.60 (2 t, 2 × 2 H, J = 6 Hz, $>NCH_2-$).

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.

1-[9-Benzoyloxy-5,5-ethylenedioxynonanethioyl]azacyclopentane. A solution of 2.53 g (7.0 mmol) of the ketone, 1.95 mL (35 mmol) of distilled ethylene glycol, and 0.011 g (0.6 mmol) of para-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 an oil: IR ($CHCl_3$) 1720 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 4.26 (t, 2 H, J = 6.5 Hz, $PhCO_2CH_2$-) 3.88 (S, 4 H, $-OCH_2-$).

m/e. Calcd for $C_{22}H_{31}NO_4S$: 405.197. Found: 405.196.

1-(5,5-Ethylenedioxy-9-hydroxynonanethioyl)-azacyclopentane (40a). According to the procedure described above for the preparation of thioamide 27a, 2.51 g (6.2 mmol) of the benzoate with 15 mL of a 0.5 M solution of lithium hydroxide in 80% aqueous methanol afforded after chromatography on 100 g of alumina (30% acetone-petroleum ether) 1.65 g (88%): IR ($CHCl_3$) 3650 (-OH), 1500 cm^{-1} (>NC=S); ^{1}H-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.

1-(9-Hydroxy-5-oxononanethioyl)azacyclopentane (40b). According to the procedure described above for the preparation of thioamide 27a, 1.82 g (5.0 mmol) of the benzoate with 12 mL of a 0.5 M solution of lithium hydroxide in 80% aqueous methanol afforded 0.983 g (76%) of the alcohol after chromatography on 120 g of silica gel (ethyl acetate): IR ($CHCl_3$) 3640 (-OH), 1715 (C=O), 1495 cm^{-1} (>NC=S); ^{1}H-NMR ($CDCl_3$) δ 3.1-3.9 (m, 3 × 2 H, $>NCH_2-$, $-OCH_2-$), 2.3-2.8 (m, 2 × 2 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 (33a). A solution of 0.217 g (1.01 mmol) of thioamide 31a 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 the chloroester 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); ^{1}H-NMR ($CDCl_3$) δ 4.13 (t, 2 × 2 H, J = 6 Hz, $-OCH_2-$), 3.40 (s, 2 × 2 H, $O=CCH_2C=O$).

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

m/e. Calcd for $C_{18}H_{28}O_6$: 340.189. Found: 340.188.

1,13-Dioxacyclotetracosane-2,4,14,16-tetrone (33b). By the procedure described above for the preparation of dimer 33a, 0.263 g (1.08 mmol) of thioamide 31b provided 0.092 g (43%): mp 122-123°C (benzene-petroleum ether); IR ($CHCl_3$) 1735 (C=O), 1705 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 4.0-4.3 (m, 2 × 2 H, $-OCH_2-$), 3.36 (s, 2 × 2 H, $O=CCH_2C=O$).

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

C, 66.49; H, 9.10.

m/e. Calcd for $C_{22}H_{36}O_6$: 396.252. Found: 396.251.

Attempted cyclization of thioamide 34. By the procedure described above for the preparation of dimer 33a, 0.203 g (1.18 mmol) of thioamide 34 provided no identifiable material.

Macrocyclic Lactones: General Procedure. To a solution of the hydroxythioamide (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 means of a syringe pump[50] a solution of the chloroester 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.

1,1-Diethoxy-5-(2,2,2-trichloroethoxyformyloxy)hexane. By the procedure described above for the preparation of the trichloroethyl carbonate, 11.40 g (59.9 mmol) of 6,6-diethoxy-2-hexanol[51] with 8.4 mL (61.0 mmol) of trichloroethyl chloroformate, 5.2 mL (64.3 mmol) of dry pyridine, and 100 mL of dry dichloromethane provided after flash chromatography (60 mm column, 9% ethyl acetate-petroleum ether) 21.7 g (99%) of the carbonate as a clear oil: IR ($CHCl_3$) 1755 cm^{-1} (C=O); ^{1}H-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-Trichloroethoxyformyloxy)hexanal (43). 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 a clear oil: IR ($CHCl_3$) 2750 (aldehyde C-H), 1750 (C=O), 1720 cm^{-1} (C=O); ^{1}H-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.

N,N-Dimethyl-3-hydroxy-7-(2,2,2-trichloroethoxyformyloxy)octanethioamide (44). A. Lithium enolate. To 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 was 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 43 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 thioamide was isolated by ether extraction ($MgSO_4$) followed by chromatography on 350 g of silica gel (1800 mL of 40% ethyl acetate-petroleum ether, 1000 mL 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); ^{1}H-NMR ($CDCl_3$) δ 4.67 (s, 2 H, $-CH_2CCl_3$), 3.41, 3.23 (2 s, 2 × 3 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 43 in 5 mL of dry THF was added over half a 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 thioamide 44.

N,N-Dimethyl-3-acetoxy-7-(2,2,2-trichloroethoxyformyloxy)octanethioamide. By the procedure described above for the preparation of acetates, 4.01 g (10.2 mmol) of alcohol 44 with 0.75 mL (10.5 mmol) of acetyl chloride, 0.85 mL (10.5 mmol) of dry pyridine, and 20 mL of dry dichloromethane 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 (broad q, 1 H, J = 6 Hz, >CHOAc), 4.71 (s,

2 H, $-CH_2CCl_3$), 3.41, 3.34 (2 s, 2 × 3 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 (45). By the procedure described above for the removal of trichloroethyl carbonates, 3.78 g (8.65 mmol) of the carbonate 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 45 as an oil: IR ($CHCl_3$) 3625 (-OH), 1735 (C=O), 1520 cm^{-1} (>NC=S); ^{1}H-NMR ($CDCl_3$) δ 5.28 (q, 1 H, J = 6 Hz, >CHOAc), 3.41, 3.34 (2 s, 2 × 3 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, 8.86; N, 5.26; S, 12.17.

