A One-Pot Bicycloannulation Method for the Synthesis of Tetrahydroisoquinoline Systems

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A highly effective method for the synthesis of the core indolo[2,3-*a*]quinolizidine skeleton found in yohimbine is described. The reaction of N-monosubstituted thioamides with bromoalkenoyl chlorides furnishes thioisomünchnones as transient 1,3-dipoles that undergo ready intramolecular cycloaddition across the tethered π-bond to give thio-bicycloannulated products in a one-pot operation. The stereochemical outcome of the intramolecular reaction is the consequence of an endo cycloaddition of the neighboring π-bond across the transient thioisomünchnone dipole. A major limitation of the method is that when a hydrogen is present in the α-position of the thioamide the initially formed thio-*N*-acyliminium ion undergoes proton loss to produce a *S*,*N*-ketene acetal at a faster rate than dipole formation. Treatment of tetrahydro-β-carboline-1-thione with 2-bromooct-7-enoyl chloride followed by reductive removal of sulfur from the cycloadduct resulted in the formation of (±)-alloyohimbanone. Attempts to cycloadd the thioisomünchnone dipole across several nucleophilic π-bonds failed, and instead, products derived from cyclization of the π-bond onto the initially formed thio-*N*-acyliminium ion were formed. The resulting *N*,*S*-ketals were further converted into several tetrahydroisoquinoline alkaloids in good yield.

Mesoionic compounds have been known for many years and have been extensively utilized as substrates for 1,3-dipolar cycloaddition chemistry.[1−8] The term mesoionic is generally restricted to five-membered heterocycles that cannot be represented satisfactorily by normal covalent structures and are best described as a resonance hybrid of all possible charged forms.[9,10] The peculiar structure and reactivity of such heterocycles continue to receive considerable attention, especially since these mesoionic compounds have been utilized as effective synthons in natural product synthesis.[11] Perhaps the two most extensively studied mesoionic heterocycles are the münchnones[12−15] and isomünchnones.[16,17] These masked 1,3-dipoles readily react with a wide variety of double and triple-bond dipolarophiles. Münchnones (**2**) are generally prepared by cyclodehydration of *N*-acylamino acids with reagents such as acetic anhydride.[18] The Rh(II)-catalyzed reaction of diazo imides, on the other hand, represents the most effective method for the preparation of isomünchnones (**4**) (Scheme 1).[19]

Over the past several years, we have become interested in the cycloaddition chemistry of the closely related thioisomünchnone system (**7**). This mesoionic betaine contains a thiocarbonyl ylide dipole within its backbone and is easily prepared by reaction of N-monosubstituted thioamides with α-haloacyl halides in the presence of Et_3N (Scheme 1).[20] Despite the considerable amount of research dealing with the chemistry of thioisomünchnones, the range of their structural variation has remained somewhat narrow.[21] In most of the cases studied, at least one of the substituent groups is an aryl moiety, presumably due to electronic stabilization of the dipole to a sufficient degree to allow for its ready formation and occasional isolation.[21,22] To broaden the utility of this particular class of mesoionic betaines for natural product synthesis, we decided to investigate the reactivity of systems where the peripheral substituents were of the

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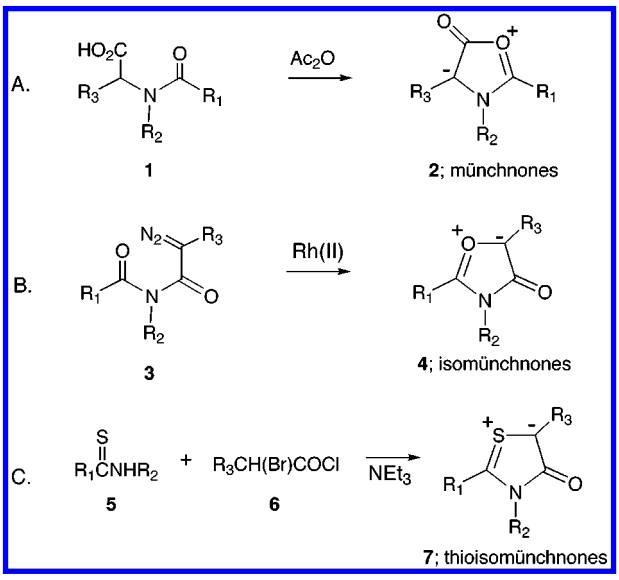
Scheme 1

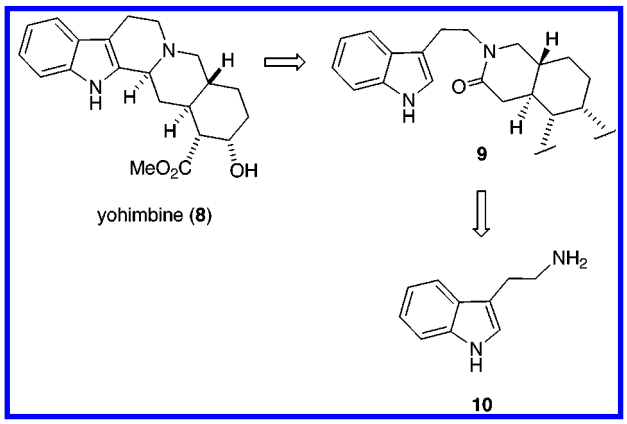


alkyl rather than aryl variety. We were specifically interested in using thioisomünchnone dipolar-cycloaddition chemistry as a key strategy for the assemblage of the core indolo[2,3-*a*]quinolizidine skeleton found in the yohimbane alkaloids.[23]

