Studies Dealing with Thionium Ion Promoted Mannich Cyclization Reactions

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Treatment of several amido-substituted thioacetals with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) produces synthetically useful thionium ions that are intercepted by the adjacent nitrogen atom to afford both five- and six-membered alkylthio-substituted lactams as transient intermediates. Further reaction of the alkylthio-substituted lactam with DMTSF generates an *N*-acyliminium ion, which undergoes cyclization with the tethered aromatic ring to produce an azapolycyclic ring system. Related cyclization sequences occur when amido thioacetals possessing simple olefinic tethers were used. The overall procedure represents an efficient one-pot approach toward various nitrogen-containing ring systems. The cyclization reaction was employed for a synthesis of the core skeleton of the erythrina alkaloid family.

Sequential transformations enable the facile synthesis of complex target molecules from simple building blocks in a single preparative step.[1−3] Their value is amplified if they also create multiple stereogenic centers.[4−12] Moreover, the utilization of a domino sequence often leads to a reduction in the amount of solvent, eluent, and undesired byproducts, thereby contributing to the protection of the environment. One of the earliest examples of a domino process reported in the literature involves cationic cyclization chemistry.[13] The synthetic potential of this reaction is well recognized, and this sequence has been greatly probed and extended in recent years.[14−16] Many different precursors have been used to initiate the cationic cascade. This cyclization sequence also plays an important role in heterocyclic natural product synthesis.[17] The reactions of *N*-acyliminium ions with tethered π-bonds are among the most important methods for preparing complex nitrogen-containing heterocycles.[17−20] Pummerer-based cyclizations are also finding widespread application in both carbo- and heterocyclic syntheses.[21−23] As part of a program concerned with new methods for alkaloid synthesis, we became interested in using a linked Pummerer/*N*-acyliminium ion cyclization sequence because

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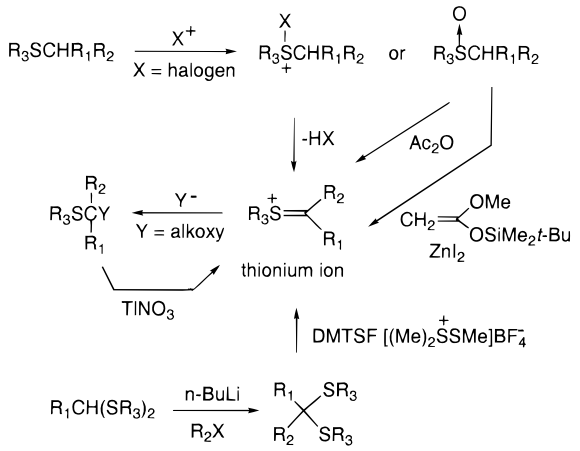
Scheme 1. Various Methods Utilized to Generate Thionium Ions

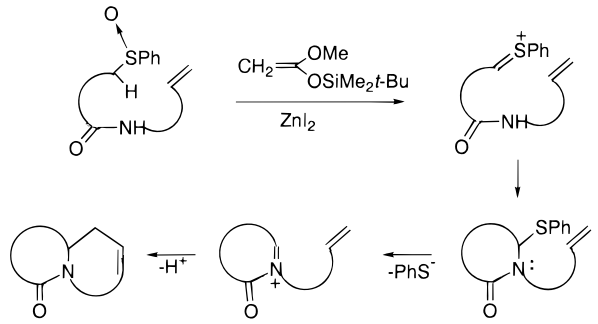


we felt that this combination offers unique opportunities for the assemblage of complex target molecules.[24,25]

The Pummerer reaction constitutes a versatile and effective method for the generation of thionium ions from sulfoxide precursors.[21−23] The initially formed cation is readily trapped by a nucleophilic species present in the reaction medium. The interaction of thionium ions with electron-rich π-systems has proved to be extremely useful in natural product synthesis.[21] Acid anhydrides or acids are generally employed as promoters in the majority of synthetic applications of the Pummerer reaction.[26] Thionium ions have also been generated from other sulfur-containing precursors (Scheme 1).[27] A reaction that is often compared to the Pummerer rearrangement is the α-halogenation of sulfides.[28] In 1981, Trost and Murayama reported that dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) exhibits a remarkably high thiophilicity for cationic initiation reactions of thioketals.[29] Surprisingly, this alternative method for thionium ion generation has not been extensively exploited in synthesis, although there are a few scattered reports where this reagent has been used in complex target molecule synthesis.[30] The paucity of examples is somewhat surprising because thioketals are easily available by metalation and alkylation reactions of thioacetals.[31] Furthermore, the normally inert thioketal group can be carried through a series of transformations before it is chemoselectively unmasked to reveal the reactive thionium ion.

While developing a Pummerer approach toward the synthesis of alkaloids,[32] we recently uncovered a versatile

Scheme 2



Scheme 3

1 2

amido annulation process based on a consecutive thionium/Mannich ion cyclization sequence.[33] A synthetic method that combines transformations of different reaction types significantly broadens the scope of such procedures in synthetic chemistry. Our early studies in this area involved a silicon-induced Pummerer reaction of amidosulfoxides that possessed tethered π-bonds (Scheme 2).[33] Although the sequential process proved valuable for a number of substrates, we faced several limitations during our attempts to extend the scope of the reaction. Thus, in every case examined, it was necessary to isolate and purify the initially formed 2-phenylthio lactam intermediate before subjecting it to various electrophilic reagents so as to induce the second ring closure. In addition, formation of the *N*-acyliminium ion intermediate required the use of a strong Lewis acid, and as a result, the yield associated with the cyclization was variable. We reasoned that by replacing the sulfoxide functionality with a thioacetal group, it might be possible to bring about a one-pot cascade. Indeed, we have found that the desired reaction (Scheme 3) occurred in high yield when DMTSF was used as the reagent to initiate the process. In this paper we report the results of these studies, which show that both cyclization steps can take place without having to add any additional reagents or catalysts. This novel transformation greatly extends the synthetic potential of thionium promoted Mannich reactions.

Results and Discussion

We began our investigations of the thionium ion promoted Mannich cyclization by first examining the intramolecular thionium ion cyclization reaction of amido thioacetal **5**. This compound was prepared by a four-step sequence involving ozonolysis of 4-pentenoic acid (**3**) followed by reaction of the resulting aldehyde with 2 equiv of thiophenol to give 4,4-bis(phenylsulfanyl)butyric acid (**4**) (Scheme 4). Sequential treatment of carboxylic acid **4** with 1,1-carbonyl diimidazole followed by 3,4-dimethoxyphenethylamine furnished thioacetal **5** in 93% yield. With the necessary functionality in place, we tested

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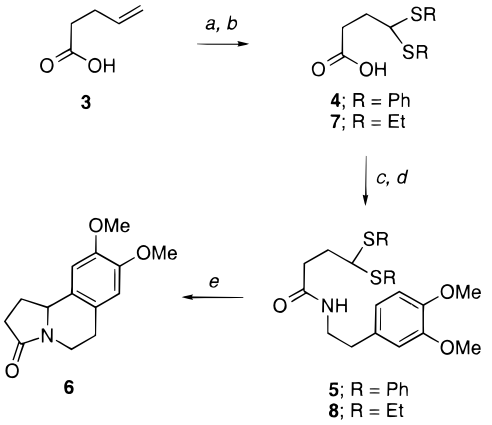
Scheme 4

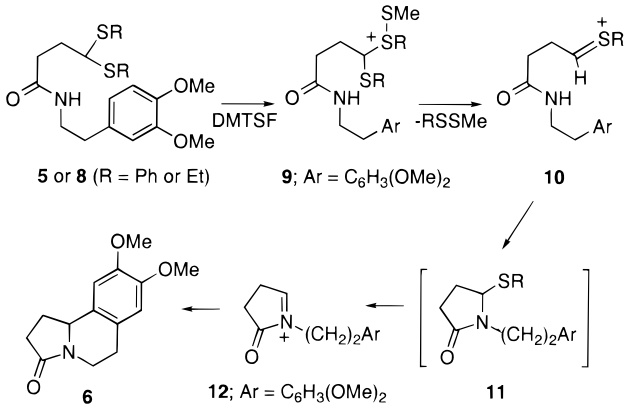


Reagents: (a) O_3, CH_2Cl_2, Me_2S; (b) PhSH, BF_3•Et_2O; (c) $(COCl)_2$ (d) 3,4-dimethoxyphenethylamine; (e) DMTSF, CH_2Cl_2, 25 °C

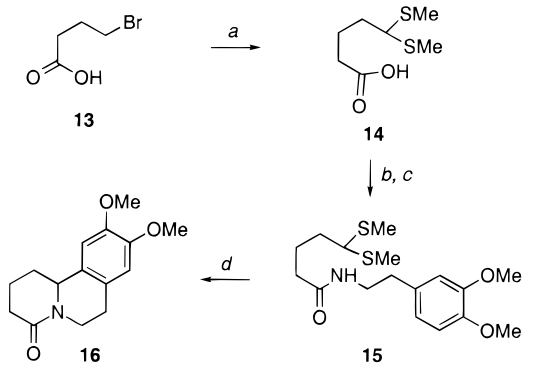
the crucial annulation reaction. Gratifyingly, when **5** was reacted with 2 equiv of DMTSF[34,35] in CH_2Cl_2 at 25 °C, the desired isoquinolinone **6** was obtained in 64% yield. Treatment of the related ethylthio acetal **8** with DMTSF also resulted in a one-pot cascade sequence, delivering isoquinolinone **6** in an improved 98% yield.