6-Acetoxy-10-methyloxacyclodecane-2,4-dione (46). According to the general procedure for macrocyclic lactone formation, 0.279 g (1.07 mmol) of alcohol 45 provided

0.062 mg (24%) of acetate 46 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); ^{1}H-NMR ($CDCl_3$) δ 2.00, 1.97 (2 s, 3 H, 2 CH_3C=O), 1.26 (d, 3 H, J = 7 Hz, >$CHCH_3$).

m/e. Calcd for $C_{12}H_{18}O_5$: 242.115. Found: 242.116.

(±)-Diplodialide A. A solution of 0.062 mg (0.26 mmol) of acetate 46 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 was 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 was 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, ^{1}H-NMR, MS) were identical to those previously reported.[14a]

Table I. Macrocyclic Lactone Formation[a]

Thioamide (MW)	Macrocyclic Lactone	% Yield	mp (bp)[a]	IR (cm^{-1})	^{1}H-NMR (δ)		m/e		Anal.		R_f
					$-OCH_2-$ (J)	$O=CCH_2C=O$	Calcd	Found	Calcd	Found	
31a (215.35)	oxacyclodecane-2,4-dione (32a)	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	0.26[e]
31b (243.40)	oxacyclododecane-2,4-dione (32b)	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]
36a (239.37)	oxacyclodec-8-yne-2,4-dione (37a)	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]
36b (241.38)	(E)-oxacyclododec-8-ene-2,4-dione (37b)	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]
36c (241.38)	(Z)-oxacyclododec-8-ene-2,4-dione (37c)	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]
38 (233.32)	1,6-dioxacyclododecane-7,9,12-trione (39)	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]
40a (301.44)	1,4,10-trioxaspiro-[4.11]hexadecane-11,13-dione (41a)	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	0.35[f]
40b (257.38)	oxacyclododecane-2,4,8-trione (41b)	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] a, Kugelrohr distilled at indicated temperature/pressure (mm); b, hexane; c, ethyl-acetatehexane; d, ether-hexane; e, 25% ethyl acetate-cyclohexane; f, 50% ethyl acetate-cyclohexane; g, 10% ethyl acetate-toluene.

References and Notes

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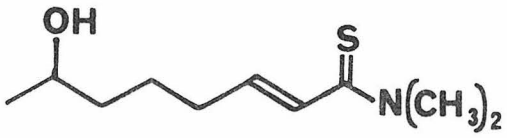
APPENDIX

Appendix A

The synthesis of α,β-unsaturated thioamide 47 and its conversion into diplodialide A are presented.



47

Experimental Section[1]

(E)-N,N-Dimethyl-7-acetoxy-2-octenamide. To a slurry of 1.126 g (23.5 mmol) of NaH (50% oil dispersion, hexane washed) in 20 mL of dry DME cooled with an ice-water bath under an argon atmosphere was added dropwise a solution of 5.20 g (23.3 mmol) of diethyl (dimethylcarbamoylmethyl)-phosphonate[2] in 20 mL of dry DME. After 5 min a solution of 3.20 g (20.2 mmol) of 5-acetoxyhexanal[3] in 5 mL of dry DME was added dropwise over 2 min. The solution was stirred for 10 min with cooling and for 3.25 h at room temperature, and the reaction was quenched with 250 mL of water. The amide was isolated by dichloromethane extraction ($MgSO_4$), was chromatographed on 180 g of silica gel (900 mL of ethyl acetate followed by 2% methanol-ethyl acetate), and was kugelrohr distilled at 145°C (0.3 mm) to yield 2.11 g (46%): IR ($CHCl_3$) 1730 (C=O), 1660 (C=C), 1605 (C=O), 910 cm^{-1} (trans CH=CH); ^{1}H-NMR ($CDCl_3$) δ 6.82 (dt, 1 H, J = 16 Hz, J' = 7 Hz, -CH=CHC=O) 6.24 (broad d, 1 H, J = 16 Hz, -CH=CHC=O), 3.02, 2.97 (2 s, 2 × 3 H, $>NCH_3$), 2.00 (s, 3 H, $CH_3C=O$), 1.17 (d, 3 H, J = 6 Hz, $>CHCH_3$).

Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.40; H, 9.31; N, 6.16. Found: C, 63.49; H, 9.32; N, 6.15.

(E)-N,N-Dimethyl-7-acetoxy-2-octenethioamide. By the procedure described above for the preparation of thioamide 13, 2.05 g (9.02 mmol) of the amide with 1.52 g (6.84 mmol) of purified phosphorus pentasulfide, 1.0 mL (7.2 mmol) of triethylamine, and 20 mL of dry dichloromethane yielded 2.57 g of a red oil which was chromatographed on 95 g of silica gel (35% ethyl acetate-cyclohexane) to give 0.756 g (35%) of a yellow oil: IR ($CHCl_3$) 1730 (C=O), 1655 (w, C=C), 1510 (>NC=S), 910 cm^{-1} (trans CH=CH); ^{1}H-NMR ($CDCl_3$) δ 7.08 (dt, 1 H, J = 14 Hz, J' = 8 Hz, -CH=CHC=S) 6.24 (broad d, 1 H, J = 14 Hz, -CH=CHC=S), 3.50 3.33 (2s, 2 × 3 H, $>NCH_3$), 2.01 (s, 3 H, $CH_3C{=}O$), 1.21 (d, 3 H, J = 6 Hz, $>CHCH_3$). An analytical sample was prepared by kugelrohr distillation at 140°C (0.005 mm).

