Cycloaddition Chemistry of Anhydro-4-hydroxy-1,3-thiazolium Hydroxides (Thioisomünchnones) for the Synthesis of Heterocycles

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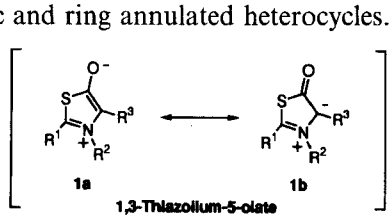
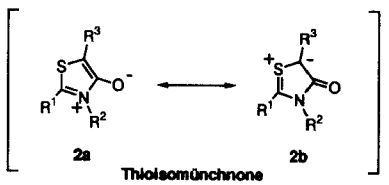
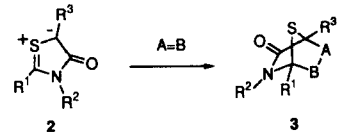
A series of α,α-disubstituted thioisomünchnones were prepared by treating acyclic or cyclic thioamides with bromoacetyl chloride in the presence of triethylamine. The resulting mesoionic dipole was found to undergo bimolecular 1,3-dipolar cycloaddition with several different dipolarophiles. When a hydrogen atom is present in the α-position of the thioamide, the initially formed *N*-acyl iminium ion undergoes proton loss to produce a *S,N*-ketene acetal at a faster rate than thioisomünchnone formation. The cycloaddition behavior of several substituted thioisomünchnones which possess a tethered alkene were also examined. The stereochemical outcome of the intramolecular reaction is the consequence of an *endo* cycloaddition of the neighboring π-bond across the transient thioisomünchnone dipole. Molecular mechanics calculations reveal that the *endo* diastereomers are significantly lower in energy than the corresponding *exo* isomers. Attempts to cycloadd the thioisomünchnone dipole across a tethered indolyl ring were unsuccessful. Instead, products derived by nucleophilic cyclization of the indolyl ring onto the thio *N*-acyl iminium ion were formed in good yield.

The 1,3-dipolar cycloaddition reaction has long been recognized as a favored strategy for the synthesis of heterocyclic rings, often with a high degree of regio and stereochemical control.[1] Experience indicates a concerted mechanism and frontier molecular orbital theory has successfully explained both the relative rates and regioselectivity of these cycloadditions.[2] During the last decade a new impulse has been given to research in this field when it was found that mesoionic compounds undergo 1,3-dipolar cycloaddition with various dipolarophiles.[3-5] Of the known mesoionic heterocycles, the structure, physical properties and reactions of münchnones, isomünchnones and sydnones have drawn the closest scrutiny.[6-13] Studies with these three mesoionic systems have generated considerable theoretical interest and have resulted in practical, unique syntheses of numerous functionalized monocyclic and ring annulated heterocycles.[14-17]





Two related mesoionic systems which are isomeric and contain a thiazole ring are the anhydro-5-hydroxy-1,3-thiazolium hydroxides **1** and the anhydro-4-hydroxy-1,3-thiazolium hydroxides **2** or thioisomünchnones.[3-7] Contained within each of these mesoionic rings is a *masked* 1,3-dipole. An azomethine ylide dipole is present within the 1,3-thiazolium-5-olate (**1**) system while thioisomünchnones possess a thiocarbonyl ylide dipole. Both mesoionic systems readily undergo 1,3-dipolar cycloaddition reactions with reactive dipolarophiles generating cycloadducts which can subsequently be converted to different heterocyclic products. Interest in the thioisomünchnone class of mesoionics may be attributed to (a) their ease of preparation from simple thioamides, (b) the interesting physical properties they possess, and (c) the propensity for its thiocarbonyl ylide dipole to undergo 1,3-dipolar cycloaddition with a wide range of dipolarophiles to produce complex heterocyclic ring systems.[18]

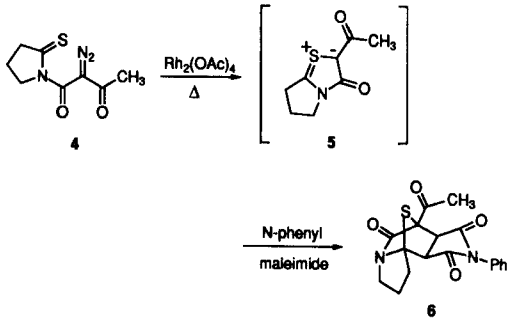


Potts and co-workers have extensively studied the bimolecular cycloaddition behavior of thioisomünchnones.[19,20] Di- and trisubstituted thioisomünchnones react with electron-deficient olefins such as dimethyl maleate and fumurate, *N*-phenylmaleimide, maleic anhydride, methyl vinyl ketone, *trans*-dibenzoylethylene, ethyl acrylate, ethyl methacrylate, ethyl crotonate, acrylonitrile and fumaronitrile to give cycloadducts of type **3**. No cycloadducts were observed with simple alkenes or when electron-rich dipolarophiles such as ethyl vinyl ether were used.[21] Despite the considerable amount of research dealing with the chemistry of anhydro-4-hydroxythiazolium hydroxides, the range of their structural variation has remained somewhat narrow. In particular, in virtually every investigation to date, at least one of the substituents R_1, R_2, or R_3 is an aryl moiety, presumably due to electronic stabilization of the dipole to a sufficient degree to allow for its isolation.[19,21] In order to broaden the utility of these mesoionic compounds for synthesis, we thought it worthwhile to investigate the possibility of generating transient thioisomünchnones in which the peripheral substituents R_1, R_2, and R_3 were of the alkyl, rather than aryl, variety. The results of this investigation are reported herein.

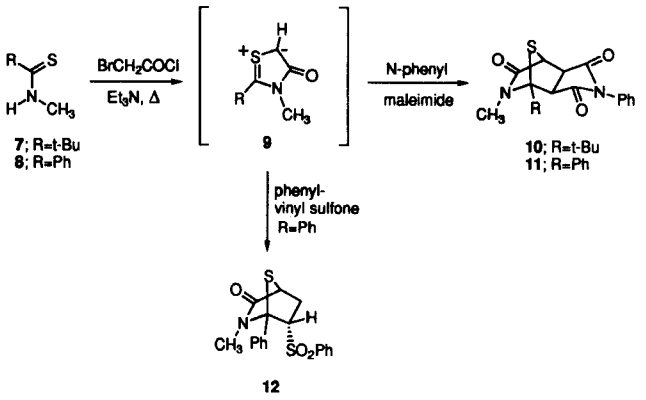
Results and Discussion

Ylide formation as a result of carbene interaction with the unshared electron pair of heteroatoms has been extensively studied.[22] In a series of papers we demonstrated that this process represents an effective approach for the formation of cyclic carbonyl ylides.[23] The Rh(II) catalyzed reaction of diazo imides has been utilized to generate the anhydro-4-hydroxy-1,3-oxazolium hydroxide (isomünchnone) ring system.[11-13] The formation and dipolar trapping of thioisomünchnones via the interaction of rhodium carbenoids derived from diazo thioamides has not been investigated to the same extent as

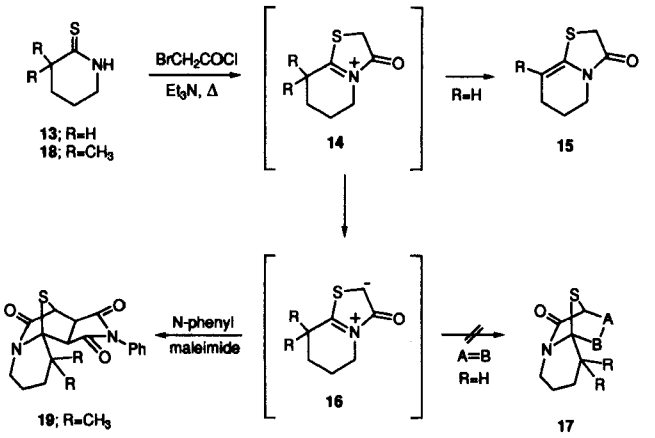
the corresponding isomünchnone system.[24] With the intention of using diazo thioamides as thioisomünchnone precursors, we commenced our study by an examination of the Rh(II) catalyzed reaction of diazo thioamide **4** with *N*-phenylmaleimide.[25] In this case, cycloadduct **6** was isolated in 63% yield when the reaction was carried out in refluxing xylene. Unfortunately, a low yield of cycloadduct **6** (< 15%) was obtained when other solvents (CH_2Cl_2, benzene, toluene) were used.

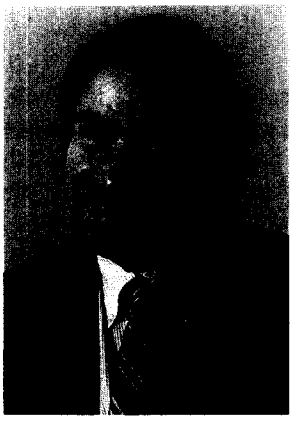


Given this problem, we decided to explore an alternate route to the thioisomünchnone system which involved using simple cyclic thiolactams as the mesoionic precursor.[19] Sequential treatment of thiolactams **7** and **8** with bromoacetyl chloride and triethylamine in the presence of one equivalent of *N*-phenylmaleimide afforded cycloadducts **10** and **11** in 54% and 64% yield, respectively. These compounds are derived by dipolar cycloaddition of the mesoionic species **9** with the added dipolarophile. Cycloaddition of thioisomünchnone **9** with an unsymmetrical dipolarophile such as phenyl vinyl sulfone afforded cycloadduct **12**. The regiochemical assignment is based on its spectral properties (see Experimental Section) and FMO considerations.[26,27] In this case, the dominant FMO interaction is between the HOMO of the dipole and the LUMO of the dipolarophile.



When a cyclic thioamide such as piperidine-2-thione **(13)** was treated with bromoacetyl chloride in the presence of a variety of trapping agents, no product of dipolar cycloaddition (i.e. **17**) across the thioisomünchnone dipole was detected in the reaction mixture.[28] Instead, 6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyridin-3(2*H*)-one **(15)** was isolated in 78% yield. This product is derived by elimination of the proton alpha to the *N*-acyl iminium ion center. Apparently, proton loss to give the *S,N*-ketene acetal **15** is faster than thioisomünchnone formation.