The ease with which the S−S bond of dimethyl(methylthio)sulfonium salts are cleaved by nucleophilic reagents was first documented by Helmkamp and coworkers in their work on the preparation of DMTSF and its addition to alkenes and alkynes.[34] These reactions and related studies by Meerwein[35] indicate that reagents such as DMTSF may be regarded as sulfenyl derivatives and can function as a potential source of alkylsulfenyl ions.[36,37] It was known from earlier work in the literature that carbon−sulfur bonds of sulfides become labile on alkylsulfenylation, and that the sulfonium ions so formed are highly reactive intermediates that seldom can be isolated.[38] It is reasonable to assume, therefore, that the conversion of **5** (or **8**) into **6** upon treatment with DMTSF follows the pathway outlined in Scheme 5. Methylthiolation of one of the thiophenyl groups with DMTSF gives an alkylthiosulfonium salt **9** that easily dissociates to generate thionium ion **10** and methyl phenyl disulfide. Attack of the amido nitrogen atom onto the cationic center produces a phenylthio-substituted lactam **11** as a transient intermediate that reacts further with additional DMTSF. Lactam **11** was not detected in the crude reaction mixture, as it readily undergoes elimination of thiophenol to produce *N*-acyliminium ion **12**. Cyclization of **12** with the tethered aromatic ring affords the isoquinolinone ring system **6**. In the case of thioacetal **8**, the greater facility of transfer of CH_3S^+ to the more nucleophilic ethylthio group is presumably responsible for the higher yield of **6** (98%) relative to that obtained with the less reactive phenylthio acetal **5** (64%).

Scheme 5

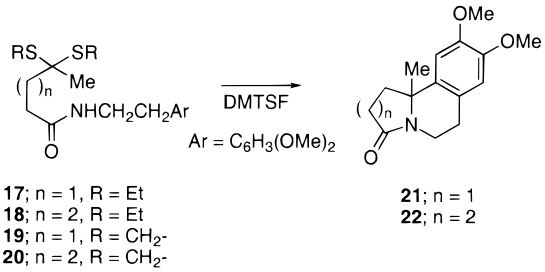


Scheme 6



Reagents: (a) $(MeS)_2CH_2$, *n*-BuLi, THF; (b) CDI, CH_2Cl_2; (c) 3,4-dimethoxyphenethylamine; (d) DMTSF, CH_2Cl_2, 25 °C

Scheme 7



17; n = 1, R = Et
18; n = 2, R = Et
19; n = 1, R = CH_2-
20; n = 2, R = CH_2-

21; n = 1
22; n = 2

The sequential thionium/Mannich cyclization worked equally well with the 6,6-ring system. The required amide precursor was readily prepared by treating excess bis(methylthio)methane with *n*-BuLi and allowing the resulting lithiate to react with 4-bromobutyric acid. As illustrated before, conversion of carboxylic acid **14** to amide **15** took place in high yield. Treating a solution of **15** in CH_2Cl_2 at 25 °C for 12 h afforded lactam **16** in 99% yield (Scheme 6).

The facile cleavage of thioacetals with DMTSF to form sulfur-stabilized carbocation intermediates prompted us to determine whether a similar reaction would occur with the related amido thioketals **17**−**20**. Indeed, we found that the outcome of this reaction was in all respects identical to that observed with the related thioacetals. Thus, a similar pattern consisting of consecutive cyclization of the intermediate thionium and *N*-acyliminium ions occurs with these four amido thioketals (Scheme 7). What is surprising, however, is the fact that it was necessary to carry out the DMTSF-induced reaction of the thioketals at reflux in CH_2Cl_2 in order for the

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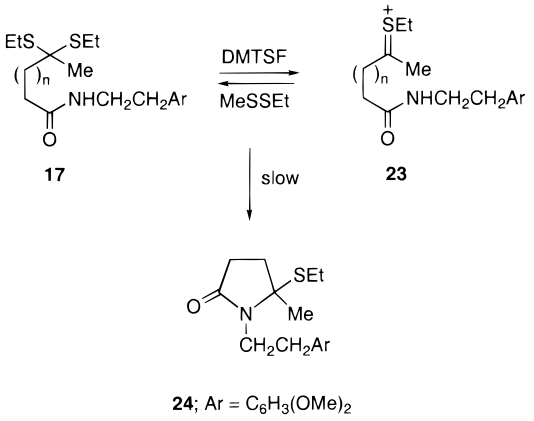
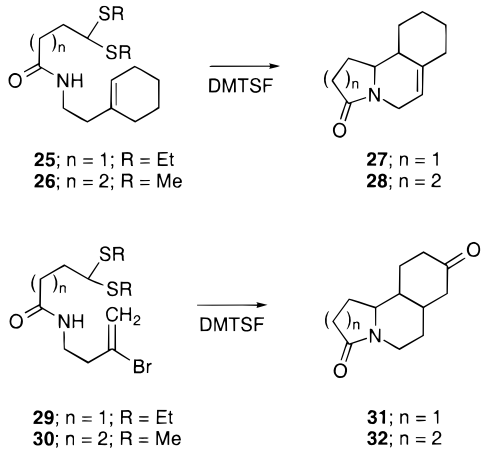
Scheme 8



24; Ar = $C_6H_3(OMe)_2$

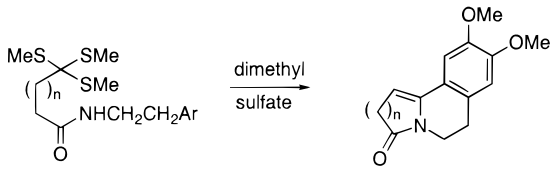
Scheme 9



cyclization to occur. The thioacetal cyclization, on the other hand, proceeded smoothly at room temperature, and the yield of cyclized product was much higher than that encountered with the thioketal system. At first glance this might seem unusual, because the thionium ion derived from the thioketal should be easier to form by virtue of its greater stability (i.e., tertiary vs secondary). Presumably, the less reactive cation **23** produced by dissociation of the thioketal is long-lived enough to react with a mono- or disulfide nucleophile present in the reaction medium. This reversible reaction regenerates the starting thioketal and thereby diminishes the rate of the overall process (Scheme 8).[39]

Because all of the previous examples involved aromatic π-bond cyclizations, we decided to study several systems that possess a simple olefinic tether. We found that treatment of the cyclohexenyl-substituted amido thioacetals **25** and **26** with DMTSF also caused a thionium ion induced Mannich reaction to occur, ultimately producing isoquinolinone derivatives **27** and **28** in 60% and 58% yield, respectively. To further explore the scope and generality of the cyclization process, we also carried out a study using the bromoalkenyl-substituted amido thioacetals **29** and **30** (Scheme 9). When **29** was subjected to the DMTSF conditions followed by an aqueous workup, the initially cyclized product was hydrolyzed to ketolactam **31** in 65% overall yield. A related set of reactions occurred with amido thioacetal **30** ultimately producing the known octahydroquinolizin-4,8-dione **32**[40] in 58% yield. These two examples further demonstrate the facility with which the thionium/iminium ion cascade can occur.

Given the success in forming azapolycyclic ring systems from the DMTSF-initiated cyclization of amido thioacetals, it seemed to us that a related reaction might also occur with amido-substituted thio-ortho esters. The extra methylthio group present in the starting material would add an additional element of functionality in the product that could be further utilized for synthetic purposes. To test this possibility, thio-ortho esters **33** and **34** were



33; n = 1, Ar = $C_6H_3(OMe)_2$
34; n = 2, Ar = $C_6H_3(OMe)_2$

35; n = 1
36; n = 2

synthesized from the appropriate carboxylic acid precursors. Treatment of these substrates with DMTSF failed to produce any characterizable material.[41] However, after some experimentation with other thiolating agents, we found that the reaction of these amides with excess dimethyl sulfate resulted in a clean cyclization to give the enamido-substituted lactams **35** and **36** in 46% and 71% yield, respectively. It should be noted that the enamido portion of the final product can also function as an *N*-acyliminium ion precursor, thus presenting the likelihood of conducting yet another Mannich-like reaction. Efforts along these lines are ongoing in our laboratory and will be reported at a future date.

As an extension of these studies, we became interested in knowing whether the method could be used to synthesize the core skeleton of the erythrina alkaloids.[42] This family of alkaloids has received considerable attention over the past decade. Many members of this family possess curare-like activity, and the alkaloidal extracts have been used in indigenous medicine. The vast majority of naturally occurring erythrina alkaloids possess the tetracyclic framework and substitution pattern shown in structure **37**. Numerous synthetic approaches into the erythrina ring system have been developed,[43] and a

(39) Another possibility suggested by one of the reviewers is that the lower rate of the overall cascade process from thioketals can be accounted for in terms of steric factors, both in the closure of the lactam ring and in the generation of the quaternary carbon present in **21** and **22**.