Anal. Calcd for $C_{12}H_{21}NO_2S$: C, 59.22; H, 8.70; N, 5.76; S, 13.18. Found: C, 59.29; H, 8.63; N, 5.72; S, 13.15.

Hydrolysis of the Acetate. By the procedure described above for the preparation of alcohol 27a, 0.756 g (3.11 mmol) of the acetate with 10.0 mL of a 0.5 M solution of lithium hydroxide in 80% aqueous methanol over 5 h gave a mixture of four compounds. Flash chromatography (25 mm column, 50% ethyl acetate-cyclohexane followed by ethyl acetate) gave a total of 0.282 g (45%) of two isomeric tetrahydropyrans, cis- and trans-N,N-dimethyl-2-(6-methyl-oxacyclohexyl)ethanethioamide, 0.115 g (19%) of the desired

alcohol as a mixture of cis and trans isomers, and 0.20 g (28%) of N,N-dimethyl-7-hydroxy-3-methoxyoctanethioamide.

Of the two tetrahydropyrans, the faster moving one (TLC) was the major isomer: R_f = 0.66 (ethyl acetate), IR ($CHCl_3$) 1525 cm^{-1} (>NC=S); ^{1}H-NMR ($CDCl_3$) δ 3.47, 3.38 (2 s, 2 × 3 H, $>NCH_3$), 1.08 (d, 3 H, J = 6 Hz, $>CHCH_3$). An analytical sample was prepared by kugelrohr distillation at 95°C (0.25 mm) of a pure fraction.

Anal. Calcd for $C_{10}H_{19}NOS$: C, 59.66; H, 9.51; N, 6.96; S, 15.93. Found: C, 59.54; H, 9.47, N, 7.02; S, 15.84.

The isomeric tetrahydropyran (R_f = 0.54, ethyl acetate): IR ($CHCl_3$) 1520 cm^{-1} (>NC=S); ^{1}H-NMR ($CDCl_3$): δ 3.47, 3.33 (2 s, 2 × 3 H, $>NCH_3$), 1.31 (d, 3 H, J = 6 Hz, $>CHCH_3$). An analytical sample was prepared by kugelrohr distillation at 95°C (0.25 mm) of a pure fraction.

Anal. Calcd for $C_{10}H_{19}NOS$: C, 59.66; H, 9.51; N, 6.96; S, 15.93. Found: C, 59.68; H, 9.61; N, 6.91; S, 15.88.

The desired alcohol was obtained as a 1:1 mixture of cis and trans alkenes, one spot by TLC (R_f = 0.46, ethyl acetate): IR ($CHCl_3$) 3650, 3450 (-OH), 1660 (C=C), 1520 cm^{-1} (>NC=S); ^{1}H-NMR ($CDCl_3$) trans: δ 7.17 (dt, 1 H, J = 15 Hz, J' = 7 Hz, $-CH=CHC=O$), 6.22 (broad d, 1 H, J = 15 Hz, $-CH=CHC=S$), 3.50, 3.32 (2 s, 2 × 3 H, $>NCH_3$), 1.17 (d, 3 H, J = 6 Hz, $>CHCH_3$); cis: δ 6.14 (broad d, 1 H, J = 11 Hz, $-CH=CHC=S$), 5.6-5.8 (m, 1 H, $-CH=CHC=S$), 3.46, 3.29 (2 s, 2 × 3 H, $>NCH_3$), 1.17 (d, 3 H, J = 6 Hz, $>CHCH_3$). An analytical sample of a pure trans sample obtained from

the carbonate was prepared by kugelrohr distillation at 140°C (0.4 mm).

Anal. Calcd for $C_{10}H_{19}NOS$: C, 59.66; H, 9.51; N, 6.96; S, 15.93. Found: C, 59.50; H, 9.44; N, 6.84; S, 15.95.

Methoxythioamide (R_f = 0.32, ethyl acetate): IR ($CHCl_3$) 3630, 3450 (-OH), 1525 cm^{-1} (>NC=S); ^{1}H-NMR ($CDCl_3$) δ 3.52, 3.40, 3.37 (3 s, 3 × 3 H, $>NCH_3$, $-OCH_3$), 1.13 (d, 3 H, J = 6 Hz, $>CHCH_3$). An analytical sample was prepared by kugelrohr distillation at 160°C (0.1 mm).

Anal. Calcd for $C_{11}H_{23}NO_2S$: C, 56.61; H, 9.93; N, 6.00; S, 13.74. Found: C, 56.72; H, 9.88; N, 6.06; S, 13.79.

(E)-N,N-Dimethyl-7-(2,2,2-trichloroethoxyformyloxy)-2-octenamide. By the procedure described above for the preparation of the unsaturated acetoxyamide 7.92 g (27.2 mmol) of aldehyde 43 with 1.52 g (31.7 mmol) of sodium hydride (50% mineral oil dispersion), 7.0 g (31 mmol) of diethyl (dimethylcarbamoylmethyl)phosphonate,[2] and 60 mL of dry DME provided after flash chromatography (60 mm column, ethyl acetate) 5.86 g (60%) of the amide as a clear oil: IR ($CHCl_3$) 1750 (carbonate C=O), 1660 (C=C), 1610 cm^{-1} (amide C=O); ^{1}H-NMR ($CDCl_3$) δ 6.80 (dt, 1 H, J = 15 Hz, J' = 7 Hz, $-CH=CHC=O$), 6.24 (dt, 1 H, J = 15 Hz, J' = 1.5 Hz, $-CH=CHC=O$), 4.77 (s, 2 H, $-CH_2CCl_3$), 3.03, 2.97 (2 broad s, 2 × 3 H, $>NCH_3$), 1.31 (d, 3 H, J = 6 Hz, $>CHCH_3$). An analytical sample was prepared by kugelrohr distillation at 140°C (0.005 mm).