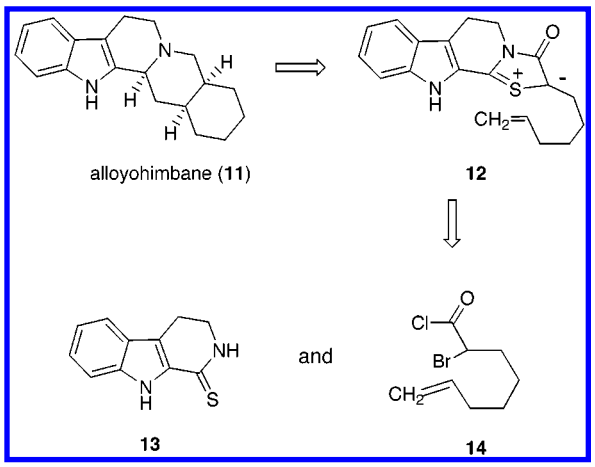
Members of the yohimbane alkaloid family possess a characteristic pentacyclic indole ring system and generally exhibit a wide range of important pharmacological properties.[24] Construction of the core indolo[2,3-*a*]quinolizidine skeleton found in yohimbine (**8**) has presented a formidable challenge to synthetic organic chemistry, and several elegant methods have been developed to achieve this goal.[25−28] Key synthetic elements in some of these approaches have included Diels−Alder cycloaddition,[29] radical cyclization,[30] oxy-Cope[31] and amino-Claisen rearrangements,[32] and photocyclization pathways.[33] A particularly viable strategy that has been extensively utilized for the construction of the polycyclic framework of the yohimbanes is to assemble appropriately functionalized derivatives of indoloquinolizidine and to elaborate them further into different target compounds (Scheme 2).[25−28]

The approach we had in mind (Scheme 3) for the synthesis of the indolo[2,3-*a*]quinolizidine skeleton was based on our previous success involving the reaction of 2-substituted thiolactams with α-bromoacetyl chloride as a method to generate anhydro-4-hydroxy-1,3-thiazolium

Scheme 2



Scheme 3



hydroxides (thioisomünchnones).[22] We envisioned that dipole **12**, derived from the reaction of thioamide **13** and α-bromo-acyl chloride **14**, would readily undergo intramolecular dipolar cycloaddition. Removal of the sulfur atom from the resulting cycloadduct followed by amide reduction should lead to alloyohimbane.[34] In this paper, we report in full the results of our studies that show that the reaction of indolo N-substituted thioamides with α-bromoacyl chlorides represents a convenient method for the synthesis of indolo[2,3-*a*]quinolizidines and related tetrahydroisoquinolines.

Results and Discussion

The successful implementation of the strategy outlined in Scheme 3 relied on the synthesis of the requisite α-bromoacyl chloride **14**. This compound and the related homologous α-bromoacyl chloride **15** ($n = 1$) were prepared starting from aldehydo esters **16** and **17**. Schreiber's ozonolysis protocol[35] was used to form these terminally differentiated aldehydic esters. Both of these compounds were converted to the corresponding carboxylic acids **18** and **19** in good yield using a standard Wittig reaction followed by alkaline saponification. Treatment of **18** and **19** with 2 equiv of LDA followed by reaction with carbon tetrabromide and then oxalyl chloride according to the Snider procedure[36] delivered the desired α-bromoacyl

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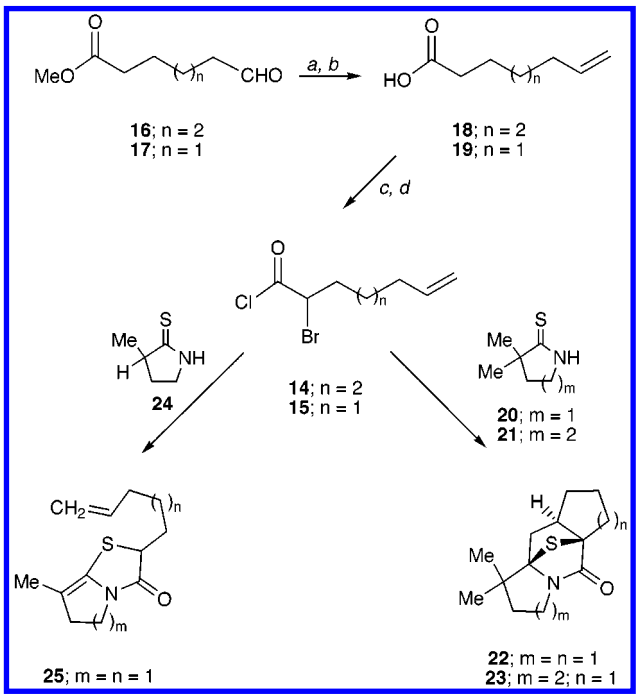
Scheme 4[a]

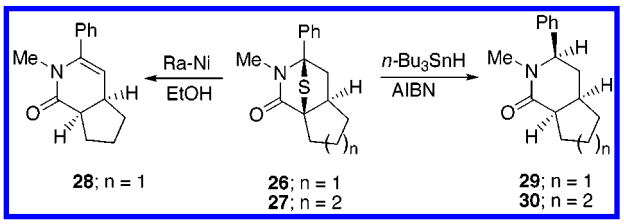


aReagents: (a) $Ph_3P{=}CH_2$; (b) KOH/MeOH; (c) LDA/CBr_4; (d) (COCl)2.