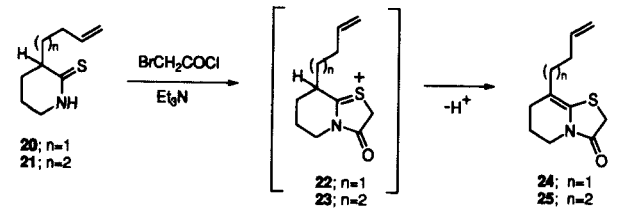


Biographical Sketch

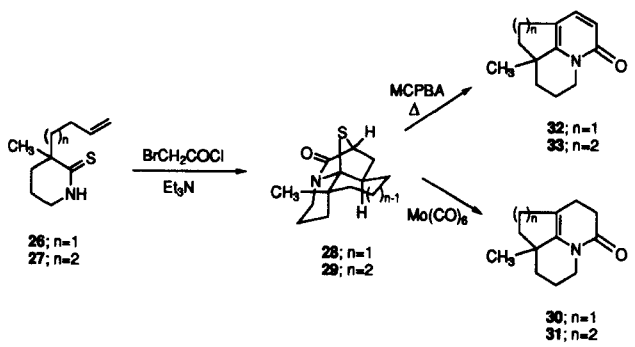
Albert Padwa is the William Patterson Timmie Professor of Chemistry at Emory University. Before that he was on the faculty at Ohio State University (1963–1966) and the State University of New York at Buffalo (1966–1979). He has held visiting positions at the University Claude Bernard, France (1978), the University of California at Berkeley (1982), the University of Wurzburg, Germany (1985), and Imperial College (London, 1990). Professor Padwa has been the recipient of an Alfred P. Sloan Fellowship (1968–1970), John S. Guggenheim Fellowship (1981–1982), Alexander von Humboldt Senior Scientist Award (1983–1985) and a Fulbright Hays Scholarship (1990). He is currently President of the International Society of Heterocyclic Chemistry. His research interests include heterocyclic chemistry, reactive intermediates, alkaloid synthesis, dipolar cycloadditions, the chemistry of strained molecules, organic photochemistry, and he is the coauthor of more than 430 publications.

In order to avoid this complication, the 3,3-dimethyl substituted piperidine-2-thione (**18**) was examined. In this case the initially generated *N*-acyl iminium ion **14** cannot undergo α-proton loss and instead thioisomünchnone formation occurs by removal of the proton adjacent to the carbonyl group. Once formed, dipole **16** readily cycloadds to the reactive dipolarophile giving cycloadduct **19** in 70% isolated yield.

Intramolecular 1,3-dipolar cycloaddition reactions represent one of the most efficient methods for the generation of complex ring systems.[29-31] In connection with our continuing interest in this area, we decided to investigate the cycloaddition behavior of thioisomünchnones which possess tethered alkenes. Thiolactams **20** and **21** were therefore treated under the aforementioned conditions. In both these cases, cycloaddition was not observed. Instead compounds **24** and **25** were isolated as the exclusive products and arise by elimination of the proton alpha to the thiocarbonyl ylide precursors **22** and **23**.[28] Once again proton loss to give a *S,N*-ketene acetal is faster than intramolecular cycloaddition.

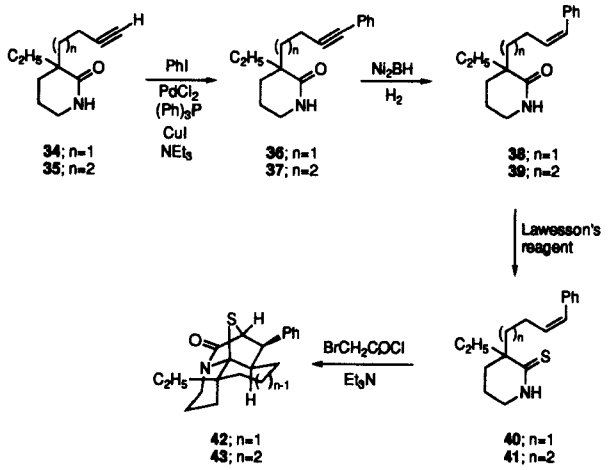


In order to prevent this elimination pathway, it was necessary to incorporate an alkyl substituent into the α-position of the thioamide. With the deprotonation pathway blocked, intramolecular dipolar cycloaddition became a viable pathway. Thus, subjection of thioamides **26** and **27** to the standard reaction conditions resulted in the formation of cycloadducts **28** and **29** in 76% and 92% yield, respectively. The depicted stereochemistry for cycloadducts **28** and **29** is the result of *endo* cycloaddition with regard to the dipole.



This assignment is based on our related work dealing with intramolecular isomünchnone cycloaddition chemistry, for which X-ray crystallographic analysis had been performed.[32]

Given the success in forming intramolecular thioisomünchnone cycloadducts of type **28** and **29**, it seemed to us that selective modification of the cycloadduct skeleton would allow application of the method toward the synthesis of more complex polyheterocyclic systems. In particular, reductive cleavage of the sulfur bridge would provide ring systems containing skeletons found in the alkaloid kingdom.[33] Raney nickel seemed to be an ideal reagent to induce this reduction, since it has been extensively utilized for desulfurization chemistry.[34] However, we found that a 1:1 mixture of enamide **30** (or **31**) and pyridone **32** (or **33**) was produced when **28** (or **29**) was subjected to Raney Nickel in ethanol. Since this reductive method was unsatisfactory, we turned toward an alternate method recently developed by Alper and Blias for the reduction of thiols.[35] This involved carrying out the reduction of the cycloadduct with molybdenum hexacarbonyl in acetic acid. Using these conditions, enamides **10** and **31** were isolated in 73% and 84% yield from cycloadducts **28** and **29**. We also discovered that treating cycloadducts **28** and **29** with *m*-chloroperbenzoic acid (MCPBA) followed by thermolysis of the resulting sulfoxides (200°C) gave pyridones **32** and **33** in good yield according to the general procedure of Kato.[36]

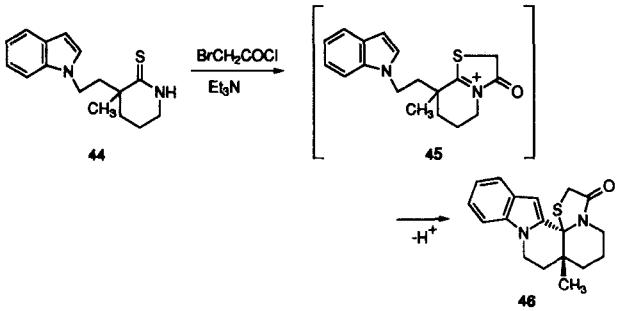


The intramolecular cycloaddition methodology was further extended by employing thiolactams **40** and **41**. These *cis*-phenyl alkenyl substituted piperidinethiones were prepared by a Castro–Stevens coupling[37] of the acetylenic NH-lactams **34** and **35** followed by a nickel boride catalyzed hydrogenation of the alkynyl group[38] and subsequent conversion to the thiolactams using Lawesson's reagent.[39] Treatment of **40** and **41** with bromoacetyl chloride and triethylamine gave cycloadducts **42** and **43** in high yield as single diastereomers. Their spectroscopic properties as well as molecular mechanics calculations (*vide infra*) support the stereochemical assignment of **42** and **43** as being the result of an *endo* cycloaddition. As expected, the cycloaddition reaction proceeded with complete stereospecificity.

In recent years, molecular mechanics has developed into an important technique for the calculation of molecular properties.[40] We have used the Still–Steliou Model 2.94 program to model energy differences in the diastereomeric transition state for the two possible cycloadducts (i.e., *endo vs. exo*).[41] The stability of the diastereomeric cycloadducts was determined by calculation of their steric energies (i.e., the direct sum of the force field increments).

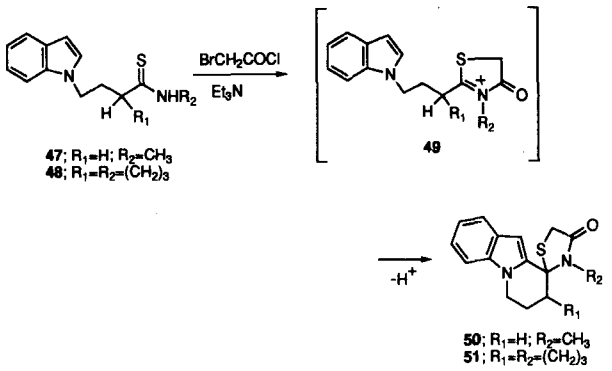
These steric energies represent the thermally averaged energies relative to the same molecule but with all bond lengths, bond angles, and torsional angles set to their strainless values and the atoms having van der Waals and electrostatic interactions corresponding to infinite separation.[42] We assume that the relative energy differences of the two lowest energy conformations of the regioisomeric cycloadducts will parallel the energy differences in the transition state. The *endo–exo* cycloadducts were subjected to energy minimization within the Model KS 2.94 program.[41] Global minima were found by making use of multiconformer generation in Model (TTY, Conf, Statistical, Coordinate) followed by Batch minimization using Bakmdl. The particular parameters used are those of the NOH (no hydrogen) field developed by Still and implemented by Steliou in the program Model. The resulting lowest energy conformations were then submitted to MMX for the calculations of strain energies.[43] The calculations reveal a 5.73 kcal difference between the *endo* cycloadduct **28** and the diastereomer resulting from *exo* cycloaddition, a 3.96 kcal difference with **29**, and a 4.75 kcal difference with **42**. The large differences in strain energy between the diastereomers (and presumably the diastereomeric transition states) provides a reasonable explanation for why these internal isomünchnone reactions presumably proceed exclusively via the *endo* orientation.

Given the propensity for thioisomünchnones to undergo intramolecular 1,3-dipolar cycloaddition with simple π-bonds, we thought it worthwhile to examine whether intramolecular cycloaddition of this mesoionic system with heteroaromatic π-systems could be realized since this would be extremely useful from a synthetic point of view. While intramolecular 1,3-dipolar cycloaddition across heteroaromatic π-bonds is not commonly encountered, its occurrence has recently been reported.[44–47] With this in mind, thiolactam **44** was treated under the standard conditions for dipole formation and cycloaddition. No product of dipolar cycloaddition across the indole π-bond was detected in the reaction mixture. Instead, indole **46** was isolated in 89% yield. Compound **46** is derived by cyclization of the dipole precursor **45** onto the 2-position of the indole ring.[48] Apparently, attack by the nucleophilic π-bond onto the reactive *N*-acyl iminium ion present in **45** occurs faster than dipole formation.



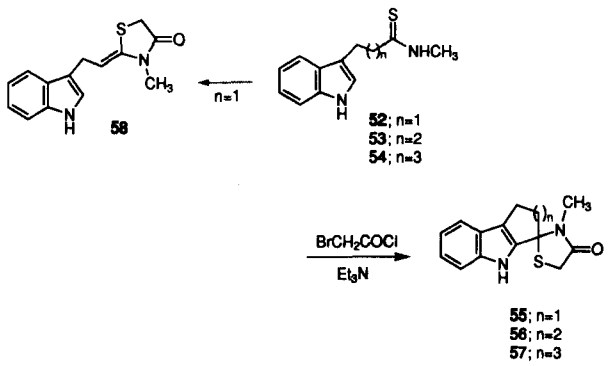
44 45 46

The same type of cyclization occurred when thioamides **47** and **48** were treated with bromoacetyl chloride in the presence of triethylamine. Once again the initially formed *N*-acyl iminium ion was attacked by the nucleophilic indole ring to give the spiro cyclized products **50** and **51**. As was pointed out earlier, thio *N*-acyl iminium ions of type **49** generally lose a proton to produce *S,N*-ketene acetals (i.e., **22** → **24**). In the above case, however, reaction with the nucleophilic indole ring is faster than proton loss.