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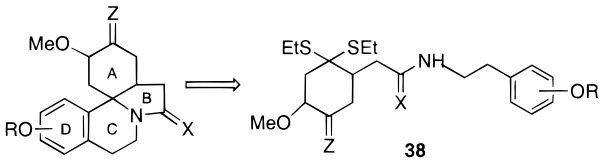
Scheme 10

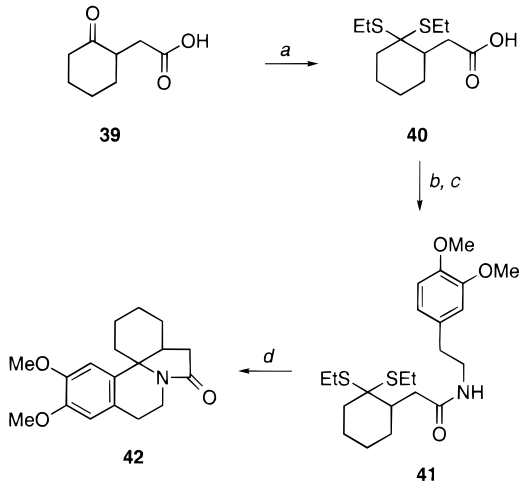


38

Erythrina alkaloids

37; X or Z = O; R = Me

Scheme 11



39 **40** **41** **42**

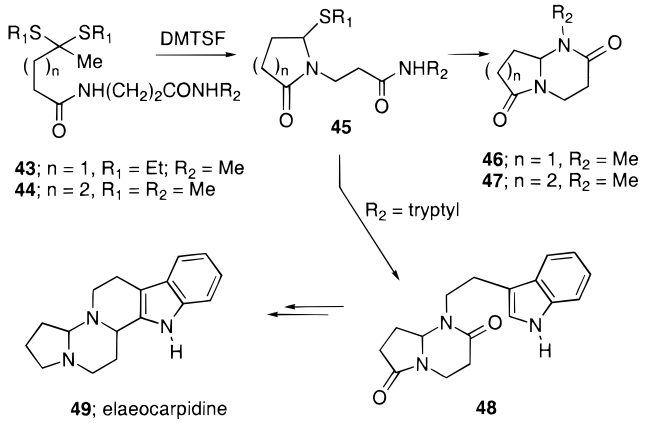
Reagents: (a) EtSH, HCl; (b) CDI, CH_2Cl_2; (c) 3,4-dimethoxyphenethylamine; (d) DMTSF, CH_2Cl_2, reflux.

prominent theme for elaborating the fully substituted carbon center at the BC ring fusion has been trapping of *N*-acyliminium ion intermediates with electron-rich aryl rings.[44] The retrosynthetic analysis to which we were attracted involved the use of an amido thioacetal such as **38** (Scheme 10). The central feature of this approach consists of a DMTSF-initiated Pummerer/Mannich ion cyclization. This sequence of reactions allows for a rapid entry into the erythrinane skeleton, where the key ABC ring system would be assembled in a single operation.

As a target to test the feasibility of this approach toward the erythrinane skeleton, we chose to study the DMTSF-induced reaction of amido thioacetal **41** as a model system. Acyclic thioketal **40** was obtained from the known ketoacid **39** and was easily converted to amide **41** in excellent yield. We were pleased to find that treatment of **41** with 2 equiv of DMTSF proceeded smoothly at reflux in CH_2Cl_2 to give the desired indoloisoquinolinone **42** in 71% yield (Scheme 11). The short number of steps to prepare **42** from easily available starting material suggests that this approach will be useful for the synthesis of some of the more highly oxygenated members of the erythrina family of alkaloids. Work along these lines will be forthcoming in future publications.

To further explore the scope and utility of the amido thioacetal cyclization sequence and its potential use in alkaloid synthesis, we also chose to study the DMTSF-promoted reaction of thioketals **43** and **44**. These systems offer the opportunity to test whether a tethered amido

Scheme 12



43; n = 1, R_1 = Et; R_2 = Me
44; n = 2, R_1 = R_2 = Me

45

46; n = 1, R_2 = Me
47; n = 2, R_2 = Me

49; elaeocarpidine **48**

group could be used as a nucleophilic center to trap the *N*-acyliminium ion derived from the transient alkylthio-substituted lactam (i.e., **45**) (Scheme 12). Our eventual goal is to utilize this sequence for a synthesis of elaeocarpidine (**49**).[45] This particular alkaloid possesses a 1,3-diazapentacyclic ring system and represents one of the few indole alkaloids that contain three nitrogen atoms. We were gratified to find that heating a sample of **43** or **44** with DMTSF in CH_2Cl_2 gave rise to the desired pyrimidine-2,6-diones **46** and **47** in 60% and 73% yield, respectively. Further efforts to streamline this protocol and to utilize the sequence to complete the synthesis of elaeocarpidine are in progress and will be reported in due course.

In conclusion, this paper describes a versatile new approach to azapolycyclic ring systems with various substitution patterns that can be applied toward the synthesis of the core skeleton of several alkaloids. The synthetic procedure described here involves the reaction of an amido-substituted thioacetal with dimethyl(methylthio)sulfonium fluoroborate (DMTSF). The initially formed thionium ion is attacked by the adjacent amido nitrogen atom to produce a transient alkylthio-substituted lactam. Further reaction of the lactam with DMTSF generates an *N*-acyliminium ion, which undergoes subsequent cyclization with the tethered aromatic ring. This reaction sequence was used for the synthesis of the azapentacyclic skeleton of the erythrina alkaloid family. Further studies of the thionium initiated Mannich reaction are in progress and will be reported in due course.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry argon. Solutions were evaporated under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column using an ethyl acetate/hexane mixture as the eluent unless specified otherwise. All solids were recrystallized from ethyl acetate/hexane for analytical data.

Standard Procedure for the Preparation of Amidodithianes. To a solution containing 1.0 mmol of the appropriate carboxylic acid in 15 mL of CH_2Cl_2 was added 1.1 mmol of 1,1′-carbonyl diimidazole. The mixture was stirred for 1 h at room temperature, and 1.1 mmol of the amine was added. After stirring for an additional 30 min at 25 °C, the

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solution was quenched by the addition of water and was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give the amidodithiane.

4,4-Bis(phenylsulfanyl)butyric Acid (4). A solution containing 2.5 mL (36 mmol) of 4-pentenoic acid in 150 mL of CH_2Cl_2 was cooled to −78 °C and was treated with a stream of ozone for 1 h. The ozonide was quenched by the addition of 5.2 mL (71 mmol) of dimethyl sulfide, and the solution was allowed to warm to room temperature and stirred for an additional 6 h. To this solution was added 9 mL (89 mmol) of thiophenol followed by 4.5 mL (36 mmol) of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred for 20 min, quenched by the addition of water, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 5.5 g (51%) of **4** as a white solid:[46] mp 89−90 °C; IR ($CHCl_3$) 3059, 1710, and 1431 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.15 (q, 2H, J = 7.2 Hz), 2.72 (t, 2H, J = 7.2 Hz), 4.47 (t, 1H, J = 7.2 Hz), 7.29−7.33 (m, 6H), 7.46−7.49 (m, 4H), and 11.42 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.6, 31.4, 57.5, 128.2, 129.2, 133.1, 133.7, and 179.0. Anal. Calcd for $C_{16}H_{16}S_2O_2$: C, 63.13; H, 5.30. Found: C, 63.41; H, 5.34.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-4,4-bis(phenylsulfanyl)butyramide (5).** To a solution containing 1.0 g (3.3 mmol) of the above carboxylic acid in 50 mL of CH_2Cl_2 was added 3.3 mL (6.6 mmol) of a 2.0 M solution of 1,1′-carbonyl diimidazole in CH_2Cl_2. To this solution was added 3 drops of DMF, and the reaction mixture was stirred at 25 °C for 2 h. The solvent and excess oxalyl chloride were removed under reduced pressure, and the residue was taken up in 40 mL of CH_2Cl_2 and cooled to 0 °C. To this solution was added 0.6 mL (3.6 mmol) of 3,4-dimethoxyphenethylamine followed by 0.5 mL (3.6 mmol) of triethylamine. The mixture was allowed to stir at 25 °C for 20 min, diluted with water, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 1.4 g (93%) of **5** as a white solid: mp 102−103 °C; IR ($CHCl_3$) 3312, 1637, and 1511 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.18 (q, 2H, J = 7.2 Hz), 2.54 (t, 2H, J = 7.2 Hz), 2.72 (t, 2H, J = 6.8 Hz), 3.47 (dd, 2H, J = 12.8 and 6.8 Hz), 3.85 (s, 3H), 3.86 (s, 3H), 4.51 (t, 1H, J = 6.8 Hz), 5.42 (brs, 1H), 6.69−6.71 (m, 2H), 6.78−6.79 (m, 1H), 7.25−7.33 (m, 6H), and 7.43−7.46 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.6, 33.8, 35.5, 56.0, 56.1, 57.4, 111.5, 112.0, 120.8, 128.0, 129.2, 131.4, 132.8, 134.0, 147.9, 149.3, and 171.7. Anal. Calcd for $C_{25}H_{29}NS_2O_3$: C, 66.78; H, 6.25; N, 3.00. Found: C, 66.60; H, 6.21; N, 2.93.