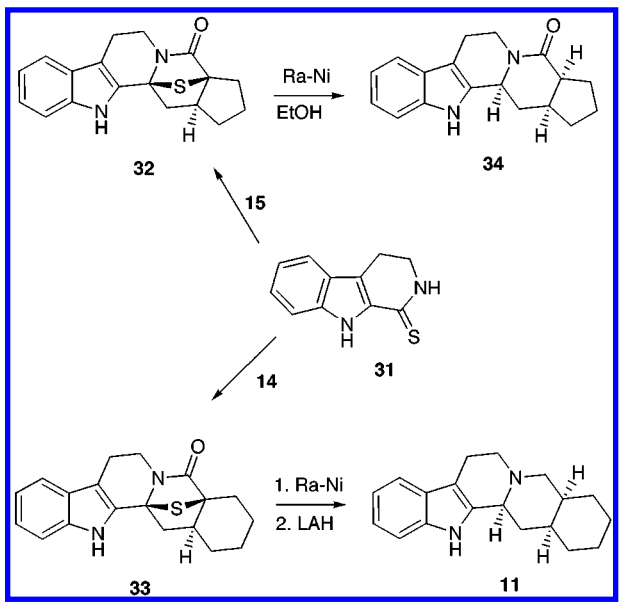
chlorides **14** and **15** in 54% and 70% yield, respectively. To test the viability of Scheme 3 as an entry into the yohimbane skeleton, we decided to first examine the intramolecular cycloaddition reaction of the thioisomünchnone dipoles generated by treating these α-bromoalkenoyl chlorides with simple cyclic thioamides. We were gratified to discover that the reaction of thioamides **20** and **21** with α-bromoacyl chloride **15** and triethylamine (1.5 equiv) in toluene at 110 °C resulted in the formation of cycloadducts **22** and **23** in 67% and 74% yield, respectively (Scheme 4). The depicted stereochemistry 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.[37] When a hydrogen atom is present in the α-position of the thioamide (i.e., **24**), the initially formed *N*-acyliminium ion undergoes proton loss (vide infra) to produce the *S*,*N*-acetal **25** at a faster rate than thioisomünchnone formation.

Given the success in forming intramolecular thioisomünchnone cycloadducts, 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, a clean reductive cleavage of the sulfur bridge is necessary if the method is to be useful for the preparation of various ring skeletons found in the alkaloid kingdom. Raney nickel seemed to be an ideal reagent to induce this reduction, since it has been extensively utilized for desulfurization chemistry.[38] Tri-*n*-(butyl)tin hydride is also known to be

Scheme 5



Scheme 6



an effective and selective reducing agent for various unsymmetric sulfides.[39] We found that cycloadduct **26**, derived from the reaction of *N*-methylthiobenzamide with acid chloride **15**, gave the unsaturated lactam **28** upon treatment with Raney nickel in ethanol.[40] In contrast, the reaction of **26** as well as the closely related cycloadduct **27** (see the Experimental Section) with *n*-Bu_3SnH and AIBN afforded the saturated lactams **29** and **30** in 81% and 75% yield, respectively (Scheme 5). [40]

The above results clearly demonstrate that this two-step sequence involving an intramolecular 1,3-dipolar cycloaddition of a thioisomünchnone dipole followed by desulfurization constitutes a simple and straightforward route for the preparation of various azapolycyclic rings. The facility of the process prompted us to use the method for the preparation of alloyohimbane (**11**) as outlined in Scheme 3. Treatment of the unprotected thiocarboline **31** with α-bromoacyl chlorides **14** and **15** afforded cycloadducts **33** and **32** in 75% and 62% yield, respectively (Scheme 6). Raney-Ni reduction of **32** gave the pentacyclic analogue **34** in 85% yield as the major diastereomer.[40] A short synthesis of (±)-alloyohimbane (**11**) was achieved in 42% yield by subjecting cycloadduct **33** to the Raney-Ni conditions followed by further reduction using lithium aluminum hydride. We also examined the cycloaddition chemistry of thioamide **31** with α-bromoacyl chloride **35**, since this would allow for the introduction of oxygen functionality onto the E-ring of the yohimbine skeleton (e.g., **8**).