47; R1=H; R2=CH3
48; R1=R2=(CH2)3
49
50; R1=H; R2=CH3
51; R1=R2=(CH2)3

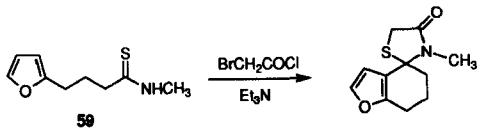
A related set of thioamide indoles, where the length of the tether was varied by one methylene unit, were also observed to undergo cyclization across the thio *N*-acyl iminium ion center. Thus, treatment of thioamides **52–54** under the standard conditions gave the spiro cyclized products **55–57** in 57%, 65% and 59% yield, respectively.



58
52; n=1
53; n=2
54; n=3
55; n=1
56; n=2
57; n=3

In the case of **52**, a small amount (6%) of *S,N*-ketene acetal **58** was also isolated and this compound was subsequently converted to **55** by stirring with trifluoroacetic acid. No signs of the homologous *S,N*-ketene acetals were observed with thioamides **53** and **54**, even when the reaction was carefully monitored by NMR spectroscopy. The formation of **58** from **52** is probably related to the greater ring strain imposed in the transition state for cyclization when a five-membered ring is involved. This allows for loss of the α-proton in competition with nucleophilic attack at the *N*-acyl iminium ion center.

In an effort to further extend the cyclization reaction to other heteroaromatic thioamides, we investigated the be-



59 60

havior of the related thioamide furan **59**. When **59** was heated in the presence of bromoacetyl chloride, the spiro cyclized furan **60** was obtained in 47% yield as a crystalline solid. The consistent formation of these spiro cyclized heteroaromatics points out the facility with which these unusual thio *N*-acyl iminium ion precursors undergo cyclization. Most importantly, intramolecular cycloaddition by a thioisomünchnone intermediate does not occur with these heteroaromatic systems. This observation strongly suggests that formation of the mesoionic thioisomünchnone betaine system from the reaction of bromoacetyl chloride and thioamides proceeds in a stepwise manner involving a thio *N*-acyl iminium ion precursor.

In conclusion, thioisomünchnones are easily accessible from thioamides and represent versatile mesoionic compounds which are useful in organic synthesis. The structurally diverse group of heterocyclic compounds that have been prepared by the intramolecular dipolar cycloaddition of these mesoionics clearly demonstrates the high potential they have in organic synthesis. We are continuing to explore the scope, generality, and synthetic applications of thioisomünchnone cycloaddition chemistry and will report additional findings at a later date.

We gratefully acknowledge the National Institutes of Health for generous support of our research program.

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in oven dried glassware under an atmosphere of dry N_2. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on silica gel column using an ethyl acetate–hexane mixture as the eluent unless specified otherwise. Satisfactory elemental analyses were obtained for all compounds; C ± 0.26, H ± 0.23, N ± 0.18, S ± 0.10 or HRMS ± 0.009.

Preparation and Rh(II) Catalyzed Reaction of *N*-(2-Diazo-1,3-dioxobutyl)pyrrolidine-2-thione (4):

To a solution of pyrrolidin-2-one (3.0 g, 35 mmol) in toluene (50 mL) was added Lawessons's reagent[39] (8.55 g, 21 mmol) and the resulting suspension was heated at reflux for 5 h. The solution was cooled to 25 °C and the solvent removed under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give pyrrolidine-2-thione (2.35 g, 66%) as a colorless solid; mp 110–111 °C.

IR ($CDCl_3$): ν = 1685, 1240 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.08 (quin, 2 H, J = 7.6 Hz), 2.79 (t, 2 H, J = 7.6 Hz), 3.55 (t, 2 H, J = 7.6 Hz), 9.26 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.5, 43.2, 49.5, 205.0.

To a solution of pyrrolidine-2-thione (0.50 g, 4.95 mmol) in dry THF (80 mL) at −78 °C under N_2 was added a 1.6 M BuLi solution (3.25 mL). The mixture was stirred for 60 min and then diketone (0.42 mL, 5.40 mmol) was added. The resulting solution was allowed to warm to 25 °C and poured into an aq sat. NH_4Cl solution (50 mL). The aqueous phase was separated and extracted with Et_2O. The combined organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give *N*-(1,3-dioxobutyl)pyrrolidine-2-thione (0.49 g, 54%) as a yellow oil.

IR (neat): ν = 1723, 1694, 1617 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.99 (quin, 2 H, J = 7.4 Hz), 2.19 (s, 3 H), 3.09 (t, 2 H, J = 7.4 Hz), 4.11 (t, 2 H, J = 7.4 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.1, 30.1, 49.9, 53.1, 53.6, 168.0, 200.4, 209.1.

A solution of 2-chloro-1-ethylpyridinium tetrafluoroborate (0.82 g, 3.57 mmol) in 70% aq MeOH solution (20 mL) was treated with sodium azide (0.23 g, 3.57 mmol) at −25 °C. After stirring for 10 min, a solution of *N*-(1,3-dioxobutyl)pyrrolidine-2-thione (0.55 g, 2.97 mmol) in 70% aq MeOH (3 mL) and anhydrous sodium acetate (0.29 g, 3.57 mmol) was added. The resulting solution was stirred for 18 h at −25 °C and was then allowed to warm to 25 °C and the solvent was removed under reduced pressure. The residue was taken up in water (20 mL) and extracted with Et_2O. The combined organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give *N*-(2-diazo-1,3-dioxobutyl)pyrrolidine-2-thione **(4)** (0.13 g, 21%) as a yellow solid; mp 82–83 °C.

IR (neat): ν = 2139, 1653, 1335 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.12 (quin, 2 H, J = 7.4 Hz), 2.48 (s, 3 H), 3.06 (t, 2 H, J = 7.4 Hz), 4.08 (t, 2 H, J = 7.4 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.3, 28.5, 47.5, 53.7, 83.2, 162.5, 189.2, 206.2.

A solution of **4** (67 mg, 0.32 mmol) and *N*-phenylmaleimide (83 mg, 0.48 mmol) in xylene (5 mL) was treated with a catalytic amount of rhodium(II) acetate and the solution was heated at reflux for 1 h. The solution was cooled to 25 °C and the solvent was removed under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 4-acetyl-4,9a-epithio-2,3a,4,7,8,9,9a,9b-octahydro-2-phenyl-1*H*-pyrrolo[3,4-*g*]indolizine-1,3,5-trione **(6)** (72 mg, 63%) as white crystals; mp 212–213 °C.

IR (neat): ν = 1721, 1510, 1396, and 1205 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.21–2.35 (m, 2 H), 2.42 (dt, 1 H, J = 14.2 and 5.9 Hz), 2.67 (s, 3 H), 2.67–2.78 (m, 1 H), 3.27 (dt, 1 H, J = 11.1 and 7.5 Hz), 3.57–3.62 (m, 1 H), 3.64 (d, 1 H, J = 6.9 Hz), 4.12 (d, 1 H, J = 6.9 Hz), 7.09–7.24 (m, 2 H), 7.39–7.48 (m, 3 H).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 26.1, 28.3, 28.5, 42.9, 49.9, 57.2, 81.7, 126.9, 129.2, 129.4, 132.0, 170.3, 173.4, 173.7, 199.8.

The reaction of **4** was also carried out in the absence of *N*-phenylmaleimide. A sample of **4** (89 mg, 0.42 mmol) in the presence of $Rh_2(OAc)_4$ in refluxing xylene (2 mL) gave thioisomünchnone **5** (60 mg, 78%) as a dark oil.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.45 (s, 3 H), 2.66 (quin, 2 H, J = 7.6 Hz), 3.28 (t, 2 H, J = 7.6 Hz), 4.09 (t, 2 H, J = 7.6 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.5, 26.1, 31.3, 47.5, 105.4, 158.1, 170.8, 189.2.

4-*tert*-Butyl-4,7-epithio-2,3a,4,5,7,7a-hexahydro-5-methyl-2-phenyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-trione (10):

To a solution of 2,2,*N*-trimethylthiopropanamide[49] **(7)** (0.10 g, 0.76 mmol) in xylene (10 mL) under N_2 was added bromoacetyl chloride (0.07 mL, 0.84 mmol) and the mixture was stirred for 3 h at 90 °C. The solution was cooled to 25 °C and treated with *N*-phenylmaleimide (0.20 g, 1.15 mmol) and triethylamine (0.21 mL, 1.53 mmol) and heated at reflux for 2 h. The solution was cooled to 25 °C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 4-*tert*-butyl-4,7-epithio-2,3a,4,5,7,7a-hexahydro-5-methyl-2-phenyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-trione **(10)** (0.14 g, 54%) as a white solid; mp 200–201 °C.

IR ($CHCl_3$): ν = 1716, 1499, 1385 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.00–1.24 (m, 9 H), 2.90 (s, 3 H), 3.44 (d, 1 H, J = 6.6 Hz), 3.57 (dd, 1 H, J = 6.6 and 1.1 Hz), 4.29 (d, 1 H, J = 1.1 Hz), 7.18–7.20 (m, 2 H), 7.37–7.46 (m, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.8, 30.1, 35.5, 49.8, 50.3, 50.7, 94.7, 126.2, 128.9, 129.1, 131.4, 172.9, 173.1, 175.9.

2,4-Diphenyl-4,7-epithio-2,3a,4,5,7,7a-hexahydro-5-methyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-trione (11):

To a solution of *N*-methylthiobenzamide[50] **(8)** (0.10 g, 0.66 mmol) in xylene (10 mL) under N_2 was added bromoacetyl chloride (0.06 mL, 0.73 mmol) and the mixture was stirred for 2 h at 50 °C.

The solution was treated with *N*-phenylmaleimide (0.17 g, 0.99 mmol) and triethylamine (0.18 mL, 1.32 mmol), and heated at reflux for 3 h. The solution was cooled to 25 °C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 2,4-diphenyl-4,7-epithio-2,3a,4,5,7,7a-hexahydro-5-methyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6-trione **(11)** (0.13 g, 64 %) as a white solid; mp 169–170 °C.

IR ($CHCl_3$): ν = 1719, 1379, 1105 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.40 (s, 3 H), 3.78 (d, 1 H, J = 6.7 Hz), 4.13 (d, 1 H, J = 6.7 Hz), 4.51 (s, 1 H), 7.16–7.47 (m, 8 H), 7.73–7.74 (m, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 27.1, 48.7, 52.6, 53.7, 86.3, 126.3, 128.7, 128.9, 129.1, 129.6, 130.2, 130.4, 131.4, 171.4, 172.5, 173.2.