8,9-Dimethoxy-1,5,6,10*b*-tetrahydro-2*H*-pyrrolo[2,1-*a*]-isoquinolin-3-one (6). To a solution containing 0.09 g (0.2 mmol) of amide **5** in 15 mL of CH_2Cl_2 was added 0.08 g (0.4 mmol) of DMTSF. The reaction mixture was stirred for 12 h at room temperature, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.035 g (64%) of **6** as a white solid: mp 97−99 °C; IR ($CHCl_3$) 1682, 1609, and 1517 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.77 (m, 1H), 2.36−2.43 (m, 1H), 2.47−2.64 (m, 3H), 2.78−2.86 (m, 1H), 2.95 (td, 1H, J = 12.8 and 4.4 Hz), 3.80 (s, 3H), 3.81 (s, 3H), 4.23 (ddd, 1H, J = 12.8, 6.0, and 2.0 Hz), 4.67 (t, 1H, J = 8.0 Hz), 6.52 (s, 1H), and 6.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.8, 28.1, 31.8, 37.0, 55.9, 56.0, 56.5, 107.6, 111.6, 125.5, 129.3, 147.8, 148.0, and 173.1. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.92; H, 6.85; N, 5.46.

4,4-Bis(ethylsulfanyl)butyric Acid (7). A solution containing 5.0 mL (70 mmol) of 4-pentenoic acid in 250 mL of CH_2Cl_2 was cooled to −78 °C and was treated with a stream of ozone for 1.5 h. The ozonide was quenched by the addition of 10 mL (140 mmol) of dimethyl sulfide. The solution was stirred at 25 °C for 5 h, and then 13 mL (180 mmol) of ethanethiol was added followed by 9.0 mL (71 mmol) of $BF_3{\cdot}Et_2O$. The reaction mixture was allowed to stir at 25 °C for 45 min, quenched with water, and extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 8.8 g (59%) of **7** as a yellow oil: IR (neat) 3106, 1710, and 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, 6H, J = 7.2 Hz), 2.12 (q, 2H, J = 7.2 Hz), 2.58−2.71 (m, 6H), 3.86 (t, 1H, J = 7.2 Hz), and 11.75 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 24.5, 30.7, 31.8, 50.4, and 179.6. Anal. Calcd for $C_8H_{16}S_2O_2$: C, 46.12; H, 7.74. Found: C, 46.18; H, 7.73.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-4,4-bis(ethylsulfanyl)-butyramide (8).** Using the standard procedure, a 0.5 g (2.4 mmol) sample of acid **7**, 0.4 g (2.6 mmol) of 1,1′-carbonyl diimidazole, and 0.5 mL (2.6 mmol) of 3,4-dimethoxyphenethylamine in 30 mL of CH_2Cl_2 gave 0.77 g (86%) of **8** as a white solid: mp 59−60 °C; IR ($CHCl_3$) 3305, 1644, and 1258 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, 6H, J = 7.2 Hz), 2.12 (q, 2H, J = 7.2 Hz), 2.38 (t, 2H, J = 7.2 Hz), 2.54−2.69 (m, 4H), 2.76 (t, 2H, J = 7.2 Hz), 3.50 (dd, 2H, J = 12.8 and 6.8 Hz), 3.81 (t, 1H, J = 7.2 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 5.55 (brs, 1H), 6.72−6.74 (m, 2H), and 6.82 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 24.5, 31.5, 34.1, 35.5, 40.9, 50.6, 56.0, 56.1, 111.6, 112.0, 120.8, 131.5, 147.9, 149.2, and 172.1. Anal. Calcd for $C_{18}H_{29}NS_2O_3$: C, 58.19; H, 7.87; N, 3.77. Found: C, 58.29; H, 7.83; N, 3.75.

To a solution containing 0.2 g (0.5 mmol) of **8** in 20 mL of CH_2Cl_2 was added 0.2 g (1.1 mmol) of DMTSF. The reaction mixture was allowed to stir at room temperature for 12 h, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.13 g (98%) of isoquinolinone **6**.

5,5-Bis(methylsulfanyl)pentanoic Acid (14). To a solution containing 2 mL (21 mmol) of bis(methylthio)methane in 60 mL of THF at −78 °C was added 10 mL (23 mmol) of a 2.3 M solution of *n*-BuLi in hexane. The solution was allowed to warm to 0 °C, stirred for 2 h, and cooled to −78 °C. To this solution was added 1.7 g (10 mmol) of 4-bromobutyric acid (**13**), and the reaction mixture was stirred at 25 °C for 3 h. The mixture was quenched by the addition of water, acidified with 10% HCl, and extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 1.6 g (80%) of **14** as a white solid: mp 39−40 °C; IR ($CHCl_3$) 3059, 1703, and 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.78−1.90 (m, 4H), 2.10 (s, 6H), 2.40 (t, 2H, J = 7.2 Hz), 3.65 (t, 1H, J = 7.2 Hz), and 11.50 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.5, 22.7, 33.4, 33.8, 54.0, and 180.0. Anal. Calcd for $C_7H_{14}S_2O_2$: C, 43.27; H, 7.26. Found: C, 43.37; H, 7.29.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-5,5-bis(methylsulfanyl)pentanamide (15).** Using the standard procedure, a 0.2 g (1.0 mmol) sample of the above acid, 0.18 g (1.1 mmol) of 1,1′-carbonyl diimidazole, and 0.2 mL (1.0 mmol) of 3,4-dimethoxyphenethylamine in 15 mL of CH_2Cl_2 gave 0.28 g (77%) of **15** as a white solid: mp 99−100 °C; IR ($CHCl_3$) 3312, 1637, and 1517 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.74−1.81 (m, 2H), 1.83−1.88 (m, 2H), 2.09 (s, 6H), 2.16 (t, 2H, J = 7.2 Hz), 2.77 (t, 1H, J = 6.8 Hz), 3.51 (dd, 2H, J = 13.2 and 6.8 Hz), 3.62 (t, 2H, J = 7.2 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 5.44 (brs, 1H), 6.72−6.75 (m, 2H), and 6.82 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.8, 24.0, 34.3, 25.5, 36.2, 40.9, 54.3, 56.1, 56.2, 111.5, 112.0, 120.8, 131.5, 147.8, 149.2, and 172.5. Anal. Calcd for $C_{17}H_{27}NS_2O_3$: C, 57.11; H, 7.61; N, 3.92. Found: C, 57.36; H, 7.68; H, 3.85.

9,10-Dimethoxy-1,2,3,6,7,11*b*-hexahydropyrrido[2,1-*a*]-isoquinolin-4-one (16). To a solution of 0.1 g (0.28 mmol) of thioacetal **15** in 10 mL of CH_2Cl_2 was added 0.12 g (0.6 mmol) of DMTSF. The reaction mixture was allowed to stir at room temperature for 12 h, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.07 g (99%) of **16** as a white solid: mp 88−90 °C; IR ($CHCl_3$) 1638, 1510, and 1446 cm^{-1}; ^1H NMR

(46) Cronin, J. P.; Dilworth, B. M.; McKervey, M. A. *Tetrahedron Lett.* **1986**, *27*, 757.

($CDCl_3$, 400 MHz) δ 1.58−1.69 (m, 1H), 1.76−1.87 (m, 1H), 1.88−1.96 (m, 1H), 2.29−2.38 (m, 1H), 2.48−2.63 (m, 3H), 2.74−2.91 (m, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 4.58 (dd, 1H, J = 10.8 and 4.4 Hz), 4.85 (ddd, 1H, J = 12.0, 4.4, and 2.0 Hz), 6.59 (s, 1H), and 6.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.7, 28.6, 31.1, 32.3, 39.8, 56.0, 56.2, 56.8, 108.3, 111.6, 127.4, 129.2, 147.8, 147.9, and 169.4. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.93; H, 7.33; N, 5.36. Found: C, 68.85; H, 7.18; N, 5.26.

4,4-Bis(ethylsulfanyl)pentanoic Acid. To a solution containing 1.0 g (8.6 mmol) of leveulinic acid and 10 mL of concentrated hydrochloric acid was added 1.6 mL (22 mmol) of ethanethiol. The reaction mixture was stirred at room temperature for 1.5 h and diluted with 50 mL of water. The mixture was extracted with CH_2Cl_2, the combined organic layer was washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 1.4 g (71%) of the title compound as a colorless oil: IR (neat) 3150, 1710, and 1445 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, 6H, J = 9.6 Hz), 1.53 (s, 3H), 2.06−2.12 (m, 2H), 2.58−2.65 (m, 6H), and 10.82 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 23.8, 27.8, 30.0, 36.2, 59.0, and 179.1. Anal. Calcd for $C_9H_{18}O_2S_2$: C, 48.61; H, 8.16. Found: C, 48.87; H, 8.20.