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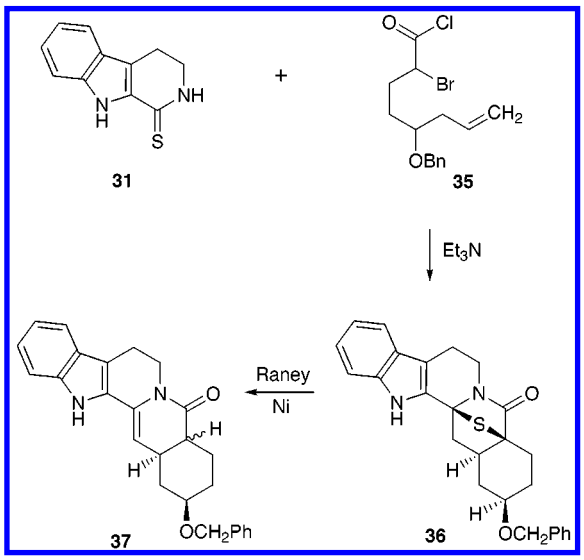
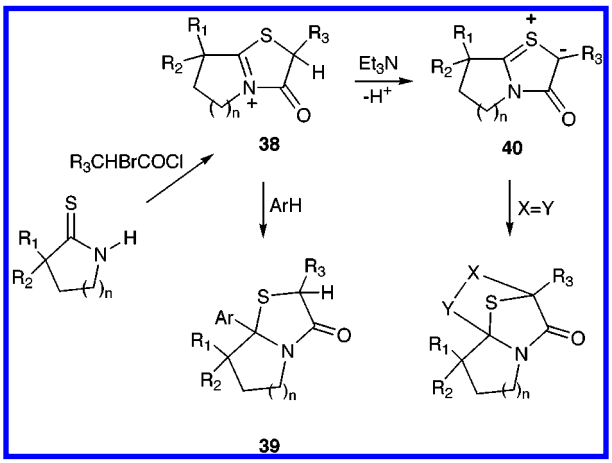
(40) The relative stereochemistry drawn is assumed and is primarily based on the fact that the cis-ring junction is lower in energy according to molecular mechanics calculations.

Scheme 7



31 35 37 36

Scheme 8

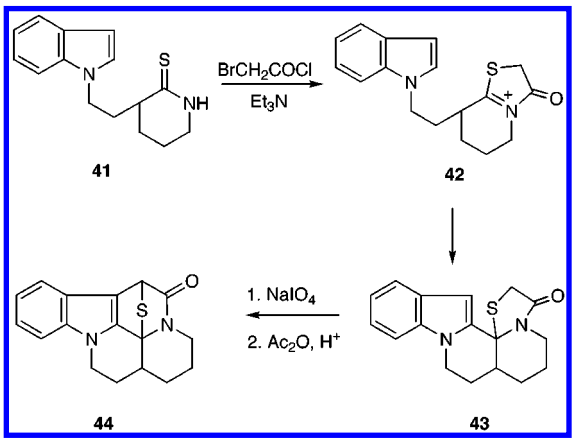


38 40 39

Indeed, when this reaction was carried out in the presence of NEt_3, cycloadduct **36** was isolated in 57% yield. The assignment of stereochemistry was based (NMR) on related substrates previously synthesized in these laboratories.[17] As was the case with related isomünchnone cycloadditions, formation of the dipolar cycloadduct is the consequence of endo-cycloaddition with respect to the thiocarbonyl ylide dipole.[17] This is in accord with molecular mechanics calculations, which show a large ground-state energy difference between the two diastereomers. We assume that the benzyloxy group is syn to the thio-bridge as this would place this substituent in the less sterically demanding equatorial position. Raney-nickel reduction resulted in the formation of the unsaturated lactam **37** as a 2:1 mixture of diastereomers (Scheme 7). The two diastereomers of **37** could be interconverted by stirring in a basic methanolic solution.

The above studies suggest that formation of the thioisomünchnone dipole from the reaction of N-monosubstituted thioamides with α-bromoacyl chlorides proceeds by the initial formation of a thio *N*-acyliminium ion (i.e., **38**). Proton abstraction from the activated α-position occurs readily in the presence of base to furnish the mesoionic betaine **40**, which undergoes subsequent dipolar cycloaddition with the available π-bond (Scheme 8). Thio *N*-acyliminium ions such as **38** have received very little attention as potential electrophilic partners in cation

Scheme 9



41 42 44 43

π-cyclizations despite the ease with which they can be formed.[41] It is well-known that carbon−carbon bond-forming reactions involving *N*-acyliminium ions play an extremely important role in the synthesis of many nitrogen heterocycles.[42] These cyclizations have been utilized as the key step in the preparation of several different alkaloid families, including the tetrahydroisoquinoline, β-carboline, and lycopodium classes.[43] By incorporating an activated π-nucleophile as a tether on the thioamide, cyclization followed by further manipulation of the resulting *S*,*N*-ketal (i.e., **39**) would also allow for the construction of the skeletal framework of several classes of alkaloids. We specifically thought it worthwhile to examine the behavior of thioamides such as **41** that contain a tethered indolo ring since this particular system could react by either of two pathways (Scheme 9). Cycloaddition of the thioisomünchone dipole derived from **41** across the pendant indole π-system[44] would represent an attractive route toward the pentacyclic skeleton found in the eburnamnine alkaloids.[45] On the other hand, the latent enamine functionality contained within the electron-rich heteroaromatic ring could also undergo π-cyclization with the initially formed thio *N*-acyliminium ion **42** prior to the deprotonation step. In fact, we observed that when thiolactam **41** was subjected to the standard conditions used for dipole formation, no product derived from thioisomünchnone cycloaddition across the indole π-bond could be detected in the reaction mixture. Instead, *S*,*N*-ketal **43** was isolated in 85% yield. Compound **43** is derived by cyclization of the dipole precursor **42** onto the 2-position of the indole ring. Apparently, attack by the nucleophilic π-bond of the indolo ring onto the *N*-acyliminium ion present in intermediate **42** occurs at a