3,6-Epithio-1-methyl-6-phenyl-5-phenylsulfonylpyridin-2-one (12):
To a solution of *N*-methylthiobenzamide **(8)** (0.24 g, 1.59 mmol) in xylene (20 mL) under N_2 was added bromoacetyl chloride (0.14 mL, 1.75 mmol) and the solution was stirred for 2 h at 50 °C. The mixture was treated with phenyl vinyl sulfone (0.32 g, 1.90 mmol) and triethylamine (0.44 mL, 3.17 mmol) and was heated at reflux for 2 h. The solution was cooled to 25 °C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give **12** (110 mg, 20 %) as a white solid; mp 170–171 °C.

IR ($CHCl_3$): ν = 1704, 1450, 1156 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.62 (ddd, 1 H, J = 13.0, 9.5, and 3.6 Hz), 2.82 (dd, 1 H, J = 13.0 and 3.6), 2.96 (s, 3 H), 4.04 (d, 1 H, J = 3.6 Hz), 4.80 (dd, 1 H, J = 9.5 and 3.6 Hz), 7.40–7.50 (m, 3 H), 7.58–7.75 (m, 5 H), 7.94–7.97 (m, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 30.3, 35.9, 51.5, 68.2, 85.6, 128.0, 128.3, 128.5, 129.5, 129.7, 131.8, 134.2, 140.3, 174.3.

10,10-Dimethyl-4,10a-epithio-1,2,3a,4,7,8,9,10,10a,10b-decahydro-2-phenyl-1,3,5-trioxopyrrolo[3,4-*a*]quinolizine (19):
To a flame dried 100 mL round bottom flask was added 3-methylpiperidin-2-one[51] (1.0 g, 8.85 mmol) and dry THF (25 mL) under N_2. After cooling to 0 °C, the solution was treated with a 1.57 M solution of BuLi in hexane (11.8 mL, 18.6 mmol). The resulting clear yellow solution was stirred for 60 min at 0 °C. The solution was cooled to − 78 °C and treated withMeI (0.61 mL, 9.73 mmol) in dry THF (5 mL). The solution was stirred for 15 min at − 78 °C and then warmed to 25 °C and quenched with a sat. aq NH_4Cl solution. The organic solution was concentrated under reduced pressure and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was recrystallized from CH_2Cl_2–hexane to give 3,3-dimethylpiperidin-2-one (1.08 g, 96 %) as a white solid; mp 102–103 °C.

IR ($CHCl_3$): ν = 1640, 1405 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.11 (s, 6 H), 1.53–1.58 (m, 2 H), 1.63–1.70 (m, 2 H), 3.18 (dt, 2 H, J = 6.0 and 2.2 Hz), 7.10 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.2, 27.0, 35.8, 37.5, 42.6, 178.7.

To a solution of the above lactam (3.0 g, 23.6 mmol) in xylene (85 mL) was added Lawesson's reagent[39] (4.77 g, 11.8 mmol) and the suspension was heated at reflux for 15 min. The resulting clear yellow solution was concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 3,3-dimethylpiperidine-2-thione **(18)** (2.60 g, 77 %) as a white solid; mp 115–116 °C.

IR ($CHCl_3$): ν = 1351 cm^{-1}.

^1H NMR ($CDCl_3$, 360 MHz): δ = 1.31 (s, 6 H), 1.62–1.65 (m, 2 H), 1.79–1.82 (m, 2 H), 3.22–3.26 (m, 2 H), 9.56 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.3, 30.6, 34.5, 41.5, 44.9, 211.4.

To a solution of **18** (0.10 g, 0.70 mmol) in xylene (10 mL) under N_2 was added bromoacetyl chloride (0.06 mL, 0.77 mmol) and the mixture was stirred 30 min at 25 °C. The solution was treated with *N*-phenylmaleimide (0.18 g, 1.05 mmol) and triethylamine, (0.19 mL, 1.40 mmol) and the resulting solution was heated at reflux for 2.5 h. The solution was cooled to 25 °C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 10,10-dimethyl-4,10a-epithio-1,2,3a,4,7,8,9,10,10a,10b-decahdyro-2-phenyl-1,3,5-trioxopyrrolo-[3,4-*a*]quinolizine **(19)** (0.18 g, 70 %) as a white solid; mp 165–166 °C.

IR ($CHCl_3$): ν = 1715, 1498, 1386 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.16 (s, 3 H), 1.50–1.57 (m, 4 H), 1.66–2.02 (m, 3 H), 2.74–2.85 (m, 1 H), 3.59 (d, 1 H, J = 6.7 Hz), 3.63 (dd, 1 H, J = 6.7 and 0.7 Hz), 4.31 (s, 1 H), 7.20–7.50 (m, 5 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.2, 23.4, 28.6, 33.6, 34.3, 34.6, 49.5, 51.9, 52.1, 90.1, 126.3, 129.0, 129.2, 131.5, 127.27, 173.1, 173.2.

2,3,5,6,7,7a,8,9,9a,9b-Decahydro-2,9b-epithio-7a-methyl-3-oxo-1*H*-cyclopenta[*i*,*j*]quinolizine (28):
A solution of 3-methylpiperidin-2-one[51] (2.98 g, 26.3 mmol) in dry THF (150 mL) was cooled to 0 °C under N_2. To this solution was added a 1.60 M BuLi solution in hexane (36.2 mL, 56.9 mmol). The resulting solution was stirred at 0 °C for 1 h and then a solution containing 4-bromobut-1-ene (4.97 g, 31.6 mmol) in dry THF (15 mL) was added via syringe. The solution was stirred for 45 min at 0 °C, warmed to 25 °C and stirred for an additional 1 h. At the end of this time, the reaction was quenched with NH_4Cl solution (10 mL). Additional water (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 3-(but-3-enyl)-3-methylpiperidin-2-one (3.67 g, 85 %) as a white crystalline solid; mp 62–63 °C.

IR ($CHCl_3$): ν = 1652, 1489 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.13 (s, 3 H), 1.40–1.58 (m, 2 H), 1.64–1.80 (m, 4 H), 1.88–2.08 (m, 2 H), 3.20 (s, 2 H), 4.80–5.00 (m, 2 H), 5.73 (ttq, 1 H, J = 16.8, 10.1 and 6.6 Hz), 6.82 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.3, 25.6, 28.5, 32.5, 38.6, 40.8, 42.5, 114.2, 138.6, 177.9.

A sample of 3-(but-3-enyl)-3-methylpiperidine-2-thione (**26**; 78 %) was prepared from the above lactam using Lawesson's reagent.[39]

IR (neat): ν = 1640, 1559, 1354 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.33 (s, 3 H), 1.47–1.63 (m, 1 H), 1.65–1.83 (m, 4 H), 1.94–2.08 (m, 3 H), 3.05–3.38 (m, 2 H), 4.91 (d, 1 H, J = 10.2 Hz), 4.99 (d, 1 H, J = 17.2 Hz), 5.71–5.89 (m, 1 H), 9.16 (bs, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.5, 28.5, 29.6, 31.1, 41.6, 45.0, 45.2, 114.4, 138.5, 211.3.

A solution of thione **26** (216 mg, 1.18 mmol) in xylene (5 mL) was stirred under N_2 and bromoacetyl chloride (204 mg, 1.30 mmol) in xylene (2 mL) was added dropwise. After stirring for 75 min at 25 °C, the solution was placed in an oil bath preheated to 170 °C and triethylamine (250 mg, 2.48 mmol) in xylene (2 mL) was immediately added. The solution was heated at reflux for 2.75 h and was then allowed to cool to 25 °C. The solution was filtered through a fritted glass funnel to remove the ammonium salts and the precipitate was rinsed with toluene (5 mL). The combined organic layer was concentrated under reduced pressure and the residue was subjected to flash silica gel chromatography to give 2,3,5,6,7,7a,8,9,9a,9b-decahydro-2,9b-epithio-7a-methyl-3-oxo-1*H*-cyclopenta[*ij*]quinolizine **(28)** (184 mg, 70 %) as a white crystalline solid; mp 101–102 °C.

IR (KBr): ν = 1695, 1453, 1360 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.19 (s, 3 H), 1.35–1.75 (m, 5 H), 1.80–2.03 (m, 4 H), 2.19 (dd, 1 H, J = 12.5 and 8.0 Hz), 2.50–2.70 (m, 2 H), 3.50–3.65 (m, 1 H), 3.84 (d, 1 H, J = 2.9 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.7, 25.2, 28.6, 35.8, 36.8, 37.0, 39.4, 41.7, 47.4, 54.7, 95.9, 177.4.

A solution of molybdenum hexacarbonyl[35] (263 mg, 0.997 mmol) was suspended in acetic acid (1 mL) and the mixture was heated at reflux for 10 min. At the end of this time, **28** (149 mg, 0.665 mmol) in acetic acid (1 mL) was added to the refluxing mixture. The reaction mixture was heated at reflux for 16 h and was then allowed to cool to 25 °C. The solvent was removed under reduced pressure and

the residue was subjected to flash silica gel chromatography to give 7a-methyl-1,2,5,6,7,7a,8,9-octahydro-3*H*-cyclopenta[*ij*]quinolizin-3-one (92 mg, 73%) **(30)** as a pale yellow oil.

IR (neat): ν = 1697, 1664, 1452 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.97 (s, 3H), 1.20 (dt, 1H, J = 13.6 and 5.4 Hz), 1.50–1.72 (m, 4H), 1.77 (dd, 1H, J = 11.9 and 6.6 Hz), 1.92–2.09 (m, 2H), 2.18–2.38 (m, 2H), 2.38–2.57 (m, 2H), 2.74 (1H, J = 12.8 and 5.3 Hz), 3.92 (dd, 1H, J = 12.7 and 4.1 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.9, 20.6, 22.4, 29.0, 32.0, 35.9, 40.3, 40.8, 41.7, 113.7, 141.6, 170.3.

To a solution of **28** (133 mg, 0.558 mmol) in CH_2Cl_2 (2 mL) was added a solution of 50% MCPBA (310 mg, 0.913 mmol) in CH_2Cl_2 (2.5 mL). The solution was stirred for 12 h at 25 °C and was then washed with a sat. $NaHCO_3$ (5 mL) solution, followed by brine (5 mL). The combined organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure to provide a yellow solid. This material was dissolved in toluene (10 mL) and heated at 200 °C for 6.5 h. At the end of this time the solution was allowed to cool to 25 °C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 7a-methyl-5,6,7,7a,8,9-hexahydro-3*H*-cyclopenta[*ij*]quinolizin-3-one **(32)** (59 mg, 52%) as a pale yellow oil.