4,4-Bis(ethylsulfanyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]pentanamide (17). Using the standard procedure, a 1.4 g (6.0 mmol) sample of the above acid, 1.0 g (6.4 mmol) of 1,1′-carbonyl diimidazole, and 1.1 mL (6.7 mmol) of 3,4-dimethoxyphenethylamine in 50 mL gave 2.1 g (90%) of **17** as a colorless oil: IR (neat) 3298, 1650, and 1258 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, 6H, J = 7.6 Hz), 1.51 (s, 3H), 2.07−2.11 (m, 2H), 2.34−2.38 (m, 2H), 2.60 (q, 4H, J = 7.6 Hz), 2.76 (t, 2H, J = 6.8 Hz), 3.50 (dd, 2H, J = 13.2 and 7.2 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 5.51 (brs, 1H), 6.72−6.74 (m, 2H), and 6.82 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 23.6, 27.9, 32.2, 35.4, 36.9, 40.9, 56.0, 56.1, 59.2, 111.5, 112.0, 120.8, 131.5, 147.9, 149.2, and 172.4. Anal. Calcd for $C_{19}H_{31}NS_2O_3$: C, 59.19; H, 8.10; N, 3.63. Found: C, 59.17; H, 8.11; N, 3.64.

8,9-Dimethoxy-10*b*-methyl-1,5,6,10*b*-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one (21). A solution containing 0.2 g (0.5 mmol) of amide **17** and 0.2 g (1.1 mmol) of DMTSF in 10 mL of CH_2Cl_2 was heated at reflux for 12 h. The reaction mixture was allowed to cool, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.1 g (76%) of **21** as a white solid: mp 120−121 °C; IR (neat) 2965, 1519, and 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (d, 1H, J = 8.0 Hz), 1.51 (s, 3H), 2.05−2.17 (m, 1H), 2.34−2.41 (m, 1H), 2.44 (tt, 1H, J = 9.6 and 1.6 Hz), 2.59−2.70 (m, 2H), 2.85−2.94 (m, 1H), 3.03−3.11 (m, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.24−4.32 (m, 1H), and 6.57 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.5, 28.3, 30.9, 34.2, 34.9, 56.0, 56.3, 61.2, 108.0, 111.6, 124.6, 134.8, 147.9, 148.2, and 172.5. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.76; H, 7.36; N, 5.25.

5,5-Bis(ethylsulfanyl)hexanoic Acid. To a solution containing 3.0 mL (25 mmol) of 4-acetylbutyric acid in 40 mL of concentrated hydrochloric acid was added 4.7 mL (63 mmol) of ethanethiol. The reaction mixture was stirred at room temperature for 12 h and diluted with 50 mL of water. The mixture was extracted with CH_2Cl_2, the combined organic layer was washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 3.9 g (65%) of the title compound as a white solid: mp 27−28 °C; IR ($CHCl_3$) 3230, 1705, and 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, 6H, J = 7.5 Hz), 1.54 (s, 3H), 1.74−1.90 (m, 4H), 2.38 (t, 2H, J = 6.9 Hz), 2.61 (q, 4H, J = 7.5 Hz), and 11.0 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 20.3, 23.7, 27.8, 34.1, 41.2, 59.7, and 179.3. Anal. Calcd for $C_{10}H_{20}O_2S_2$: C, 50.81; H, 8.53. Found: C, 51.02; H, 8.52.

5,5-Bis(ethylsulfanyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]hexanamide (18). Using the standard procedure, a 0.5 g (2.0 mmol) sample of the above carboxylic acid, 0.4 g (2.0 mmol) of 1,1′-carbonyl diimidazole, and 0.4 mL (2.0 mmol) of 3,4-dimethoxyphenethylamine in 20 mL of CH_2Cl_2 gave 0.8 g (95%) of **18** as a white solid: mp 60−61 °C; IR ($CHCl_3$) 3298, 1637, and 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 6H, J = 10.4 Hz), 1.53 (s, 3H), 1.70−1.75 (m, 2H), 1.78−1.87 (m, 2H), 2.14 (t, 2H, J = 7.2 Hz), 2.60 (q, 4H, J = 10.4 Hz), 2.77 (t, 2H, J = 6.9 Hz), 3.50 (dd, 2H, J = 13.2 and 6.9 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 5.43 (brs, 1H), 6.72−6.75 (m, 2H), and 6.82 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 21.3, 23.6, 27.8, 35.6, 36.8, 40.9, 41.4, 56.1, 56.2, 59.7, 111.5, 112.0, 120.7, 131.5, 147.7, 149.1, and 172.3. Anal. Calcd for $C_{19}H_{31}NS_2O_3$: C, 60.11; H, 8.32; N, 3.51. Found: C, 60.14; H, 6.32; N, 3.48.

9,10-Dimethoxy-11*b*-methyl-1,2,3,6,7,11*b*-hexahydropyrido[2,1-*a*]isoquinolin-4-one (22). A solution containing 0.1 g (0.3 mmol) of **18** and 0.1 g (0.6 mmol) of DMTSF in 10 mL of CH_2Cl_2 was heated at reflux for 24 h. The mixture was allowed to cool, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.5 g (78%) of **22** as a white solid: mp 97−98 °C; IR ($CHCl_3$) 1634, 1513, and 1253 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 3H), 2.08 (q, 1H, J = 11.2 Hz), 2.34−2.47 (m, 2H), 2.59−2.75 (m, 2H), 2.84−2.96 (m, 1H), 3.03−3.11 (m, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 3.89−3.91(m, 2H), 4.30 (dd, 1H, J = 13.2 and 6.8 Hz), and 6.57 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.4, 28.24, 30.9, 34.2, 34.8, 56.0, 56.2, 60.9, 61.1, 107.9, 111.6, 124.5, 134.7, 147.9, 148.1, and 172.4. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.55; H, 7.42; N, 5.01.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-3-(2-methyl-[1,3]dithiolane-2-yl)propionamide (19).** Using the standard procedure, 0.6 g (3.0 mmol) of 3-(2-methyl-[1,3]dithiolan-2-yl)-propionic acid,[35] 0.5 g (3.3 mmol) of 1,1′-carbonyl diimidazole, and 1.1 mL (6.7 mmol) of 3,4-dimethoxyphenethylamine in 50 mL of CH_2Cl_2 gave 0.96 g (86%) of **19** as a colorless oil: IR (neat) 3309, 1656, and 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.76 (s, 3H), 2.21−2.25 (m, 2H), 2.39−2.43 (m, 2H), 2.77 (t, 2H, J = 6.8 Hz), 3.24−3.37 (m, 4H), 3.50 (dd, 2H, J = 12.8, 6.8 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 5.60 (brs, 1H), 6.72−6.74 (m, 2H), and 6.82 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.0, 34.4, 35.4, 40.3, 40.5, 40.9, 56.0, 56.1, 66.5, 111.5, 112.0, 120.0, 131.5, 147.8, 149.2, and 172.5. Anal. Calcd for $C_{17}H_{25}NS_2O_3$: C, 57.44; H, 7.09; N, 3.94. Found: C, 57.29; H, 7.20; N, 3.74.

A solution containing 0.12 g (0.34 mmol) of **19**, 0.15 g (0.74 mmol) of DMTSF, and 10 mL of dichloroethane was heated at reflux for 24 h. The reaction mixture was allowed to cool, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.07 g (76%) of **21**.

4-(2-Methyl-[1,3]dithiolan-2-yl)butyric Acid. A solution containing 1.0 mL (8.4 mmol) of 4-acetylbutyric acid and 0.7 mL (8.0 mmol) of ethanedithiol was cooled to 0 °C. To this solution was added 2.2 mL (18 mmol) of BF_3·OEt_2, and the reaction mixture was stirred at 0 °C for 5 h. The mixture was quenched by the addition of 0.5 mL of methanol, diluted with 50 mL of water, and extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 1.6 g (92%) of the title compound as a colorless oil: IR (neat) 3199, 1708, and 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78 (s, 3H), 1.86−1.93 (m, 2H), 1.95−2.00 (m, 2H), 2.40 (t, 2H, J = 6.8 Hz), 3.30−3.37 (m, 4H), and 10.32 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.6, 32.6, 34.1, 40.2, 45.1, 66.5, and 179.5. Anal. Calcd for $C_8H_{14}O_2S_2$: C, 46.57; H, 6.84. Found: C, 46.62; H, 6.82.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-4-(2-methyl-[1,3]dithiolan-2-yl)butyramide (20).** Using the standard procedure, a 0.5 g (2.4 mmol) sample of the above carboxylic acid, 0.4 g (2.5 mmol) of 1,1′-carbonyl diimidazole, and 0.5 mL (2.7 mmol) of 3,4-dimethoxyphenethylamine in 20 mL of CH_2Cl_2 gave 0.85 g (96%) of **20** as a colorless oil: IR (neat) 3305, 1640, and 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.75 (s, 3H), 1.82−1.94 (m, 4H), 2.18 (t, 2H, J = 7.2 Hz), 2.77 (t, 2H, J = 7.2 Hz), 3.25−3.37 (m, 4H), 3.50 (dd, 2H, J = 12.8 and 6.8 Hz), 3.86 (s, 3H), 3.87 (s, 3H), 5.62 (brs, 1H), 6.72−6.74 (m, 2H), and 6.82 (d, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.6, 32.5, 35.4, 36.6, 40.1, 40.8, 45.2, 56.0, 56.1, 60.5, 66.6, 111.4, 111.9,

120.8, 131.5, 147.8, 149.1, and 172.5. Anal. Calcd for $C_{18}H_{27}NS_2O_3$: C, 58.51; H, 7.36; N, 3.79. Found: C, 58.49; H, 7.34; N, 3.85.