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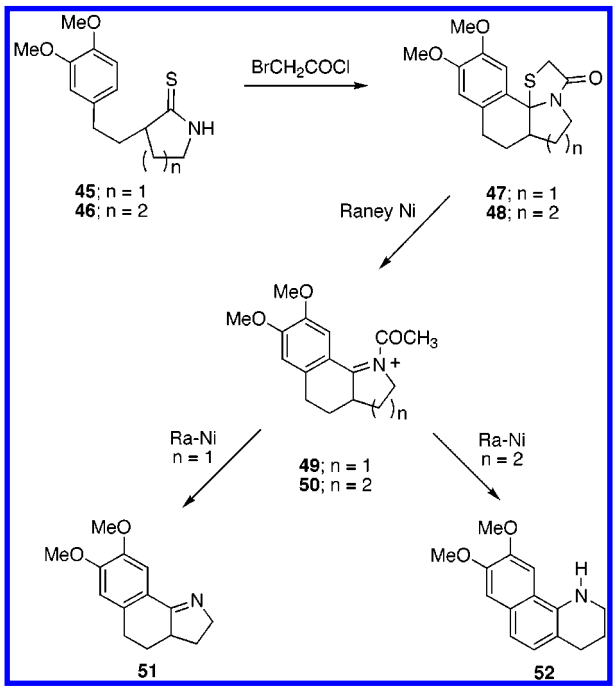
Scheme 10

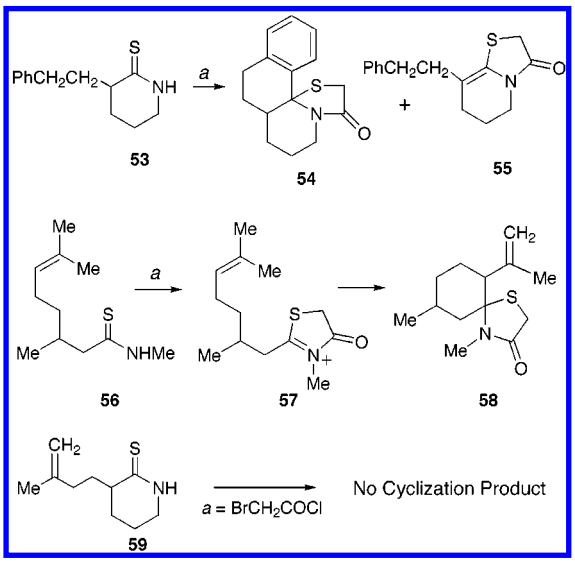


faster rate than dipole formation even in the presence of triethylamine. By taking advantage of the newly formed and highly functionalized *S*,*N*-ketal **43**, we were able to indirectly effect the desired 1,3-dipolar cycloaddition in a stepwise fashion. Thus, oxidation of **43** to the corresponding sulfoxide followed by a Pummerer-induced cyclization[46] gave the thio-bridged compound **44** in 65% overall yield. Compound **44** is formally the product derived from cycloaddition of a thioisomünchnone across the indole π-bond but in a higher oxidation state.

To further study the *N-acyliminium ion generation/π-cyclization sequence*, both the five- (**45**) and six-membered (**46**) cyclic thiolactams containing a 3,4-dimethoxyphenethyl tether were prepared. In the absence of Et_3N, treatment of either **45** or **46** with bromoacetyl chloride provided the cyclized *S*,*N*-ketals **47** or **48** in 88% and 95% yields, respectively. Reductive cleavage of the sulfur bridge using Raney nickel gave imine **51** (91%) starting from **47** and amine **52** (90%) when *S*,*N*-ketal **48** was used. Both products can be rationalized by sulfur atom extrusion to first produce the N-acetylated iminium ions **49** and **50**. Deacylation of **49** provides **51**, whereas the deacylation reaction of **50** was followed by further air oxidation to form the fully aromatic tetrahydroisoquinoline **52** (Scheme 10).

So that a cross section of additional information could be obtained in regard to the cationic π-cyclization step, a series of N-monosubstituted thioamides containing a variety of different π-bonds were required. Compounds ranging from simple aromatics to alkenyl tethered systems were considered. Ultimately, substrates **53**, **56**, and **59** were studied as these thioamides contain easily attainable π-bond functionality (Scheme 11). Treatment of 2-phenethylpiperidine-2-thione (**53**) with bromoacetyl chloride afforded a 2:1 mixture of *N*,*S*-ketal **54** and thiazolo[3,2-*a*]pyridone **55**. These two products are derived from competitive pathways of the initially formed thio *N*-acyliminium ion. Ketal **54** comes about by cyclization of the iminium ion onto the tethered aromatic ring. With this system, loss of a proton to give **55** also competes with π-cyclization since the attacking aromatic ring is not highly activated toward electrophilic substitution as was the case with thioamides **41**, **45**, and **46**. In a closely related process, the reaction of the dimethyloctenyl substituted thioamide **56** with bromoacetyl chloride furnished iminium ion **57**, and this was followed by consecutive cyclization and deprotonation to give *S*,*N*-ketal **58** in 63% yield. Unfortunately, all of our attempts to induce cyclization with a 1,1-disubstituted alkene such as **59** under a variety of conditions failed to produce any characterizable products.