IR (neat) 1649, 1578, 1453 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.15 (s, 3H), 1.53 (dt, 1H, J = 12.3 and 4.9 Hz), 1.80–2.22 (m, 5H), 2.50 (dd, 1H, J = 14.8 and 8.3 Hz), 2.77 (ddd, 1H, J = 14.8, 10.5, and 6.4 Hz), 3.78 (ddd, 1H, J = 14.9, 9.2 and 6.5 Hz), 3.95 (ddd, 1H, J = 14.9, 6.8, and 3.9 Hz), 6.34 (d, 1H, J = 9.0 Hz), 7.23 (d, 1H, J = 9.0 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.4, 23.3, 26.7, 32.4, 40.7, 41.6, 116.1, 116.5, 137.2, 154.2, 163.4.

2,3,6,7,7a,8,9,10,10a,10b-Decahydro-2,10b-epithio-7a-methyl-3-oxo-1*H*,5*H*-benzo[*ij*]quinolizine (29):

A solution of 3-methylpiperidin-2-one[51] (6.96 g, 61.5 mmol) in dry THF (200 mL) was cooled to 0 °C under N_2. To this solution was added 1.60 M BuLi solution in hexane (85 mL, 135 mmol). The solution was stirred at 0 °C for 1 h and then a solution of 5-bromopent-1-ene (10.4 g, 76.9 mmol) in dry THF (15 mL) was added via syringe. The solution was stirred for 45 min at 0 °C and was then warmed to 25 °C and stirred for an additional 1 h. At the end of this time, the reaction was quenched with sat. NH_4Cl solution (10 mL). Additional water (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 3-(pent-4-enyl)-3-methylpiperidin-2-one (8.87 g; 80%) as a white crystalline solid; mp 56–57 °C.

IR ($CHCl_3$): ν = 1645, 1489 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.10 (s, 3H), 1.20–1.50 (m, 4H), 1.58–1.80 (m, 4H), 1.90–2.03 (m, 2H), 3.20 (s, 2H), 4.80–5.00 (m, 2H), 5.73 (ttq, 1H, J = 16.9, 10.0 and 6.7 Hz), 6.96 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.3, 23.3, 25.5, 32.3, 34.1, 39.0, 40.9, 42.5, 114.3, 138.5, 178.1.

A sample of 3-(pent-4-enyl)-3-methylpiperidine-2-thione (**27**; 73%) was prepared from the above lactam using Lawesson's reagent[39].

IR (neat): ν = 1555, 1351 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.30–1.40 (m, 2H), 1.30 (s, 3H), 1.47–1.68 (m, 2H), 1.71–2.07 (m, 6H), 3.14–3.40 (m, 2H), 4.91 (dd, 1H, J = 10.3 and 0.8 Hz), 4.97 (dd, 1H, J = 17.3 and 1.3 Hz), 5.68–5.88 (m, 1H), 9.24 (bs, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.5, 23.5, 29.6, 31.1, 34.1, 42.1, 45.0, 45.2, 114.5, 138.6, 211.5.

A solution of thione **27** (112 mg, 0.568 mmol) in xylene (5 mL) was stirred under N_2 and then bromoacetyl chloride (89 mg, 0.57 mmol) in xylene (2 mL) was added. The solution was allowed to stir overnight at 25 °C and was heated to reflux and triethylamine (115 mg) in xylene (2 mL) was immediately added. The solution was heated at reflux for 90 min and then allowed to cool to 25 °C. The mixture was filtered through a Celite pad which was rinsed with toluene (5 mL). The combined organic layer was concentrated under reduced pressure and the residue was subjected to flash chromatography to give 2,3,6,7,7a,8,9,10,10a,10b-decahydro-2,10b-epithio-7a-methyl-3-oxo-1*H*,5*H*-benzo[*ij*]quinolizine **(29)** (109 mg, 81%) as a white solid: mp 135–136 °C.

IR (KBr): ν = 1700, 1440, 1353 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.14 (s, 3H), 1.22–1.33 (m, 1H), 1.35–1.74 (m, 7H), 1.76–2.00 (m, 3H), 2.08–2.22 (m, 2H), 2.53 (dt, 1H, J = 12.7 and 4.3 Hz), 3.65–3.78 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.9, 20.9, 28.7, 31.6, 33.5, 34.2, 37.6, 37.7, 39.1, 39.4, 50.5, 88.8, 178.2.

A solution of molybdenum hexacarbonyl[35] (110 mg, 0.403 mmol) was suspended in acetic acid (1 mL) and was heated at reflux for 1 h under N_2. At the end of this time **29** (64 mg, 0.268 mmol) in acetic acid (0.5 mL) was added via syringe to the refluxing solution. After heating for 10 h, the reaction mixture was allowed to cool to 25 °C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 7a-methyl-1,2,6,7,8,9,10-octahydro-3*H*,5*H*-benzo[*ij*]quinolizin-3-one **(31)** (46 mg, 84%) as a colorless oil.

IR (neat): ν = 1655, 1375, 1210 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.03 (s, 3H), 1.20–1.37 (m, 1H), 1.39–1.62 (m, 5H), 1.64–1.87 (m, 3H), 1.95 (dd, 1H, J = 17.4 and 6.1 Hz), 2.08–2.38 (m, 4H), 2.76 (dt, 1H, J = 12.6 and 4.5 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.5, 19.1, 25.1, 25.4, 29.0, 31.0, 31.9, 36.7, 37.9, 40.7, 114.3, 136.2, 170.4.

To a solution of **29** (197 mg, 0.83 mmol) in CH_2Cl_2 (5 mL) was added a solution of 50% MCPBA (310 mg, 0.91 mmol) in CH_2Cl_2 (5 mL). The solution was stirred for 2 h at 25 °C and was then washed with sat. solutions of $NaHSO_3$ (5 mL) and $NaHCO_3$ (5 mL). The combined organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure to provide a yellow solid. This material was dissolved in toluene (10 mL) and the mixture was heated at 200 °C for 5 h. At the end of this time the solution was allowed to cool to 25 °C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 6,7,7a,8,9,10-hexahydro-3*H*,5*H*-benzo[*ij*]quinolin-3-one **(33)** (89 mg, 53%) as a clear oil.

IR (neat): ν = 1645, 1630, 1520 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.17 (s, 3H), 1.37–1.56 (m, 2H), 1.60–1.73 (m, 5H), 1.98–2.15 (m, 1H), 2.45–2.55 (m, 2H), 3.70 (dt, 1H, J = 14.7 and 7.3 Hz), 4.35 (dt, 1H, J = 17.7 and 7.3 Hz), 6.31 (d, 1H, J = 9.2 Hz), 6.97 (d, 1H, J = 9.1 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.1, 17.7, 25.4, 26.5, 33.0, 37.7, 39.5, 111.6, 116.2, 140.4, 147.7, 162.4.

1(*β*),2(*β*),6,7,7a(*β*),8,9,9a(*α*),9(*β*)-Decahydro-2,9-epithio-7a-ethyl-1-phenyl-3*H*-cyclopenta[*ij*]quinolizin-3-one (42):

A sample of 3-(3-butenyl)piperidin-2-one was prepared in 91% yield as a white solid, mp 56–57 °C, from 2-piperidin-2-one and 4-bromobut-1-ene.

IR (KBr): ν = 1655, 1500, 1470 925 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.42–2.21 (m, 9H), 3.12 (m, 2H), 4.89 (d, 1H, J = 10.3 Hz), 4.96 (d, 1H, J = 16.9 Hz), 5.74 (m, 1H), 7.16 (brs, 1H).

^{13}C NMR ($CDCl_3$): δ = 21.2, 25.9, 30.6, 31.1, 40.2, 42.2, 114.8, 138.2, 175.4.

This lactam was converted into 3-(3-butenyl)-3-ethylpipridin-2-one in 63% yield by alkylation with iodoethane.

IR (neat): ν = 1651, 1483, 905 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.71 (t, 3H, J = 7.4 Hz), 1.33 (m, 2H), 1.55 (m, 6H), 1.88 (m, 2H), 3.07 (s, 2H), 4.74 (d, 1H, J = 10.0 Hz), 4.83 (d, 1H, J = 17.4 Hz), 5.61 (m, 1H), 7.31 (brs, 1H).

^{13}C NMR ($CDCl_3$): δ = 8.5, 19.8, 28.6, 29.0, 30.2, 31.1, 37.4, 42.3, 44.2, 114.1, 138.7, 177.2.

This lactam was converted into 3-(but-3-ynyl)-3-ethylpiperidin-2-one **(34)** in 73% yield by reaction with bromine followed by dehydrobromination using 5 equiv of $KN(TMS)_2$; mp 87–88°C.

IR (KBr): ν = 1651, 839, 707 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.87 (t, 3H, J = 7.4 Hz), 1.52 (sex, 1H, J = 7.2 Hz), 1.67–1.80 (m, 6H), 1.92 (m, 2H), 2.23 (m, 2H), 3.26 (m, 2H), 6.12 (brs, 1H).

^{13}C NMR ($CDCl_3$): δ = 8.4, 14.0, 19.6, 29.1, 30.5, 36.9, 42.5, 44.4, 68.1, 84.7, 176.4.

3-Ethyl-3-(4-phenylbut-3-ynyl)piperidin-2-one **(36)** was prepared in 95% yield as a white solid, mp 94–95°C, by a Castro–Stevens reaction[37] of the above alkyne and iodobenzene.

IR (KBr): ν = 1651, 1483, 751, 685 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.88 (t, 3H, J = 7.4 Hz), 1.54 (m, 1H), 1.69–1.84 (m, 6H), 2.00 (m, 1H), 2.44 (t, 2H, J = 8.1 Hz), 3.34 (s, 2H), 6.68 (brs, 1H), 7.23 (m, 2H), 7.33 (m, 3H).

^{13}C NMR ($CDCl_3$): δ = 8.3, 14.8, 19.5, 28.19, 30.5, 36.8, 42.3, 44.2, 80.3, 90.1, 123.7, 127.3, 128.0, 131.2, 176.4.

3-Ethyl-3[(*Z*)-4-phenylbut-3-enyl]piperidin-2-one **(38)** was prepared in 96% yield as a colorless oil by nickel boride catalyzed hydrogenation[38] of the above compound.

IR (KBr): ν = 1651, 1490, 693 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.84 (t, 3H, J = 7.4 Hz), 1.41–1.87 (m, 8H), 2.19–2.42 (m, 2H), 3.16 (s, 2H), 5.59 (dt, 1H, J = 11.4 and 7.4 Hz), 6.35 (d, 1H, J = 11.4 Hz), 6.95 (brs, 1H), 7.13–7.31 (m, 5H).

^{13}C NMR ($CDCl_3$): δ = 8.4, 19.6, 23.4, 28.7, 30.9, 38.0, 42.2, 44.4, 126.2, 127.9, 128.4, 128.6, 132.41, 137.3, 176.9.