A solution containing 0.14 g (0.4 mmol) of **20**, 0.16 g (0.8 mmol) of DMTSF, and 10 mL of dichloroethane was heated at reflux for 36 h. The reaction mixture was allowed to cool, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.68 g (75%) of **22**.

***N*-((2-Cyclohex-1-enyl)ethyl)-4,4-bis(ethylsulfanyl)butyramide (25).** Using the standard procedure, 0.7 g (3.2 mmol) of 4,4-bis(ethylsulfanyl)butyric acid, 0.5 g (3.4 mmol) of 1,1′-carbonyl diimidazole, and 0.5 mL (4.0 mmol) of 2-(1-cyclohexenyl)ethylamine in 30 mL of CH_2Cl_2 gave 1.0 g (98%) of **25** as a white solid: mp 41−42 °C; IR ($CHCl_3$) 3305, 1650, 1444 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, 6H, J = 7.2 Hz), 1.53−1.65 (m, 4H), 1.90−1.93 (m, 2H), 1.97−2.03 (m, 2H), 2.10−2.16 (m, 4H), 2.41 (t, 2H, J = 7.2 Hz), 2.56−2.73 (m, 4H), 3.33 (dd, 2H, J = 12.4 and 7.2 Hz), 3.84 (t, 1H, J = 7.2 Hz), 5.45−5.49 (m, 1H), and 5.52 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 22.5, 23.0, 42.5, 25.4, 28.0, 31.5, 34.1, 37.3, 37.8, 50.6, 123.8, 134.8, and 171.9. Anal. Calcd for $C_{16}H_{29}NS_2O$: C, 60.91; H, 9.26; N, 4.44. Found: C, 60.72; H, 9.12; N, 4.41.

1,5,7,8,9,10,10*a*,10*b*-Octahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one (27). To a solution containing 0.1 g (0.3 mmol) of **25** and 20 mL of CH_2Cl_2 was added 0.13 g (0.7 mmol) of DMTSF. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography to give 0.03 g (48%) of **27** as a colorless oil: IR (neat) 2926, 1697, and 1418 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40−1.72 (m, 5H), 1.82−1.91 (m, 2H), 1.99−2.28 (m, 4H), 2.37−2.43 (m, 2H), 2.60 (td, 1H, J = 12.8 and 4.0 Hz), 3.07 (dt, 1H, J = 9.6 and 7.6 Hz), 4.15 (ddd, 1H, J = 12.8, 5.6, and 1.2 Hz), and 5.59−6.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9, 24.1, 26.3, 26.8, 31.5, 34.5, 41.6, 44.6, 63.9, 124.5, 136.4, and 173.7. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.51; H, 9.01; N, 7.12.

***N*-(2-Cyclohex-1-enyl)-5,5-bis(methylsulfanyl)pentanamide (26).** Using the standard procedure, 0.64 g (3.3 mmol) of 5,5-bis(methylsulfanyl)pentanoic acid, 0.6 g (3.5 mmol) of 1,1′-carbonyl diimidazole, and 0.5 mL (3.7 mmol) of 2-(1-cyclohexenyl)ethylamine in 25 mL of CH_2Cl_2 gave 0.95 g (95%) of **26** as a white solid: mp 48−49 °C; IR ($CHCl_3$) 3312, 1644, and 1431 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.54−1.67 (m, 4H), 1.79−1.62 (m, 6H), 1.99−2.03 (m, 2H), 2.10 (s, 6H), 2.13−2.21 (m, 4H), 3.33 (dd, 2H, J = 12.0 and 6.9 Hz), 3.63 (t, 1H, J = 9.2 Hz), 5.41 (brs, 1H), and 5.45−5.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.0, 22.7, 23.1, 24.1, 25.6, 28.2, 34.4, 36.3, 37.3, 37.9, 54.4, 123.7, 134.7, and 172.2. Anal. Calcd for $C_{15}H_{27}NS_2O$: C, 59.73; H, 9.03; N, 4.65. Found: C, 59.92; H, 8.99; N, 4.63.

1,2,3,6,8,9,11,11*a*,11*b*-Decahydropyrido[2,1-*a*]isoquinolin-4-one (28). To a solution of 0.1 g (0.33 mmol) of **26** in 10 mL of CH_2Cl_2 was added 0.12 g (0.6 mmol) of DMTSF. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography to give 0.03 g (49%) of **28** as a colorless oil: IR (neat) 2920, 1644, and 1444 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84−0.91 (m, 1H), 1.05−1.14 (m, 1H), 1.24−1.28 (m, 2H), 1.38−1.47 (m, 1H), 1.75−1.87 (m, 2H), 1.92−2.02 (m, 3H), 2.06−2.12 (m, 1H), 2.15−2.17 (m, 2H), 2.28−2.45 (m, 3H), 2.87−2.94 (1H), 4.81 (ddd, 1H, 12.4, 4.0, and 3.2 Hz), and 5.51−5.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 21.9, 25.3, 26.9, 27.4, 33.2, 34.6, 43.5, 62.4, 77.4, 112.8, 136.2, and 201.9. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.87; H, 9.21; N, 6.69.

***N*-(3-Bromobut-3-enyl)-4,4-bis(ethylsulfanyl)butyramide (29).** Using the standard procedure, 0.6 g (2.9 mmol) of 4,4-bis(ethylsulfanyl)butyric acid, 0.5 g (3.0 mmol) of 1,1′-carbonyl diimidazole, and 0.4 g (2.9 mmol) of 3-bromo-3-butenylamine in 25 mL of CH_2Cl_2 gave 0.94 g (94%) of **29** as a colorless oil: IR (neat) 3284, 1639, and 1445 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, 6H, J = 7.6 Hz), 2.13 (q, 2H, J = 7.6 Hz), 2.43 (q, 2H, J = 7.6 Hz), 2.56−2.73 (m, 6H), 3.48 (q, 2H, J = 6.4 Hz), 3.84 (t, 1H, J = 7.2 Hz), 5.51 (d, 1H, J = 2.0 Hz), 5.65−5.66 (m, 1H), and 5.75 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 24.5, 31.4, 34.0, 37.7, 41.2, 50.5, 119.4, 131.2, and 172.3. Anal. Calcd for $C_{12}H_{22}NS_2OBr$: C, 42.35; H, 6.52; N, 4.12. Found: C, 42.48; H, 6.57; N, 4.13.

Hexahydroindolizin-3,7-dione (31). A solution containing 0.1 g (0.3 mmol) of **29** and 15 mL of CH_2Cl_2 was cooled to −40 °C. To this was added 0.13 g (0.65 mmol) of DMTSF. The reaction mixture was stirred at room temperature for 3.5 h, and the solvent was removed under reduced pressure. The crude residue contained 7-bromo-7-fluorohexahydroindolizin-3-one[40] as a1:1 mixture of diastereomers. Without purification, this mixture was taken up in 5 mL of 98% formic acid, and 0.14 g (0.4 mmol) of $Hg(OAc)_2$ was added. The reaction mixture was stirred at room temperature for 12 h, poured into water, and extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.03 g (65%) of **31** as a white solid: mp: 54−55 °C; IR ($CHCl_3$) 1710, 1620, and 1420 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.72−1.81 (m, 1H), 2.30 (dd, 1H, J = 14.4 and 12.0 Hz), 2.35−2.53 (m, 5H), 2.62 (ddd, 1H, J = 14.4, 10.0, and 1.6 Hz), 2.97−3.04 (m, 1H), 3.81−3.88 (m, 1H), and 4.43 (ddd, 1H, J = 13.2, 6.8, and 3.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 29.9, 38.2, 40.1, 48.8, 56.6, 173.9, and 206.5. Anal. Calcd for $C_8H_{11}NO_2$: C, 62.71; H, 7.24; N, 9.15. Found: C, 62.59; H, 7.08; N, 9.26.

***N*-(3-Bromobut-3-enyl)-5,5-bis(methylsulfanyl)pentanamide (30).** Using the standard procedure, 0.6 g (3.1 mmol) of 5,5-bis(methylsulfanyl)pentanoic acid, 0.5 g (3.1 mmol) of 1,1′-carbonyl diimidazole, and 0.46 g (3.1 mmol) of 3-bromo-3-butenylamine in 25 mL of CH_2Cl_2 gave 0.9 g (91%) of **30** as a colorless oil: IR (neat) 3284, 1653, and 1432 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.76−1.92 (m, 4H), 2.09 (s, 6H), 2.21 (t, 2H, J = 6.8 Hz), 2.64 (td, 2H, J = 6.4 and 6.8 Hz), 3.47 (q, 2H, J = 6.4 Hz), 3.63 (t, 1H, J = 6.8 Hz), 5.51 (d, 1H, J = 1.6 Hz), 5.65−5.66 (m, 1H), and 5.77 (brs, 1H); ^1C NMR ($CDCl_3$, 100 MHz) δ 12.8, 23.9, 34.2, 36.0, 37.6, 41.2, 54.2, 119.3, 131.2, and 172.7. Anal. Calcd for $C_{11}H_{20}NS_2OBr$: C, 40.49; H, 6.18; N, 4.29. Found: C, 40.67; H, 6.22; N, 4.26.