Anal. Calcd for $C_{13}H_{20}Cl_3NO_4$: C, 43.29; H, 5.59; N, 3.88. Found: C, 43.42; H, 5.69; N, 4.00.

(E)-N,N-Dimethyl-7-(2,2,2-trichloroethoxyformyloxy)-2-octenethioamide. By the procedure described above for the preparation of thioamide 13, 3.91 g (10.8 mmol) of the amide with 1.48 g (6.7 mmol) of purified phosphorus pentasulfide, 1.50 mL (10.8 mmol) of triethylamine, and 40 mL of dry dichloromethane yielded after chromatography on 250 g of silica gel (1500 mL of 30% ethyl acetate-cyclohexane followed by 2% methanol-ethyl acetate) 1.076 g (26%) of the thioamide as a bright yellow oil: IR ($CHCl_3$) 1750 (C=O), 1650 (C=C), 1510 cm^{-1} (>NC=S); ^{1}H-NMR ($CDCl_3$) δ 6.93 (dt, 1 H, J = 15 Hz, J' = 7 Hz, -CH=CHC=S), 6.49 (broad d, 1 H, J = 15 Hz, -CH=CHC=S), 4.74 (s, 2 H, $-CH_2CCl_3$), 3.51, 3.31 (2 s, 2 × 3 H, $>NCH_3$), 1.32 (d, 3 H, J = 6 Hz, $>CHCH_3$). An analytical sample was prepared by kugelrohr distillation at 160°C (0.005 mm).

Anal. Calcd for $C_{13}H_{20}Cl_3NO_3S$: C, 41.44; H, 5.35; N, 3.72; S, 8.51. Found: C, 41.46; H, 5.36; N, 3.79; S, 8.54.

Also recovered were 1.404 g (36%) of the starting amide as a red oil. Yield based on recovered starting material was 35%.

(E)-N,N-Dimethyl-7-hydroxy-2-octenethioamide (47). Hydrolysis of the carbonate. By the procedure described above for the removal of trichloroethyl carbonates, 0.500 g (1.32 mmol) of the carbonate with 0.52 g (8.0 mmol) of zinc

powder and 5.0 mL of glacial acetic acid provided after chromatography on 30 g of silica gel (75% ethyl acetate-cyclohexane) 0.206 g (77%) of alcohol 47 as a yellow oil.

Cis- and trans-(±)-Diplodialide A (2). According to the general procedure for macrocyclic lactone formation, 0.207 g (1.03 mmol) of alcohol 47 provided 0.011 g (6%) of an oil. VPC analysis (180°C, 10% SE-30 on Chromosorb WAW DMCS) revealed that it was a 3:1 mixture of cis:trans diplodialide A 2. ^{1}H-NMR ($CDCl_3$) contained peaks previously reported for both isomers.[4]

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PROPOSITIONS

ABSTRACTS OF PROPOSITIONS

PROPOSITION 1

The synthesis of γ-ketothioamides by the thiazolium- or cyanide-catalyzed 1,4-addition of aldehydes to α,β-unsaturated thioamides is proposed.

PROPOSITION 2

A study of the complexation of aminepolycarboxylate crown ethers with lanthanide elements is proposed.

PROPOSITION 3

It is proposed that the elementary isotope separation factors of a cryptate with calcium ions and that the cryptate's application to calcium isotope separation be investigated.

PROPOSITION 4

The preparation and characterization of a binuclear copper(II) complex with sulfur brudging atoms is proposed.

PROPOSITION 5

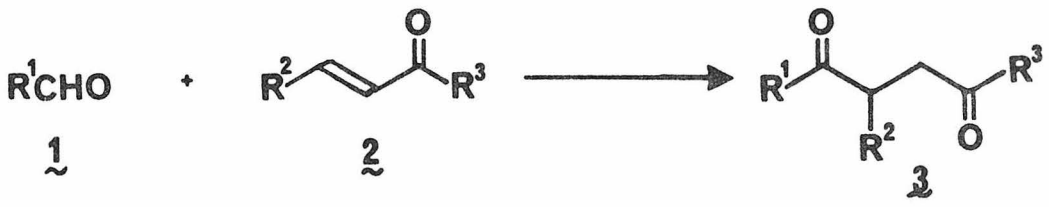
The synthesis of 1,2-oxazines by means of the 1,4-cycloaddition reaction of furans with nitroso compounds is proposed.

PROPOSITION 1

The synthesis of γ-ketothioamides by the thiazolium- or cyanide-catalyzed 1,4-addition of aldehydes to α,β-unsaturated thioamides is proposed.

In recent years much interest has been expressed in the synthesis of 1,4-dicarbonyl compounds. Such interest has been due in part to their potential use in prostaglandin synthesis and in part to the fact that the 1,4-dicarbonyl functionality represents a moderate synthetic challenge because of its "umpolung"[1] relationship. Such umpolung relationships cannot be synthesized using the normal polarities of the carbon skeleton.