Scheme 11



As an extension of these studies, the reaction of thioamide **60** with bromoacetyl chloride was investigated so as to evaluate the effect of placing an electron-rich aromatic ring on the thioamide functionality. The presence of an aryl group possessing an electron-donating substituent positioned para to the thio-*N*-acyliminium ion not only allows for cation stabilization by extended charge delocalization but also creates additional sites for cyclization. This reaction proved to be an extremely efficient one affording phenanthridine **62** in 77% yield. Desulfurization of **62** with Raney-nickel gave the acetylated phenanthridine **63** in 83% yield (Scheme 12).

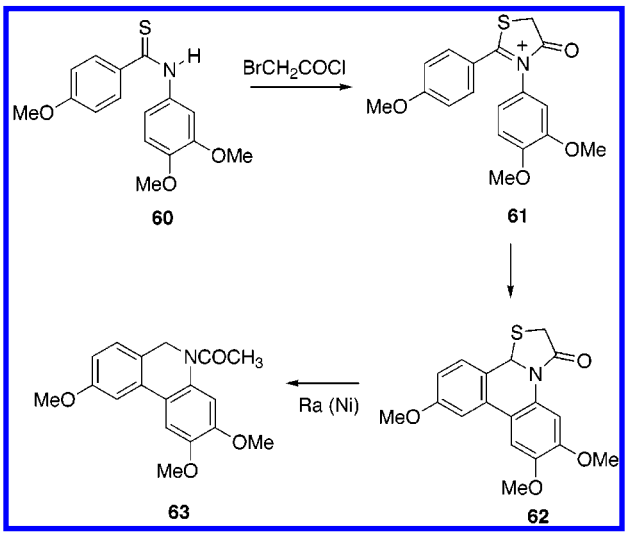
Given the success of this cyclization method for forming the phenanthridine skeleton, it seemed to us that this sequence of reactions could also be used for the synthesis of various isoquinoline ring systems. The tetrahydroisoquinoline skeleton is widely represented in many plant families and provides a challenging target for synthesis.[47] The great majority of the published syntheses are plagued by the harsh experimental conditions necessary for ring closure that limit their use with precursor compounds containing sensitive functional groups.[48] The π-cyclization procedure outlined in VIII represents an efficient and mild approach toward this important class of nitrogen heterocycles. To highlight this new strategy, the synthesis of the alkaloid salsolidine (**67**) was carried out. When thioamide **64** was treated with bromoacetyl

(46) Padwa, A.; Gunn, D. E.; Osterhout, M. H. *Synthesis* **1997**, 1353.

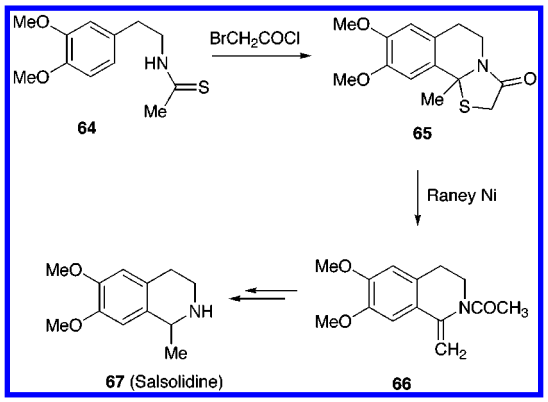
(47) Shamma, M. *The Isoquinoline Alkaloids*; Academic Press: New York, 1978. Lundstrom, J. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. 21, p 255.

(48) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

Scheme 12



Scheme 13

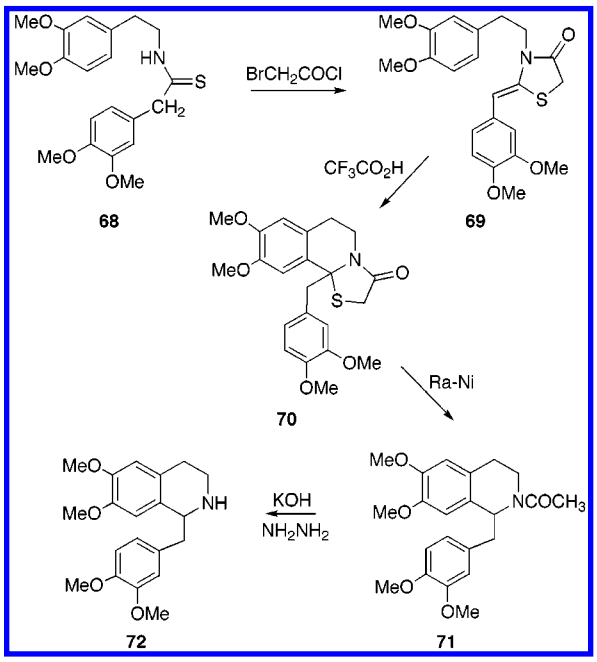


chloride, the cyclized *S*,*N*-ketal **65** was obtained in 98% yield. Removal of the sulfur atom with Raney nickel gave **66** (71%) (Scheme 13).