3-Ethyl-3-[(*Z*)-4-phenylbut-3-enyl]piperidine-2-thione **(40)** was prepared from the above lactam using Lawesson's reagent[39] in 93% yield as a colorless oil.

IR (KBr): ν = 1549, 1439, 1351, 1073, 693 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.87 (t, 3H, J = 7.4 Hz), 1.60 (m, 6H), 1.98 (m, 1H), 2.13 (m, 1H), 2.33 (m, 2H), 3.24 (m, 2H), 5.61 (dt, 1H, J = 11.4 and 7.3 Hz), 6.35 (d, 1H, J = 11.4 Hz), 7.16–7.33 (m, 5H), 9.30 (brs, 1H).

^{13}C NMR ($CDCl_3$): δ = 8.5, 19.3, 23.5, 27.2, 34.9, 41.8, 44.9, 48.5, 126.3, 127.9, 128.5, 128.8, 132.3, 137.3.

Treatment of the above thiolactam with bromoacetyl chloride in the standard manner gave cycloadduct **42** in 85% yield as white solid, mp 173–174°C.

IR (KBr): ν = 1690, 1452, 1353, 1267, 704 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.86 (t, 3H, J = 7.4 Hz), 1.03–1.19 (m, 1H), 1.21–1.34 (m, 2H), 1.43 (m, 1H), 1.63 (m, 3H), 1.82 (td, 1H, J = 12.4 and 2.4 Hz), 1.92–2.03 (m, 2H), 2.76 (m, 1H), 3.14 (dq, 1H, J = 8.3 and 3.0 Hz), 3.67 (t, 2H, J = 8.3 Hz), 4.06 (s, 1H), and 7.23 (m, 5H).

^{13}C NMR ($CDCl_3$): δ = 9.3, 18.9, 25.3, 29,9, 30.5, 37.8, 40.0, 40.3, 47.6, 53.0, 57.4, 96.3, 126.2, 127.7, 128.0, 138.8, 177.5.

1(*β*),2(*β*),6,7,7a(*β*),8,9,10,10a(*α*),10b(*β*)-Decahydro-2,10b-epithio-7a-ethyl-1-phenyl-3*H*,5*H*-benzo[*ij*]quinolizin-3-one (43):
A sample of (pent-4-enyl)piperidin-2-one was prepared in 92% yield as a white solid, mp 46–47°C, from piperidin-2-one and 5-bromopent-1-ene.

IR (KBr): ν = 1655, 1495, 1360, 920 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.32–1.49 (, 4H), 1.62 (m, 2H), 1.80 (m, 3H), 1.98 (m, 2H), 2.16 (m, 1H), 3.20 (m, 2H), 4.77 (d, 1H, J = 10.2 Hz), 4.87 (d, 1H, J = 17.0 Hz), 5.72 (m, 1H), 7.12 (brs, 1H).

^{13}C NMR ($CDCl_3$): δ = 21.0, 25.8, 26.1, 30.9, 33.5, 40.6, 42.0, 114.2, 138.4, 175.1.

This lactam was converted into 3-ethyl-3-(pent-4-enyl)piperidin-2-one in 66% yield by alkylation with iodoethane.

IR (neat): ν = 1651, 1490, 1454, 905 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.75 (t, 3H, J = 7.4 Hz), 1.23–1.40 (cm, 5H), 1.50–1.64 (m, 5H), 1.90 (q, 2H, J = 6.6 Hz), 3.11 (m, 2H), 4.80 (dd, 1H, J = 11.0 and 1.5 Hz), 4.86 (dd, 1H, J = 17.3 and 1.5 Hz), 5.66 (m, 1H), 6.98 (brs, 1H).

^{13}C NMR ($CDCl_3$): δ = 8.4, 19.6, 23.4, 28.8, 30.9, 34.0, 37.7, 42.2, 44.2, 114.1, 138.4, 177.2.

This amide was converted into 3-ethyl-3-(pent-4-ynyl)piperidin-2-one **(35)** in 56% yield by reaction with bromine followed by dehydrobromination using 5 equiv of KN $(TMS)_2$.

IR (neat): ν = 3300, 2112, 1651 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.77 (t, 3H, J = 7.4 Hz), 1.15–2.07 (m, 12H), 3.13 (m, 2H), 4.53 (m, 1H), 6.90 (brs, 1H).

^{13}C NMR ($CDCl_3$): δ = 8.3, 18.7, 19.6, 23.3, 28.9, 30.8, 37.3, 42.2, 44.1, 68.1, 84.0, 176.9.

3-Ethyl-3-(5-phenylpent-4-ynyl)piperidin-2-one **(37)** was prepared as a yellow oil by a Castro–Stevens reaction[37] of the above alkyne and iodobenzene.

IR (neat): 1651, 1483, 751, 685 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.86 (t, 3H, J = 7.4 Hz), 1.42–1.74 (m, 10H), 2.34 (t, 2H, J = 5.5 Hz), 3.20 (m, 2H), 6.83 (brs, 1H), 7.23 (m, 3H), 7.34 (m, 2H).

^{13}C NMR ($CDCl_3$): δ = 8.7, 19.9, 20.0, 23.9, 29.2, 31.1, 37.7, 42.5, 44.5, 80.1, 90.1, 124.0, 127.5, 128.1, 131.5, 177.2.

3-Ethyl-3-[(*Z*)-5-phenylpent-4-enyl]piperidin-2-one **(39)** was prepared in 82% yield as a colorless oil by nickel boride catalyzed hydrogenation[38] of the above compound.

IR (neat): ν = 1651, 1483 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.86 (t, 3H, J = 7.4 Hz), 1.47 (m, 4H), 1.69 (m, 6H), 2.31 (q, 2H, J = 7.2 Hz), 3.20 (m, 2H), 5.64 (dt, 1H, J = 11.7 and 7.2 Hz), 6.35 (d, 1H, J = 11.7 Hz), 6.59 (brs, 1H), 7.24 (m, 5H).

^{13}C NMR ($CDCl_3$): δ = 8.7, 20.0, 24.8, 29.1, 29.2, 31.2, 38.1, 42.6, 44.7, 126.4, 128.1, 128.7, 128.9, 132.8, 137.7, 177.3.

3-Ethyl-3[(*Z*)-5-phenylpent-4-enyl)piperidine-2-thione **(41)** was prepared from the above lactam using Lawesson's reagent[39] in 82% yield as a yellow oil.

IR (neat): ν = 1549, 1344, 1073, 693 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.85 (t, 3H, J = 7.4 Hz), 1.25–1.76 (m, 8H), 1.96 (m, 2H), 2.32 (q, 2H, J = 7.0 Hz), 3.21 (m, 2H), 5.66 (dt, 1H, J = 11.7 and 7.0 Hz), 6.39 (d, 1H, J = 11.7 Hz), 7.25 (m, 5H), 9.59 (brs, 1H).

^{13}C NMR ($CDCl_3$): δ = 8.8, 19.6, 24.8, 27.6, 29.2, 35.2, 42.0, 45.1, 48.7, 126.5, 128.1, 128.8, 129.0, 132.7, 138.0, and 210.5.

Treatment of the above thiolactam with bromoacetyl chloride in the standard manner gave cycloadduct **43** in 88% yield as a white solid, mp 183–184°C.

IR (KBr): ν = 1695, 1358, 700 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.81 (t, 3H, J = 7.4 Hz), 0.92 (m, 1H), 1.08–1.25 (m, 3H), 1.39 (m, 2H), 1.52 (d, 1H, J = 7.7 Hz), 1.69 (m, 4H), 4.11 (sex, 1H, J = 7.4 Hz), 2.66 (m, 2H), 3.42 (d, 1H, J = 8.4 Hz), 3.83 (m, 2H), 7.23 (m, 5H).

^{13}C NMR ($CDCl_3$): δ = 7.4, 18.5, 20.2, 26.3, 30.2, 32.7, 33.4, 36.8, 40.3, 44.7, 48.8, 55.0, 89.8, 126.6, 127.9, 128.3, 138.5, 177.7.

Indolo[1,2-*a*]-6a-methyl-octahydro-1-thia-3a-azacyclopenta[*d*]naphthylen-3-one (46):
To a flame dried 250 mL round bottom flask was added (1.95 g, 17.3 mmol) of 3-methylpiperidin-2-one[51] and dry THF (100 mL) under N_2. The solution was cooled to 0°C and treated with a 2.1 M solution of butyllithium in hexane (17.3 mL, 36.4 mmol) and the mixture was allowed to stir for 60 min at 0°C. The clear yellow solution was treated with 1-(2-iodoethyl)-1*H*-indole (4.9 g, 19.1 mmol) in dry THF (10 mL). The solution was allowed to warm to 25°C and was stirred overnight. The reaction was quenched with sat. aq. NH_4Cl and the organic solution was concentrated under reduced pressure. The aqueous phase was extracted with CH_2Cl_2 (15 mL) and the combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and the solvent was removed under

reduced pressure. The residue was subjected to flash silica gel chromatography to give 3-(2-indol-1-yl)ethyl-3-methylpiperidin-2-one (1.32 g, 30%) as a clear oil.

IR (neat): ν = 1657, 1489, 1319 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.32 (s, 3H), 1.58–1.83 (m, 4H), 1.91–2.01 (m, 1H), 2.16–2.26 (m, 1H), 3.20–3.31 (m, 2H), 4.11–4.33 (m, 2H), 6.52 (d, 1H, J = 3.1 Hz), 7.11 (d, 1H, J = 3.1 Hz), 7.10–7.16 (m, 1H), 7.22–7.27 (m, 1H), 7.41–7.44 (m, 1H), 7.46 (s, 1H), 7.65–7.67 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.8, 25.5, 32.8, 39.6, 39.8, 42.2, 42.3, 100.8, 109.2, 118.9, 120.6, 121.1, 127.4, 128.3, 135.5, 176.8.

To a solution of the above compound (0.99 g, 3.87 mmol) in toluene (13 mL) was added Lawessons's reagent[39] (0.78 g, 1.93 mmol) and the resulting suspension was heated at reflux for 15 min. The clear yellow solution was cooled to 25°C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give (0.72 g, 69%) of 3-(2-indol-1-yl)ethyl-3-methylpiperidine-2-thione **(44)** as a yellow solid; mp 121–122°C.