One common approach to 1,4-dicarbonyl compounds has been the use of acyl anion equivalents,[2] one example being the thiazolium- or cyanide-catalyzed addition of aldehydes to α,β-unsaturated carbonyl compounds.[3]

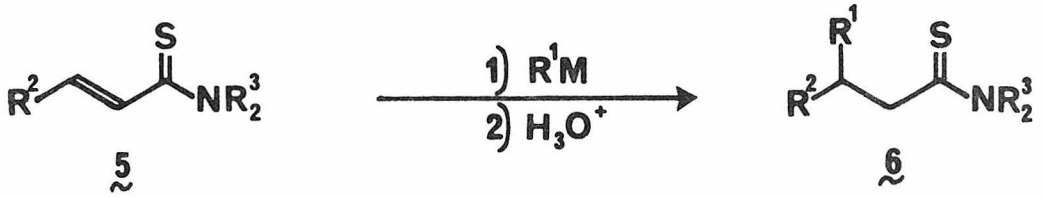


The catalyst reacts with the aldehyde to form a proposed intermediate carbon anion (4)

4

which adds to form the dicarbonyl compound. The use of thiazolium salts is precedented by the action of thiamine in biological systems.[4]

Recently, Yoshida and co-workers reported that α,β-unsaturated N,N-dialkylthioamides readily add organometallic species[5] and enolates[6] to afford the 1,4-addition products



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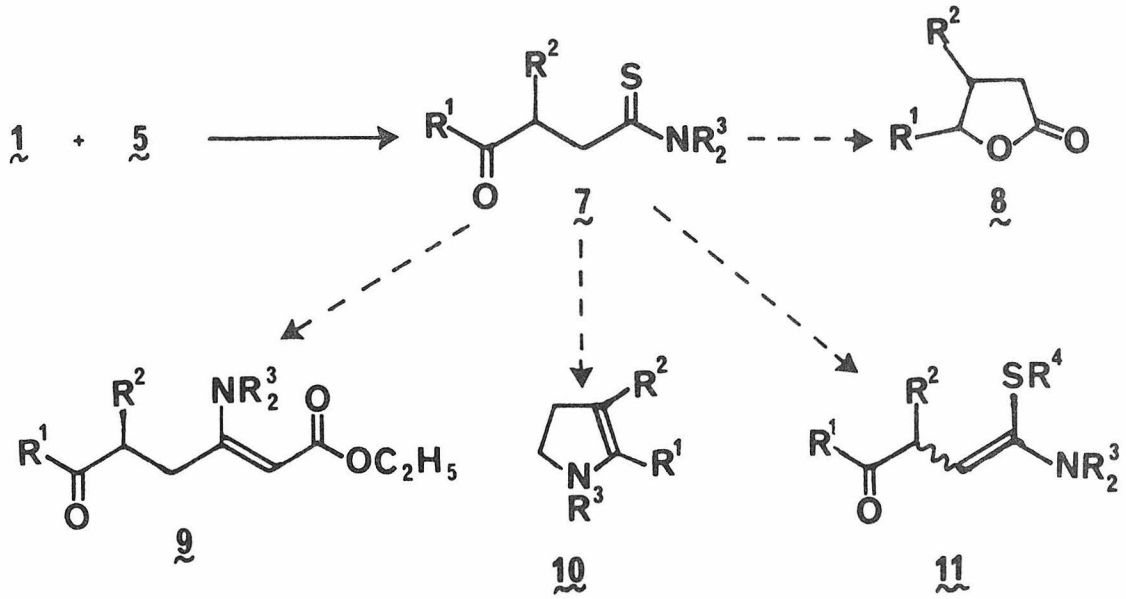
It is proposed that the 1,4-addition of aldehydes to α,β-unsaturated thioamides under the catalytic influence of cyanide ion and thiazolium salts be investigated. The γ-ketothioamides (7) thus obtained would be versatile synthetic intermediates, for both the thioamide and the ketone could be utilized in a variety of transformations.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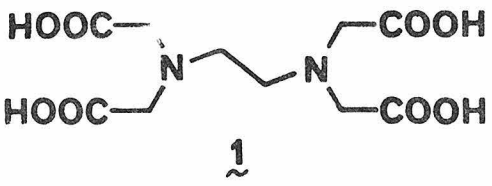
PROPOSITION 2

A study of the complexation of aminepolycarboxylate crown ethers with lanthanide elements is proposed.

Separation of the lanthanide elements[1] is a demanding endeavor because all members of the series possess similar physical and chemical properties. Common methods of separation include solvent extraction and ion-exchange chromatography, both of which depend on selective chelation of the lanthanides by the chelating species. Thus aminepolycarboxylates such as ethylenediaminetetraacetic acid (EDTA) (1) N-hydroxyethylethylenediaminetriacetic acid (HEDTA) (2), and diethylenetriaminepentaacetic acid (DTPA) (3)



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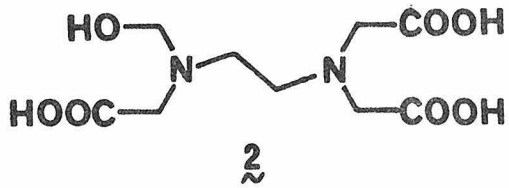

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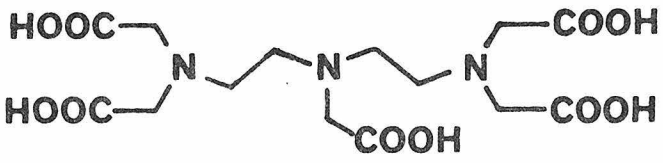


3

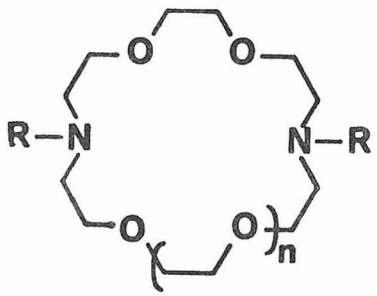
are often used in ion-exchange chromatography because their complexes[2] with lanthanide ions exhibit relatively large variations in stability. The stability constants K vary by

a factor of up to 10^4 over the entire lanthanide series.