Octahydroquinolizin-4,8-dione (32). A solution containing 0.1 g (0.3 mmol) of **30** and 15 mL of CH_2Cl_2 was cooled to −40 °C. To this solution was added 0.14 g (0.7 mmol) of DMTSF. The reaction mixture was stirred at room temperature for 4 h, and the solvent was removed under reduced pressure. The residue contained 8-bromo-8-fluoro-octahydroquinolizin-4-one[40] as a 1:1 mixture of diastereomers. This mixture was taken up in 5 mL of 98% formic acid, and 0.15 g (0.46 mmol) of $Hg(OAc)_2$ was added. The reaction mixture was stirred at room temperature for 12 h, poured into water, and extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.03 g (58%) of **32** as a colorless oil: IR (neat) 1725, 1645, and 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.58−1.66 (m, 1H), 1.76−1.85 (m, 1H), 1.87−1.97 (m, 1H), 2.07−2.15 (m, 1H), 2.42−2.50 (m, 6H), 2.88−2.95 (m, 1H), 3.71 (dq, 1H, J = 9.2 and 6.0 Hz), and 4.91 (ddd, 1H, J = 4.0, 6.0, and 13.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 29.8, 32.9, 40.8, 41.1, 48.3, 55.1, 169.7, and 207.1. Anal. Calcd for $C_9H_{13}NO_2$: C, 64.63; H, 7.84; N, 8.38. Found: C, 64.49; H, 7.68; N, 8.17.

4,4,4-Tris(methylsulfanyl)butyric Acid. To a solution containing 3.8 mL (8.7 mmol) of a 2.3 M solution of *n*-BuLi in hexane and 20 mL of THF at −78 °C was added 1.1 mL (8.0 mmol) of tris(methylthio)methane. The mixture was allowed to stir at this temperature for 10 min, and 2.9 mL (32 mmol) of methyl acrylate was added. The reaction mixture was allowed to stir at −78 °C for 2 h, warmed to room temperature, and quenched by the addition of water. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography to give 0.76 g (40%) of 4,4,4-tris(methylsulfanyl)-butyric acid methyl ester as a colorless oil: IR (neat) 1736, 1431, and 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.10 (s,

9H), 2.23 (t, 2H, J = 7.8 Hz), 2.70 (t, 2H, J = 7.8 Hz), and 3.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.1, 30.0, 32.5, 51.9, 70.8, and 173.7.

To a solution containing 0.5 g (2.0 mmol) of this ester in 25 mL of Et_2O was added 0.4 g (3.1 mmol) of potassium trimethylsilanoate. The reaction mixture was allowed to stir at room temperature for 12 h, and 25 mL of 10% aqueous HCl was added. The mixture was allowed to stir for 15 min and was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.43 g (93%) of the title compound as a white solid: mp 77−78 °C; IR ($CHCl_3$) 3107, 1708, and 1403 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.11 (s, 9H), 2.23 (t, 2H, J = 8.0 Hz), 2.75 (t, 2H, J = 8.0 Hz), and 9.10 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.2, 30.2, 32.4, 70.8, and 179.2. Anal. Calcd for $C_7H_{14}O_2S_3$: C, 37.14; H, 6.23. Found: C, 37.25; H, 6.29.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-4,4,4-tris(methylsulfanyl)butyramide (33).** To a solution containing 0.23 g (1.0 mmol) of the above carboxylic acid and 15 mL of CH_2Cl_2 was added 0.17 g (1.1 mmol) of 1,1′-carbonyl diimidazole. The mixture was stirred for 30 min, and 0.2 mL (1.1 mmol) of 3,4-dimethoxyphenethylamine was added. The solution was stirred at room temperature for 30 min, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.4 g (100%) of **33** as a white solid: mp 50−51 °C; IR ($CHCl_3$) 3293, 1648, and 1237 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.09 (s, 9H), 2.25 (dd, 2H, J = 8.1 and 5.4 Hz), 2.47 (dd, 2H, J = 8.1 and 5.4 Hz), 2.77 (t, 2H, J = 6.9 Hz), 3.50 (dd, 2H, J = 12.9 and 6.9 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 5.56 (brs, 1H), 6.72−6.75 (m, 2H), and 6.83 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.3, 32.3, 32.8, 35.5, 41.0, 56.1, 56.2, 71.1, 111.4, 111.9, 120.7, 131.4, 147.7, 149.1, and 172.0. Anal. Calcd for $C_{17}H_{27}N_1O_3S_3$: C, 52.41; H, 6.99; N, 3.60. Found: C, 52.27; H, 7.03; N, 3.59.

8,9-Dimethoxy-5,6-dihydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one (35). A solution containing 0.08 g (0.2 mmol) of the above amide **33**, 0.05 mL (0.5 mmol) of dimethyl sulfate, and 10 mL of CH_2Cl_2 was heated at reflux for 36 h. The mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography to give 0.025 g (46%) of **35** as a yellow solid: mp 114−115 °C; IR ($CHCl_3$) 1697, 1597, and 1517 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.87 (t, 2H, J = 6.0 Hz), 3.21 (d, 2H, J = 2.8 Hz), 3.70 (t, 2H, J = 6.0 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 5.42 (t, 1H, J = 2.8 Hz), 6.66 (s, 1H), and 6.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.6, 37.1, 38.4, 56.2, 56.3, 94.8, 106.7, 111.1, 119.7, 126.9, 139.7, 148.5, 150.0, and 176.8. Anal. Calcd for $C_{14}H_{15}N_1O_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.77; H, 6.31; N, 5.87.

5,5,5-Tris(methylsulfanyl)pentanoic Acid. To a solution containing 0.3 mL (2.1 mmol) of tris(methylthio)methane and 15 mL of THF at −78 °C was added 1.0 mL (2.3 mmol) of a 2.3 M solution of *n*-BuLi in hexane. The reaction mixture was allowed to stir at this temperature for 10 min, and 0.17 g (1.0 mmol) of 4-bromo butanoic acid was added. The reaction mixture was allowed to warm to room temperature, stirred for 3 h, quenched by the addition of 10% aqueous HCl, and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.25 g (100%) of the title compound as a white solid: mp 64−65 °C; IR ($CHCl_3$) 3119, 1697, and 1424 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.89−2.05 (m, 4H), 2.11 (s, 9H), 2.43 (t, 2H, J = 6.6 Hz), and 8.10 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.3, 20.5, 33.8, 37.3, 70.9, and 179.1. Anal. Calcd for $C_8H_{16}S_3O_2$: C, 39.97; H, 6.71. Found: C, 40.05; H, 6.82.

2-(3,4-Dimethoxyphenyl)ethyl-5,5,5-tris(methylsulfanyl)pentanamide (34). To a solution containing 0.24 g (1.0 mmol) of the above carboxylic acid and 15 mL of CH_2Cl_2 was added 0.17 g (1.1 mmol) of 1,1′-carbonyl diimidazole. The mixture was stirred for 30 min, and 0.2 mL (1.1 mmol) of 3,4-dimethoxyphenethylamine was added. The solution was allowed to stir at room temperature for 30 min, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.36 g (90%) of **34** as a white solid: mp 83−84 °C; IR ($CHCl_3$) 3303, 1659, and 1517 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.87−2.01 (m, 4H), 2.10 (s, 9H), 2.19 (t, 2H, J = 7.2 Hz), 2.77 (t, 2H, J = 6.8 Hz), 3.50 (dd, 2H, J = 6.8 and 6.0 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 5.50 (brs, 1H), 6.72−6.75 (m, 2H), and 6.82 (d, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.2, 21.3, 35.0, 36.1, 37.4, 40.9, 56.1, 56.2, 71.0, 111.5, 112.0, 131.5, 147.8, 149.2, and 172.4. Anal. Calcd for $C_{18}H_{29}N_1O_3S_3$: C, 53.57; H, 7.24; N, 3.47. Found: C, 53.67; H, 7.21; N, 3.42.

9,10-Dimethoxy-2,3,6,7-tetrahydropyrido[2,1-*a*]isoquinolin-4-one (36). A solution containing 0.1 g (0.25 mmol) of amide **34**, 0.06 mL (0.5 mmol) of dimethyl sulfate, and 10 mL of CH_2Cl_2 was heated at reflux for 12 h. The reaction mixture was allowed to cool to room temperature, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.05 g (71%) of **36** as a yellow solid: mp 73−75 °C; IR ($CHCl_3$) 1664, 1604, and 1517 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.38−2.45 (m, 2H), 2.57 (t, 2H, J = 7.8 Hz), 2.77 (t, 2H, J = 6.0 Hz), 3.88 (s, 3H), 3.89 (s, 3H), 3.90 (t, 2H, J = 6.0 Hz), 5.68 (t, 1H, J = 5.4 Hz), 6.61 (s, 1H), and 7.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.8, 29.1, 31.5, 38.7, 56.2, 56.3, 100.8, 106.9, 110.7, 122.5, 127.4, 135.7, 148.1, 149.2, and 169.9. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.35; H, 6.42; N, 5.21.