IR (neat): ν = 1734, 1559, 1456, 1354 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.38 (s, 3H), 1.55–1.80 (m, 4H), 1.95–2.05 (m, 1H), 2.56–2.62 (m, 1H), 3.07–3.27 (m, 2H), 4.20 (t, 2H, J = 8.1 Hz), 6.52 (d, 1H, J = 3.2 Hz), 7.14 (d, 1H, J = 3.2 Hz), 7.11–7.16 (m, 1H), 7.23–7.28 (m, 1H), 7.52–7.55 (m, 1H), 7.64–7.67 (m, 1H), 9.72 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.0, 29.8, 30.8, 42.0, 42.2, 43.7, 45.0, 100.7, 109.2, 118.8, 120.4, 120.9, 127.4, 128.1, 135.4, 208.5

To a solution of the above indole (0.125 g, 0.46 mmol) in xylene (12 mL) was added bromoacetyl chloride (0.042 mL, 0.51 mmol) under N_2 and the mixture was stirred for 45 min. The solution was treated with triethylamine (0.128 mL, 0.92 mmol) and heated at reflux for 2 h and then cooled to 25°C and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give indolo[1,2-*a*]-6a-methyl-octahydro-1-thia-3a-azacyclopenta[*d*]naphthylen-3-one **(46)** (128 mg, 89%) as a yellow oil.

IR (neat): ν = 1685, 1277, 1217 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.28 (s, 3H), 1.43–1.53 (m, 2H), 1.65 (dt, 1H, J = 13.3 and 3.7 Hz), 1.74–1.84 (m, 1H), 1.92 (dd, 1H, J = 14.6 and 5.2 Hz), 2.35 (dt, 1H, J = 13.3 and 6.7 Hz), 2.98 (dt, 1H, J = 13.3 and 3.7 Hz), 3.64 (d, 1H, J = 15.5 Hz), 3.82 (d, 1H, J = 15.5 Hz), 3.89 (dt, 1H, J = 12.6 and 5.2 Hz), 4.22 (dd, 2H, 12.6 and 6.7 Hz), 6.29 (s, 1H), 7.09–7.30 (m, 3H), 7.54–7.57 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.6, 22.3, 30.8, 32.9, 37.3, 38.3, 40.3, 72.9, 97.6, 109.4, 120.4, 120.7, 121.7, 128.3, 136.4, 139.1, 170.4.

Spiro[6,7,8,9-tetrahydropyrido[1,2-*a*]indole-9,2′-3′-methylthiazolidin-4′-one] (50):

To a solution of 4-(indol-1-yl)-*N*-methylbutyramide (1.62 g, 7.5 mmol) in toluene (25 mL) was added Lawesson's reagent[39] (1.52 g, 3.75 mmol) and the suspension was heated at reflux for 15 min. The clear yellow solution was cooled to 25°C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 4-(indol-1-yl)-*N*-methylthiobutyramide **(47)** (1.0 g, 57%) as a yellow oil.

IR (neat): ν = 1512, 1464 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.23–2.40 (m, 4H), 2.93 and 2.94 (s, 3H), 4.12 (t, 2H, J = 6.4 Hz), 6.50 (d, 1H, J = 2.5 Hz), 7.05 (d, 2H, J = 2.5 Hz), 7.09–7.33 (m, 4H), 7.62–7.65 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.1, 32.6, 42.2, 44.7, 101.1, 109.3, 119.2, 120.7, 121.3, 127.6, 128.2, 135.7, 204.0.

To a solution containing the above thioamide (0.13 g, 0.57 mmol) xylene (10 mL) was added bromoacetyl chloride (0.051 mL, 0.62 mmol) under N_2 and the mixture was stirred for 3 h at 25°C. The solution was treated with triethylamine (0.16 mL, 1.14 mmol) and heated at reflux for 2 h. The solution was cooled to 25°C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give spiro[6,7,8,9-tetrahydropyrido[1,2-*a*]indole-9,2′-3′-methylthiazolidin-4′-one **(50)** (0.061 g, 41%) as a yellow oil.

IR (neat): 1665, 1440, 1245 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.20–2.48 (m, 4H), 2.89 (s, 3H), 3.70 (d, 1H, J = 15.5 Hz), 3.82 (d, 1H, J = 15.5 Hz), 3.76–3.85 (m, 1H), 4.28–4.34 (m, 1H), 6.34 (s, 1H), 7.12–7.31 (m, 3H), 7.57–7.60 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.2, 28.7, 32.1, 34.3, 41.2, 68.8, 97.9, 109.3, 120,3, 120.7, 121.8, 127.5, 136.4, 137.4, 171.1.

Indolo[1,2-*a*]-octahydro-1-thia-3a-azacyclopenta[*d*]naphthylen-3-one (51):

To a solution of 3-(2-indol-1-yl)ethylpiperidin-2-one (2.95 g, 12.2 mmol) in toluene (50 mL) was added Lawesson's reagent[39] (2.46 g, 6.1 mmol) and the mixture was heated at reflux for 45 min. The clear yellow solution was cooled to 25°C and the solvent was removed under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 3-(2-indol-1-yl)ethylpiperidine-2-thione **(48)** (2.0 g, 63%) as a light yellow solid; mp 79–80°C.

IR (neat): ν = 1577, 1551, 1472 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.40–1.53 (m, 1H), 1.63–1.88 (m, 3H), 2.15 (quin, 1H, J = 7.5 Hz), 2.60–2.72 (m, 2H), 3.18–3.27 (m, 2H), 4.37 (t, 2H, J = 7.2 Hz), 6.52 (d, 1H, J = 3.0 Hz), 7.09–7.25 (m, 2H), 7.21 (d, J = 3.0 Hz), 7.45–7.48 (m, 1H), 7.663–7.66 (m, 1H), 9.32 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.5, 25.6, 35.3, 43.7, 44.2, 44.3, 101.0, 109.0, 118.5, 120.7, 121.3, 128.4, 135.8, 205.5.

To a solution of **48** (0.20 g, 0.77 mmol) in dry CH_2Cl_2 (20 mL) was added bromoacetyl chloride (0.07 mL, 0.85 mmol) under N_2 and the mixture was stirred at 25°C for 1.25 h. The solution was treated with triethylamine (0.22 mL, 1.55 mmol) and heated at reflux for 2 h. The solution was cooled to 25°C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give indolo[1,2-*a*]-octahydro-1-thia-3a-azacyclopenta[*d*]naphthylen-3-one **(51)** (0.148 g, 65%) as a white solid; mp 151–152°C.

IR (neat): ν = 1685, 1470, 1410 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.40 (dt, 1H, J = 13.0 and 2.6 Hz), 1.50–1.68 (m, 1H), 1.70–1.82 (m, 2H), 2.14 (dt, 1H, J = 14.3 and 3.9 Hz), 2.30–2.42 (m, 1H), 2.48–2.62 (m, 1H), 2.81 (dt, 1H, J = 12.5 and 3.1 Hz), 3.66 (d, 1H, J = 15.6 Hz), 3.86 (d, 1H, J = 15.6 Hz), 3.81–3.92 (m, 1H), 4.20–4.27 (m, 2H), 6.29 (s, 1H), 7.10–7.31 (m, 3H), 7.55–7.58 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.3, 25.1, 25.6, 32.5, 37.7, 40.2, 42.3, 68.0, 97.3, 109.5, 120.5, 120.8, 122.0, 128.0, 136.9, 137.5, 170.3.

Spiro[1,2,3,4-tetrahydrocyclopenta[*b*]indole-3,2′,3′-methylthiazolidin-4′-one] (55):

To a solution of 3-(1*H*-indol-3-yl)propionic acid (4.0 g, 21.1 mmol) in dry THF (100 mL) was added 1,1′-carbonyldiimidazole (3.6 g, 22.2 mmol) under N_2 and the mixture was stirred for 4 h at 25°C. The solution was treated with 40% aq methylamine solution (200 mL) and was stirred overnight. The excess methylamine and solvent were removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (15 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 3-(1*H*-indol-3-yl)-*N*-methylpropionamide (4.16 g, 98%) as a yellow oil.

IR (neat): ν = 1727, 1651, 1458, 1412 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.51 (t, 2H, J = 7.6 Hz), 2.63 and 2.65 (s, 3H), 4.15 (t, 2H, J = 7.6 Hz), 6.47–6.49 (m, 1H), 6.86 (s, 1H), 7.05–7.20 (m, 2H), 7.30–7.35 (m, 1H), 7.54–7.58 (m, 1H), 9.34 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.1, 25.9, 37.0, 111.1, 113.9, 118.2, 118.5, 121.3, 121.6, 126.8, 136.2, 173.9.

To a solution of the above compound (4.0 g, 19.8 mmol) in toluene (70 mL) was added Lawesson's reagent[39] (4.0 g, 9.9 mmol) and the

mixture was heated at reflux for 30 min. The clear yellow solution was cooled to 25 °C and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 3-(1*H*-indol-3-yl)-*N*-methylthiopropanamide **(52)** (3.94 g, 91 %) as colorless crystals; mp 80–81 °C.

IR (neat): ν = 1734, 1454 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.91 (t, 2 H, J = 7.3 Hz), 2.93 and 2.95 (s, 3 H), 3.20 (t, 2 H, J = 7.3 Hz), 6.90 (d, 1 H, J = 1.5 Hz), 7.06–7.20 (m, 2 H), 7.30–7.33 (m, 2 H), 7.55–7.58 (m, 1 H), 8.19 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.8, 32.7, 47.1, 111.2, 114.0, 118.5, 119.1, 121.8, 126.8, 136.0, 148.4, 205.3.

To a solution of **52** (0.10 g, 0.46 mmol) in CH_2Cl_2 (10 mL) under N_2 was added bromoacetyl chloride (0.042 mL, 0.50 mmol) and the mixture was stirred for 2 h at 25 °C. The solution was treated with triethylamine (0.127 mL, 0.92 mmol) and was heated at reflux for 2 h. The solution was cooled to 25 °C and the solvent was removed under reduced pressure. The resulting dark orange residue was subjected to flash silica gel chromatography to give spiro[1,2,3,4-tetrahydrocyclopenta[*b*]indole-3,2′,3′-methylthiazolidin-4′-one] **(55)** (0.069 g, 57 %) as a yellow solid; mp 154–155 °C.

IR ($CHCl_3$): ν = 1665, 1440, 1245 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.68 (s, 3 H), 2.91–3.05 (m, 4 H), 3.72 (d, 1 H, J = 15.7 Hz), 3.84 (d, 1, J = 15.7 Hz), 7.09–7.26 (m, 2 H), 7.33–7.37 (m, 1 H), 7.48–7.51 (m, 1 H), 8.43 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.8, 27.7, 33.4, 45.7, 73.5, 104.9, 112.5, 119.7, 120.0, 123.0, 123.6, 139.7, 142.4, 170.2.

Another fraction isolated from the column contained 2-[2-(1*H*-indol-3-yl)-ethylidene]-3-methylthiazolidin-3-one **(58)** (17 mg, 6 %) as an oily red solid.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.04 (s, 3 H), 3.50 (d, 2 H, J = 7.3 Hz), 3.78 (s, 2 H), 5.15 (t, 1 H, J = 7.3 Hz), 7.02 (s, 1 H), 7.07–7.21 (m, 2 H), 7.33–7.38 (m, 1 H), 7.60–7.63 (m, 1 H), 7.99 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.9, 29.3, 32.1, 99.6, 111.2, 114.7, 119.0, 119.4, 121.4, 122.1, 127.2, 135.9, 136.4, 170.1.