$$K = \frac{[\text{Complexed M}]}{[\text{Free Complex}][\text{Free M}]}$$

Polyether crowns[3] and cryptates[4] are of potential use in lanthanide separation. It has already been noticed that the dependence of the stability constants of crown complexes on the ionic radii is much more pronounced for bivalent ions than for univalent ions.[5,6] Such a trend should extend to trivalent ions.[5] Indeed, the possibility of separating the lanthanides by the use of crown ethers has already motivated investigations into the crown complexes of the lanthanide elements,[7] and encouraging results have been obtained.[8,9]

It is proposed that the stability constants of amine-polycarboxylate crown ethers 6-11 with lanthanide salts be



	n=O	1
R=H	4	5
CH_2CO_2H	6	7
$(CH_2)_2CO_2H$	8	9
$(CH_2)_2N(CH_2CO_2H)_2$	10	11

determined. By combining the known radius-discriminating effect of the crown ethers with the known lanthanide-discriminating effect of the aminepolycarboxylates, it is

hoped that larger differences in stability constants among the lanthanides can be achieved. If so, the modified crown ethers may have application in lanthanide separation schemes. Crown ethers 6 and 8 have already been reported.[4] The complexes formed with alkali and alkaline earth cations are more stable than for the corresponding N-methyl derivatives. Selectivities are modified in favor of cations of higher charge density, and thus cavity size effects are diminished. Whether these trends are also observed in the lanthanide series remains to be seen.

The proposed crown ethers would be readily available from the previously reported[10] amines 4 and 5. Alkylation of the amines with chloroacetic acid or 3-chloropropionic acid should afford amines 6, 7, 8, and 9. Alkylation of the amines with chloroacetamide followed by reduction with borane or lithium aluminum hydride and alkylation with chloroacetic acid should afford amines 10 and 11.

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PROPOSITION 3

It is proposed that the elementary isotope separation factors of a cryptate with calcium ions and that the cryptate's application to calcium isotope separation be investigated.

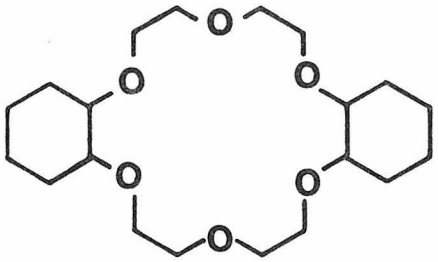
With the onset of the nuclear age, a large demand for pure isotopes of various elements has arisen. With this demand has come a proliferation of separation techniques.[1] These include physical techniques such as gaseous diffusion (^{235}U), thermal diffusion (noble gases), mass spectrometry (most elements), distillation (^{2}H), and centrifugation (^{235}U) as well as chemical techniques such as chemical reflux (^{10}B, ^{15}N), exemplified by the Nitrox process for production of ^{15}N:

$$^{15}NO + H^{14}NO_3 \rightleftharpoons {}^{14}NO + H^{15}NO_3 \ .$$

The existence of chemical techniques of isotope separation is a quantum mechanical phenomenon[2] arising from the difference in ground state vibrational energy levels and from the fact that vibrational energies of molecules cannot be treated classically. Through the use of quantum statistical thermodynamics, it can be shown[2] that in order for large separative effects to be obtained chemically, it is necessary to equilibrate a compound possessing large

numbers of high frequency shifts upon isotopic substitution with another compound possessing smaller numbers of lower frequency shifts. The heavier isotope will concentrate in the more strongly bound compound. It is generally difficult to achieve such a situation in practice.

The application of crown polyethers and cryptates to isotope separation has provided some encouraging preliminary results. Using solvent extraction techniques and dicyclohexyl-18-crown-6 (1)



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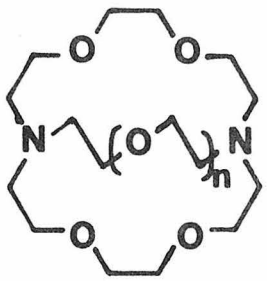
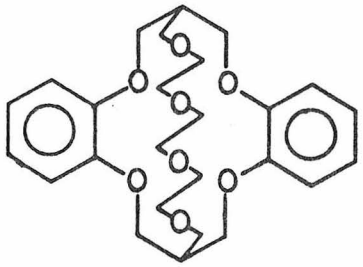


2a, n=0
2b, n=1

Jepson and DeWitt[3] were able to obtain single stage separation factors per mass unit (α) of 1.001 in the separation of ^{40}Ca and ^{44}Ca. Impressive results were obtained by Knochel and Wilken.[4] By the use of cryptates 2a and 2b, they obtained values for α of 1.08 for the separation of ^{22}Na and ^{24}Na in methanol solution. Little effect was noticed in water.

Theoretically, use of a solvent of lower complexing ability or a chelating material of stronger complexing ability should increase the separation factors achieved in

the above systems. The recently reported[5] cryptate 3



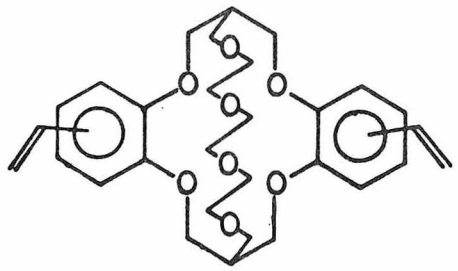
3

forms complexes of greater stability with sodium and potassium cations than does cryptate 2b. This is because these ions form more stable complexes with oxygen-bearing ligands than with nitrogen-bearing ligands. For the same reason, cryptate 3 should also form more stable complexes with calcium cations.