2-[2,2-Bis((ethylsulfanyl)cyclohexyl)]acetic Acid (40). To a solution containing 1.0 g (6.0 mmol) of (2-oxocyclohexyl)-acetic acid (**39**)[47] in 20 mL of concentrated HCl was added 1.1 mL (16 mmol) of ethanethiol. The reaction mixture was stirred for 12 h at room temperature, diluted with water, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 1.1 g (68%) of **40** as a white solid: mp 99−100 °C; IR($CHCl_3$) 3049, 1701, and 1447 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (q, 6H, J = 7.6 Hz), 1.23−1.40 (m, 1H), 1.59−1.86 (m, 7H), 2.00−2.05 (m, 1H), 2.22 (dd, 1H, J = 10.4 and 15.6 Hz), 2.29−2.36 (m, 1H), 2.55−2.68 (m, 4H), 3.28 (dd, 1H, J = 15.6 and 2.4 Hz), and 10.80 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 14.3, 22.3, 22.6, 22.9, 24.9, 28.2, 36.3, 36.5, 42.3, 64.3, and 180.0. Anal. Calcd for $C_{12}H_{22}S_2O_2$: C, 54.92; H, 8.45. Found: C, 55.17; H, 8.53.

2-[2,2-Bis(ethylsulfanylcyclohexyl)]-*N*[(2-(3,4-dimethoxyphenyl)ethyl] Acetamide (41). Using the standard procedure, a 1.0 g (4.0 mmol) sample of carboxylic acid **40**, 0.7 g (4.0 mmol) of 1,1′-carbonyl diimidazole, and 0.7 mL (4.0 mmol) of 3,4-dimethoxyphenethylamine in 50 mL of CH_2Cl_2 gave 1.6 g (99%) of **41** as a clear oil: IR($CHCl_3$) 3309, 1643, and 1519 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (dt, 6H, J = 8.4 and 7.6 Hz), 1.25−1.32 (m, 1H), 1.52−1.68 (m, 3H), 1.74−1.88 (m, 2H), 2.02−2.05 (m, 1H), 2.38 (tt, 1H, J = 10.4 and 3.2 Hz), 2.47−2.70 (m, 4H), 2.75 (t, 2H, J = 6.8 Hz), 3.50 (ddd, 1H, J = 7.2, 6.0, and 2.8 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 5.49 (t, 1H, J = 5.6 Hz), 6.72−6.74 (m, 2H), and 6.81 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 22.1, 22.7, 22.9, 25.3, 28.4, 35.5, 36.5, 39.0, 40.9, 42.5, 56.0, 56.1, 64.4, 111.5, 112.0, 120.8, 131.5, 147.8, 149.2, and 172.6. Anal. Calcd for $C_{22}H_{35}NS_2O_3$: C, 62.08; H, 8.29; N, 3.29. Found: C, 62.19; H, 8.27; N, 3.26.

11,12-Dimethoxy-1,2,3,4,4*a*,5,8,9-octahydroindolo[1*a*,7*a*]-isoquinolin-6-one (42). To a solution containing 0.16 g (0.4 mmol) of amide **41** in 10 mL of CH_2Cl_2 was added 0.16 g (0.8 mmol) of DMTSF. The reaction mixture was heated at reflux for 12 h, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.08 g (71%) of **42** as a white solid: mp 117−118 °C; IR($CHCl_3$) 1682, 1513, and 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51−1.57 (m, 2H), 1.62−1.75 (m, 3H), 1.82−1.90 (m, 2H), 2.00−2.09 (m, 1H), 2.35 (dd, 2H, J = 7.6 and 3.0 Hz), 2.55−2.60 (m, 1H), 2.69 (dq, 1H, J = 16.4 and 3.0 Hz), 3.00 (ddd, 1H, J = 16.0, 10.0, and 7.6 Hz), 3.19−3.26 (m, 1H), 3.85 (s, 3H), 3.89

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(s, 3H), 4.08−4.14 (m, 1H), 6.59 (s, 1H), and 6.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5, 20.9, 27.3, 27.4, 35.0, 36.0, 36.7, 37.8, 56.0, 56.3, 62.4, 108.3, 112.0, 125.9, 135.0, 147.4, and 147.9. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.56; H, 7.61; N, 4.52.

4,4-Bis(ethylsulfanyl)-*N*-(2-methylcarbamoylethyl)butyramide (43). Using the standard procedure, 0.1 g (0.47 mmol) of carboxylic acid **7**, 0.09 g (0.5 mmol) of 1,1′-carbonyl diimidazole, and 0.05 g (0.5 mmol) of 3-amino-*N*-methylpropionamide[48] in 10 mL of CH_2Cl_2 gave 0.12 g (92%) of **43** as a white solid: mp 118−119 °C; IR ($CHCl_3$) 3305, 1644, and 1551 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, 6H, J = 7.6 Hz), 2.12 (q, 2H, J = 7.6 Hz), 2.39−2.44 (m, 4H), 2.57−2.70 (m, 4H), 2.82 (d, 3H, J = 8.0 Hz), 3.53 (q, 2H, J = 6.0 Hz), 3.82 (t, 1H, J = 6.8 Hz), 5.73 (brs, 1H), and 6.37 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 24.5, 26.5, 31.5, 34.1, 35.6, 35.7, 50.6, 172.2, and 172.4. Anal. Calcd for $C_{12}H_{24}N_2O_2S_2$: C, 49.28; H, 8.27; N, 9.58. Found: C, 49.08; H, 8.26; N, 9.50.

1-Methylhexahydropyrolo[1,2-*a*]pyrimidine-2,6-dione (46). To a solution containing 0.3 g (1.0 mmol) of thioacetal **43** and 15 mL of CH_2Cl_2 was added 0.4 g (2.2 mmol) of DMTSF. The mixture was allowed to warm to room temperature, stirred for 12 h, concentrated under reduced pressure, and subjected to silica gel chromatography to give 0.1 g (60%) of **46** as a white solid: mp 65−67 °C; IR ($CHCl_3$) 2926, 1710, and 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.89−1.95 (m, 1H), 2.43−2.54 (m, 5H), 2.93 (s, 3H), 3.03−3.11 (m, 1H), 4.28 (ddd, 1H, J = 13.2, 5.6, and 2.8 Hz), and 5.00 (t, 1H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 29.3, 29.6, 31.8, 35.4, 72.1, 167.7, and 172.6. Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.30; H, 7.32; N, 16.71.

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5,5-Bis(methylsulfanyl)-*N*-(2-methylcarbamoylethyl)-pentanamide (44). Using the standard procedure, a 0.5 g (2.6 mmol) sample of 5,5-bis(methylsulfanyl)pentanoic acid (**14**), 0.44 g (2.7 mmol) of 1,1′-carbonyl diimidazole, and 0.24 g (2.7 mmol) of 3-amino-*N*-methylpropionamide[48] gave 0.5 g (75%) of **44** as a white solid: mp 115−116 °C; IR ($CHCl_3$) 3292, 1737, and 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.75−1.79 (m, 2H), 1.83−1.87 (m, 2H), 2.08 (s, 6H), 2.18 (t, 2H, J = 7.2 Hz), 2.40 (t, 2H, J = 6.0 Hz), 2.81 (d, 3H, J = 4.0 Hz), 3.52 (q, 2H, J = 4.0 Hz), 3.62 (t, 1H, J = 7.2 Hz), 5.78 (brs, 1H), and 6.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.8, 23.9, 26.5, 34.2, 35.5, 35.6, 36.1, 54.2, 172.3, and 172.8. Anal. Calcd for $C_{11}H_{22}N_2O_2S_2$: C, 47.45; H, 7.96; N, 10.06. Found: C, 47.49; H, 7.98; N, 10.09.

1-Methylhexahydropyrido[1,2-*a*]pyrimidine-2,6-dione (47). To a solution containing 0.13 g (0.5 mmol) of thioacetal **44** in 10 mL of CH_2Cl_2 was added 0.2 g (1.0 mmol) of DMTSF. The reaction mixture was heated at reflux for 12 h, concentrated under reduced pressure, and subjected to silica gel chromatography to give 0.06 g (73%) of **47** as a white solid: mp 75−77 °C; IR ($CHCl_3$) 2954, 1652, and 1410 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.69−1.77 (m, 2H), 1.89−1.98 (m, 1H), 2.34−2.46 (m, 3H), 2.48−2.59 (m, 3H), 2.88 (ddd, 1H, J = 12.9, 11.1, and 5.1 Hz), 2.96 (s, 3H), 4.74 (ddd, 1H, J = 12.9, 5.4, and 2.7 Hz), and 4.85 (dd, 1H, J = 8.1 and 5.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.7, 29.3, 29.6, 32.3, 32.7, 37.9, 71.4, 168.7, and 168.8. Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.17; H, 7.70; N, 15.27.

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