Treatment of **58** (100 mg, 0.36 mmol) in dry CH_2Cl_2 (5 mL) in the presence of a catalyic amount of trifluoroacetic acid for 48 h gave **55** in 85 % yield.

Spiro[2,3,4,9-tetrahydro-1*H*-carbazole-1,2′-3′-methylthiazolidin-4′-one] (56):

To a solution of 4-(1*H*-indol-3-yl)butyric acid (2.5 g, 12.3 mmol) in dry THF (50 mL) under N_2 was added 1,1′-carbonyldiimidazole (2.10 °C, 12.9 mmol) and the mixture was stirred for 4 h at 25 °C. The solution was treated with 40 % aq methylamine (100 mL) and was stirred overnight. The excess methylamine and solvent were removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (15 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 4-(1*H*-indol-3-yl)-*N*-methylbutyramide (2.64 g, 100 %) as a clear oil.

IR (neat): ν = 1727, 1541, 1459 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.06 (quin, 2 H, J = 7.2 Hz), 2.17 (t, 2 H, J = 7.2 Hz), 2.67 and 2.69 (s, 3 H) (1 : 1 mixture of rotamers), 2.77 (t, 2 H, J = 7.2 Hz), 6.12 (d, 1 H, J = 4.5 Hz), 6.85 (s, 1 H), 7.10–7.23 (m, 2 H), 7.31–7.34 (m, 1 H), 7.59–7.62 (m, 1 H), 9.09 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.5, 25.9, 26.0, 35.6, 111.1, 114.6, 118.4, 118.5, 121.3, 121.6, 127.0, 136.2, 174.1.

To a solution of the above amide (2.31 g, 10.6 mmol) in toluene (45 mL) was added Lawesson's reagent[39] (2.16 g, 5.35 mmol) and the mixture was heated at reflux for 1 h. The clear yellow solution was cooled to 25 °C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 4-(1*H*-indol-3-yl)-*N*-methylthiobutyramide **(53)** (2.30 g, 93 %) as a white solid; mp 91–92 °C.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.17 (quin, 2 H, J = 7.4 Hz), 2.62 (t, 2 H, J = 7.4 Hz), 2.78 (t, 2 H, J = 7.4 Hz), 3.04 and 3.06 (s, 3 H), 6.92 (d, 1 H, J = 1.7 Hz), 7.08–7.34 (m, 4 H), 7.55–7.59 (m, 1 H), 8.00 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.0, 29.5, 32.8, 42.0, 111.1, 115.2, 118.7, 119.1, 121.6, 121.9, 127.3, 136.1, 206.1.

To a solution of **53** (0.15 g, 0.64 mmol) in xylene (15 mL) under N_2 was added bromoacetyl chloride (0.059 mL, 0.71 mmol) and the mixture was stirred for 2 h at 25 °C. The solution was treated with triethylamine (0.18 mL, 1.28 mmol) and was heated at reflux for 2 h. The mixture was cooled to 25 °C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give spiro[2,3,4,9-tetrahydro-1*H*-carbazole-1,2′-3′-methylthiazolidin-4′-one] **(56)** (0.112 g, 65 %) as a white solid; mp 225–226 °C.

IR (neat): ν = 1655, 1455, 1380 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.12–2.24 (m, 3 H), 2.38 (dt, 1 H, J = 12.7 and 3.4 Hz), 2.71 (m, 1 H), 2.78 (s, 3 H), 2.83–2.92 (m, 1 H), 3.82 (s, 2 H, J = 16.5 Hz), 7.07–7.14 (m, 1 H), 7.20–7.26 (m, 1 H), 7.36–7.39 (m, 1 H), 7.50–7.53 (m, 1 H), 9.25 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.5, 21.5, 28.6, 32.7, 37.1, 67.5, 111.4, 116.0, 119.0, 123.3, 126.6, 131.4, 136.9, 171.4.

Spiro[5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole-9,2′-3′-methylthiazolidin-4′-one] (57):

A solution of 5-(1*H*-indol-3-yl)pentanoic acid[52] (2.01 g, 9.31 mmol) in dry THF (25 mL) and 1,1′-carbonyldiimidazole (1.82 g, 11.2 mmol) was stirred at 25 °C for 4 h. The mixture was poured into 40 % aq methylamine (50 mL) and stirred overnight at 25 °C. The solution was concentrated under reduced pressure and the aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 5-(1*H*-indol-3-yl)-*N*-methylpentanoic acid methylamide (1.52 g, 71 %) as a yellow oil.

IR (neat): ν = 1734, 1654, 1410 cm^{-1}.

^1H NMR (($CDCl_3$, 300 MHz): δ = 1.64–1.75 (m, 4 H), 2.06–2.20 (m, 2 H), 2.68 and 2.69 (s, 3 H), 2.69–2.80 (m, 2 H), 5.89 (s, 1 H), 6.86 (d, 1 H, J = 1.8 Hz), 7.03–7.20 (m, 2 H), 7.29–7.32 (m, 1 H), 7.56–7.59 (m, 1 H), 8.67 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.7, 25.8, 26.0, 29.6, 36.2, 111.1, 115.6, 118.5, 118.6, 121.4, 121.5, 127.2, 136.3, 174.0.

To a solution of the above amide (1.38 g, 6.0 mmol) in toluene (25 mL) was added Lawesson's reagent[39] (1.21 g, 3.0 mmol) and the mixture was heated at reflux for 5 min. The clear yellow solution was cooled to 25 °C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 5-(1*H*-indol-3-yl)-*N*-methylpentanthioic acid methylamide **(54)** (1.41 g, 95 %) as a yellow oil.

IR (neat): ν = 1619, 1541, 1456, 1377 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.60–1.81 (m, 4 H), 2.52 (t, 2 H, J = 7.2 Hz), 2.74 (t, 2 H, J = 7.2 Hz), 2.97 and 2.99 (s, 3 H), 6.86 (s, 1 H), 7.09–7.38 (m, 3 H), 7.38 (s, 1 H), 7.57–7.60 (m, 1 H), 8.09 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.6, 28.9, 29.0, 32.6, 46.2, 111.1, 115.6, 118.6, 118.8, 121.7, 121.6, 127.1, 136.0, 205.8.

A solution of **54** (0.10 g, 0.41 mmol) in xylene (10 mL) was treated with bromoacetyl chloride (0.035 mL, 0.45 mmol) and the mixture was stirred at 25 °C. The solution was then treated with triethylamine (0.113 mL, 0.81 mmol) and was heated at reflux for 2 h. The solution was cooled to 25 °C and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give spiro[5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole-9,2′-3′-methylthiazolidin-4′-one] **(57)** (0.067 g, 59 %) as a white solid; mp 230–231 °C.

IR ($CHCl_3$): ν = 1666, 1386, 1211 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.82–1.99 (m, 2 H), 2.02–2.18 (m, 3 H), 2.55–2.67 (m, 3 H), 2.88 (s, 3 H), 2.85–2.97 (m, 2 H), 3.71 (d, 1 H, J = 15.7 Hz), 3.82 (d, 1 H, J = 15.7 Hz), 7.06–7.24 (m, 1 H), 7.34–7.37 (m, 1 H), 7.50–7.53 (m, 1 H), 9.21 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.8, 23.8, 27.1, 29.1, 32.6, 38.8, 73.6, 111.1, 118.7, 119.3, 122.8, 128.3, 134.3, 135.5, 171.1.

Spiro[4,5,6,7-tetrahydrobenzofuran-4,2'-3'-methylthiazolidin-4'-one] (60):

To a stirred solution of (furan-2-yl)butyric acid[53] (12.4 g, 80.1 mmol) in CH_2Cl_2 (100 mL) was added 1,1'-carbonyldiimidazole (15.6 g, 96.1 mmol) over a period of 20 min. After stirring for 2 h, the solution was poured into 40% aq methylamine (20 mL) at 0 °C. The solution was allowed to warm to 25 °C overnight and was then acidified with 6 N HCl at 0 °C and was extracted with CH_2Cl_2 (25 mL). The combined organic extracts were washed with water (5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give (furan-2-yl)-*N*-methylbutyramide (11.93 g, 89%) as a pale yellow oil.

IR (neat): ν = 1654, 1559 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.86–1.98 (m, 2H), 2.16 (t, 2H, J = 7.5 Hz), 2.61 (t, 2H, J = 7.3 Hz), 2.72 and 2.74 (s, 3H), 5.95 (dd, 1H, J = 3.0 and 0.7 Hz), 6.04 (bs, 1H), 6.22 (dd, 1H, J = 3.0 and 1.9 Hz), 7.20–7.28 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.0, 26.1, 27.1, 35.4, 105.1, 110.0, 140.8, 155.1, 173.2.

To a solution containing the above amide (2.3 g, 13.8 mmol) in toluene (20 mL) was added Lawesson's reagent[39] (2.78 g, 6.9 mmol) and the mixture was heated at reflux for 5 min. The solution was cooled to 25 °C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give *N*-methyl-2-furanthiobutylamide **(59)** (1.92 g, 76%) as a yellow oil.

IR (neat): ν = 1538, 1453, 1375 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.03 (quin, 2H, J = 7.3 Hz), 2.58 (t, 2H, J = 7.3 Hz), 2.60 (t, 2H, J = 7.3 Hz), 3.03 and 3.05 (s, 3H), 5.92–5.96 (m, 1H), 6.18–6.22 (m, 1H), 7.20–7.23 (m, 1H), 8.13 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 26.5, 27.3, 32.5, 45.0, 105.0, 109.8, 140.6, 154.6, 205.0.

To a solution of **59** (0.20 g, 1.09 mmol) in dry CH_2Cl_2 (10 mL) was added bromoacetyl chloride (0.10 mL, 1.20 mmol) under N_2 and the mixture was stirred overnight. The slurry was treated with triethylamine (0.17 mL, 1.20 mmol) and heated at reflux for 3 h. The solution was cooled to 25 °C and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give spiro[4,5,6,7-tetrahydrobenzofuran-4,2'-3'-methylthiazolidin-4'-one] **(60)** (0.114 g, 47%) as a colorless solid: mp 161–162 °C.

IR ($CHCl_3$): 1683, 1410 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.91–2.10 (m, 4H), 2.47–2.60 (m, 2H), 2.64 (s, 3H), 3.54 (d, 1H, J = 15.6 Hz), 3.62 (d, 1H, J = 15.6 Hz), 6.15 (d, 1H, J = 1.9 Hz), 7.21 (d, 1H, J = 1.9 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.3, 22.1, 27.8, 32.4, 36.0, 69.3, 107.6, 119.1, 141.8, 153.3, 170.6.

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