It is proposed that the isotope separation factor of cryptate 3 with calcium isotopes and that the application of cryptate 3 to calcium isotope separation be investigated (See Table I). The method of Knöchel and Wilken[4] for determining α factors, suitably modified for calcium ions, appears most amenable. By measuring the ratio of ^{22}Na and ^{24}Na on an ion-exchange resin in the presence of cryptates 2a and 2b as well as in the absence of the cryptates, they were able to determine the separation factor. Mass spectrometry would be used to determine the mass ratios.[3]

If improved separation factors are obtained, separation of calcium isotopes could be attempted by mounting the cryptates on a polymer support. Two general methods for

including crown ethers in polymer supports have already been described. Blasius and co-workers[6] have copolymerized crown ethers containing an aryl ring with formaldehyde and other aryl compounds. Such a method could be applied directly to cryptate 3. Smid and co-workers[7] have copolymerized vinyl derivatives of the crown ethers with styrene or butadiene. This method would demand a vinyl derivative of cryptate 3 such as cryptate 4.



4

Use of appropriate polymeric cryptates may allow convenient chromatographic separation of calcium isotopes.

Table I. Natural Abundance of Calcium Isotopes[a]

Isotope	% abundance
^{40}Ca	96.17
^{42}Ca	0.64
^{43}Ca	0.145
^{44}Ca	2.06
^{46}Ca	0.0033
^{48}Ca	0.18

[a]Taken from Reference 3.

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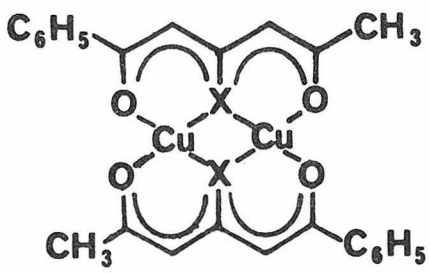
PROPOSITION 4

The preparation and characterization of a binuclear copper(II) complex with sulfur bridging atoms is proposed.

Recently much interest[1] has been shown in homobinuclear and heterobinuclear metal complexes. Such compounds can possess interesting magnetic[2] and electrochemical[3] properties. Binuclear complexes containing Cu(II) ions are of potential use in understanding the mode of operation of enzymes such as laccases which contain "type 3" Cu(II) centers[4] and which are important in the reduction of molecular oxygen. A type 3 Cu(II) center is characterized by an absorption band at 330 nm, the lack of an electron spin resonance signal, and the ability to act as a two-electron oxidation-reduction system. Apparently it consists of two Cu(II) ions which are strongly antiferromagnetically coupled. Such antiferromagnetic coupling is widely observed[5] in synthetic binuclear Cu(II) complexes and is a result of the electronic nature of the bridge system between the Cu(II) ions rather than of a direct Cu(II)-Cu(II) bond. For instance, the neutral Cu(II) chelate with 1-phenyl-1,3,5-hexanetrionate(-2), $Cu_2(BAA)_2$ (1a),[6] strongly antiferromagnetically coupled with a singlet-triplet separation of 800 cm^{-1}. Hence, the complex is nearly diamagnetic at room temperature. This system was recently reported[3] to undergo two sequential reversible



1a, X=O
b, X=S

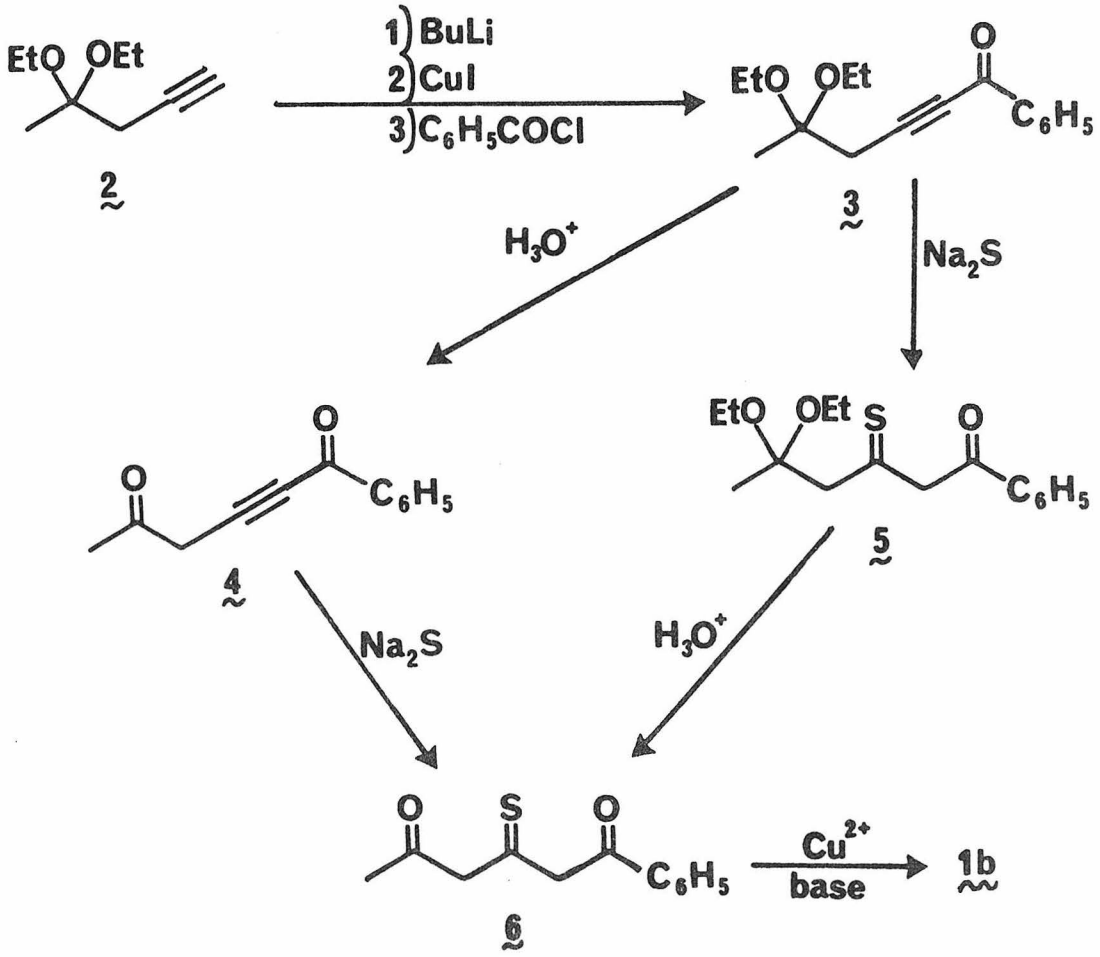
one-electron reductions at identical $E_{1/2}$-values. This means that both electrons are available at the same potential and that this system possibly mimics type 3 Cu(II) centers So far, this is the only reported binuclear Cu(II) complex to undergo such a reduction.