This sequence represents a formal synthesis of (±)-salsolidine (**67**), since compound **66** had been previously hydrogenated in an enantioselective manner and then deacetylated to produce salsolidine.[49]

The successful synthesis of the salsolidine precursor **66** by the thio *N*-acyliminium ion cyclization route prompted us to use a similar method for the preparation of the alkaloid tetrahydropapaverine (**72**).[49] In this case, the reaction of thioamide **68** with bromoacetyl chloride in refluxing toluene provided the *S*,*N*-ketene acetal **69** as the exclusive product in 84% yield (Scheme 14). Having the double bond in conjugation with the aromatic ring undoubtedly facilitates deprotonation of the initially formed thio-*N*-acyliminium ion. We found, however, that treatment of **69** with trifluoroacetic acid at 25 °C induced a Mondon-type cationic cyclization[50] to give the desired *N*,*S*-ketal **70** in 93% yield. Raney-nickel reduction of **70** furnished *N*-acyltetrahydropapaveroline **71** in 68% yield. Deacetylation of **71** according to the procedure of Kitamura and co-workers afforded tetrahydropapaverine (**72**).[49]

Scheme 14



In summary, we have shown that a range of novel heterocyclic compounds can be rapidly and convergently assembled from the reaction of N-monosubstituted thioamides with bromoalkenoyl chlorides. Intramolecular dipolar cycloaddition of the thioisomünchnone dipole followed by desulfurization results in the formation of a structurally diverse group of heterocyclic compounds. Thio-*N*-acyliminium ions have also been generated from the reaction of thioamides with bromoacetyl chloride. In the presence of tethered π-nucleophiles, cyclization occurs to produce *S*,*N*-ketals which can be further converted into various alkaloid skeletons. We are continuing to explore the synthetic applications of thioisomünchnone cycloaddition chemistry and will report additional findings at a later date.

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. Solid samples were recrystallized from an ethyl acetate/hexane solvent combination unless specified.

2-Bromooct-7-enoic Chloride (14). A mixture of 2.2 g (15 mmol) of 7-octenoic acid (**18**)[36] and 10 mL of HMPA in 50 mL of THF at −10 °C was treated with 70 mL of a 0.5 M LDA solution in THF. After being stirred for 2 h at −10 °C, the mixture was cooled to −78 °C and was treated with a solution of 12 g (35 mmol) of carbon tetrabromide in 3 mL of THF. The solution was allowed to warm to room temperature over 1 h, and stirring was continued for an additional 1 h at room temperature. The solution was quenched with brine and acidified with 2 N HCl, and the product was extracted with ether. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Chromatography of the residue on silica gel afforded 2.2 g (64%) of 2-bromooct-7-enoic acid, which was immediately used in the next step.

To a solution of 2.2 g (10 mmol) of the above acid in 20 mL of benzene was added 7.9 mL (16 mmol) of oxalyl chloride (2.0 M solution in CH_2Cl_2) followed by a drop of DMF. After the

(49) Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J. Org. Chem.* **1994**, *59*, 297.

(50) Mondon, A.; Hansen, K. F.; Boehme, K.; Faro, H. P.; Nestler, H. J.; Vilhuber, H. G.; Böttcher, K. *Chem. Ber.* **1970**, *103*, 615. Mondon, A.; Seidel, P. R. *Chem. Ber.* **1971**, *104*, 2937. Mondon, A.; Nestler, H. J. *Chem. Ber.* **1979**, *112*, 1329.

mixture was stirred for 2 h at room temperature, the solvent was removed under reduced pressure to give 2.2 g (85%) of **14** as a pale yellow oil that was sufficiently pure to be used in the next step without further purification: IR (neat) 2930, 2856, 1777, 1455, and 912 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35−1.99 (m, 4H), 2.01−2.05 (m, 4H), 4.41 (t, 1H, J = 6.7 Hz), 4.86−4.95 (m, 2H), and 5.64−5.73 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.2, 27.9, 33.2, 34.6, 54.0, 115.0, 137.9, and 170.1. Anal. Calcd for $C_8H_{12}OBrCl$: C, 40.34; H, 5.05. Found: C, 40.15; H, 5.02.

2-Bromohept-6-enoyl Chloride (15). A mixture of 3.0 g (23 mmol) of 6-heptenoic acid (**19**)[36] and 1 mL of HMPA in 50 mL of THF at −10 °C was treated with 100 mL of a 0.5 M LDA solution in THF. After being stirred for 2 h at −10 °C, the mixture was cooled to −78 °C and was treated with a solution of 18 g (54 mmol) of carbon tetrabromide in 3 mL of THF. The solution was allowed to warm to room temperature over 1 h, and stirring was continued for an additional 1 h at room temperature. The solution was quenched with brine and acidified with 2 N HCl, and the product was extracted with ether. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Chromatography of the residue on silica gel followed by distillation at 110−115 °C (2 mm) gave 3.8 g (78%) of 2-bromohept-6-enoic acid as a light yellow oil: IR (neat) 2923, 1710, 1422, 1281, and 912 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42−1.68 (m, 2H), 1.93−2.38 (m, 4H), 4.24 (t, 1H, J = 7.6 Hz), 4.97−5.06 (m, 2H), 5.70−5.84 (m, 1H), and 10.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.8, 33.0, 45.4, 77.5, 115.0, 137.1, and 175.4. Anal. Calcd for $C_7H_{11}O_2Br$: C, 40.60; H, 5.35. Found: C, 40.48; H, 5.27.