It is proposed that the effect on the magnetic and electrochemical properties of substituting sulfur for oxygen as the bridging atom in $Cu_2(BAA)_2$ (1a) be investigated Sulfur substitution has already proven to be a helpful probe in acetylacetone complexes.[7] For example, spin-pairing is more likely to be observed with the thio-β-diketones. Examples include Fe(III) trischelates[8] and Ni(II) bis-chelates.[9] Photoelectron spectroscopy of Ni(II) chelates indicates that there is greater d-orbital interaction with the ligand bonds in the sulfur analogues.[10] Thus use of sulfur as the bridging atom may result in greater interaction between the two Cu(II) ions. The effect of this increased interaction on the magnetic and electrochemical

properties should provide valuable data relating to metal-metal interactions in general and to type 3 Cu(II) centers in particular.

Preparation of the complex is outlined in Scheme I. Acetylenic ketone 3 may be prepared from acetylene 2[11] by the procedure of Bourgain and Normant.[12] Hydrolysis and reaction with sodium sulfide[13] should provide thioketone 6, and complexation of the thioketone with Cu(II) should provide the desired complex (1b).

Scheme I



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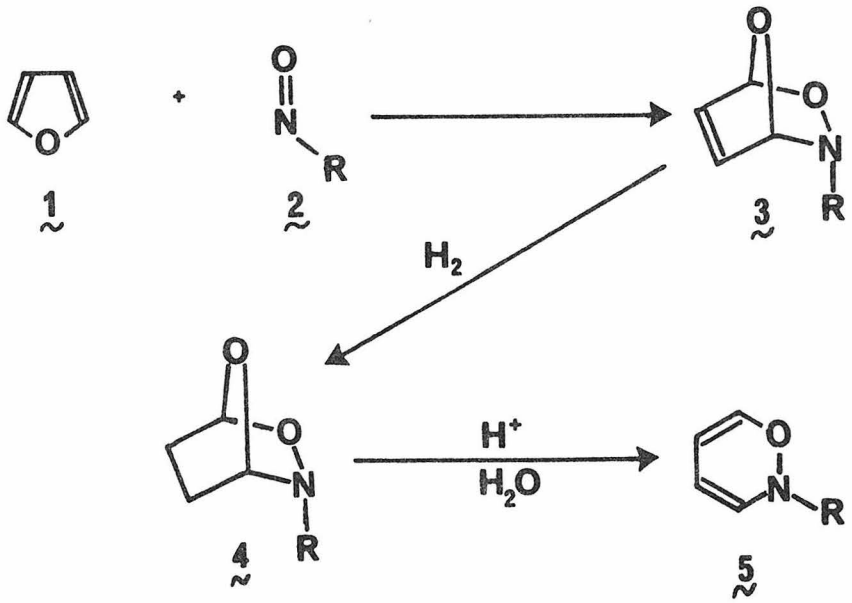
PROPOSITION 5

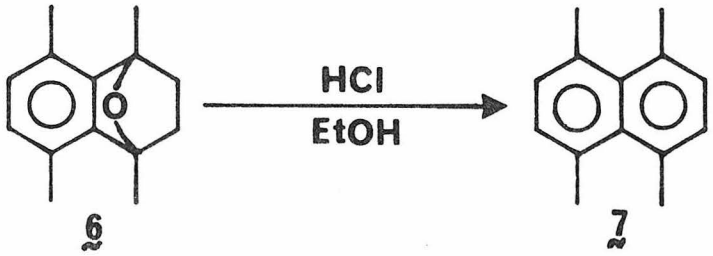
The synthesis of 1,2-oxazines by means of the 1,4-cycloaddition reaction of furans with nitroso compounds is proposed.

Although the dihydro and tetrahydro derivatives of 1,2-oxazines have received a fair amount of attention, compounds containing the parent ring system are extremely rare, and no general route exists for their synthesis.[1] These compounds are of interest because of their physical and chemical properties as well as because of their potential use in synthesis as dienes and butanedial equivalents.

It is proposed that the synthesis of 1,2-oxazines (5) by means of the 1,4-cycloaddition of furans with nitroso compounds be investigated. The synthetic plan is outlined below:



The acid catalyzed dehydration of bicycle 4 is precedented[2] by the dehydration of bicycle 6.



6 7

Due to the large number of furan derivatives readily available[3] and to the known[4] regioselectivity of the 1,4-cycloaddition of nitroso compounds to dienes, a wide variety of 1,2-oxazines would be potentially available by the proposed route.

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