To a solution of 0.9 g (4.3 mmol) of the above acid in 10 mL of benzene was added 4.4 mL (8.7 mmol) of oxalyl chloride (2.0 M solution in CH_2Cl_2) followed by a drop of DMF. After the mixture was stirred for 2 h at room temperature, the solvent was removed under reduced pressure to give 0.9 g (90%) of bromoacid chloride **15** as a clear oil that was sufficiently pure to be used in the next step without further purification: IR (neat) 2932, 1785, 1443, 990, and 915 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40−1.55 (m, 2H), 1.93−2.15 (m, 4H), 4.42 (t, 1H, J = 6.4 Hz), 4.90−4.99 (m, 2H), 5.63−5.72 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.8, 32.6, 33.9, 53.9, 115.7, 137.0, and 169.9.

5-Aza-2,2-dimethyl-13-thiatetracyclo[5.5.1.0^{1,5}.0^{7,11}]-tridecan-6-one (22). To a stirred solution containing 0.2 g (1.6 mmol) of thioamide **20**[22] in 20 mL of toluene was added 0.4 g (1.7 mmol) of acid chloride **15** at room temperature. After being stirred for 15 min at room temperature, the mixture was heated at 60 °C for 1 h. A 0.5 mL (3.5 mmol) sample of triethylamine was added, and the reaction mixture was heated at reflux for 1.5 h. The mixture was filtered, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.25 g (67%) of **22** as a white solid: mp 67−68 °C; IR (KBr) 2954, 1716, 1460, 1346, and 1203 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.09 (s, 3H), 1.13 (s, 3H) 1.68−2.14 (m, 9H), 2.28−2.36 (m, 1H), 2.46−2.49 (m, 1H), 3.10−3.20 (dt, 1H, J = 7.5 and 4.3 Hz), and 3.45−3.52 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.2, 24.3, 24.9, 26.1, 32.1, 39.8, 40.4, 41.0, 41.7, 48.4, 76.1, 94.1, and 178.2. Anal. Calcd for $C_{13}H_{19}NOS$: C, 65.78; H, 8.07; N, 5.90. Found: C, 65.89; H, 8.04; N, 5.92.

6-Aza-2,2-dimethyl-14-thiatetracyclo[6.5.1.0^{1,6}.0^{8,12}]-tetradecan-7-one (23). A stirred solution of 0.14 g (1 mmol) of thioamide **21**[22] in 20 mL of toluene was treated with 0.25 g (1.1 mmol) of acid chloride **15** at room temperature. After being stirred for 30 min, the mixture was heated at 90 °C for 1.5 h. A 0.3 mL (2.2 mmol) sample of triethylamine was added, and the mixture was heated at reflux for an additional 2 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 0.19 g (74%) of **23** as a white solid: mp 90−92 °C; IR (KBr) 2948, 2859, 1702, 1442, and 1353 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.04 (s, 3H), 1.09 (s, 3H), 1.43−1.50 (m, 2H), 1.50−2.18 (m, 10H), 2.32−2.45 (m, 2H), and 3.77 (dd, 1H, J = 7.8 and 5.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.2, 26.1, 26.4, 27.7, 31.1, 33.4, 34.8, 34.9, 36.6, 36.7, 50.7, 72.2, 89.6, and 178.5. Anal. Calcd for $C_{14}H_{21}NOS$: C, 66.89; H, 8.42; N, 5.57. Found: C, 66.81; H, 8.40; N, 5.57.

7-Methyl-2-pent-4-enyl-2,5,6-trihydrothiapyrrolizin-3-one (25). To a stirred solution containing 0.1 g (1.0 mmol) of 3-methylpyrrolidine-2-thione (**24**)[51] in 10 mL of toluene was added 0.2 g (1.0 mmol) of acid chloride **15** at room temperature. After being stirred for 10 min at room temperature, the mixture was heated at 110 °C for 45 min. A 0.3 mL (2.0 mmol) sample of triethylamine was added, and the reaction mixture was heated at reflux for an additional 30 min. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.18 g (80%) of **25** as a light yellow oil: IR (neat) 3069, 2920, 1689, 1423, and 1126 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.34−1.53 (m, 4H), 1.56 (s, 3H), 1.70−1.83 (m, 1H), 1.97−2.09 (m, 3H), 2.77 (t, 1H, J = 8.6 Hz), 3.64 (t, 1H, J = 8.6 Hz), 4.26−4.30 (m, 1H), 4.88−4.97 (m, 2H) and 5.64−5.76 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.7, 25.8, 33.0, 33.4, 36.8, 41.5, 55.9, 106.5, 114.9, 129.8, 137.7, and 167.1. Anal. Calcd for $C_{12}H_{17}NOS$: C, 64.54; H, 7.68; N, 6.28. Found: C, 64.43; H, 7.61; N, 6.12.

8-Methyl-7-phenyl-10-thia-8-azatricyclo[5.2.1.0^{1,5}]decan-9-one (26). To a solution of 0.05 g (0.3 mmol) of *N*-methylthiobenzamide in 5 mL of toluene was added 0.08 g (0.4 mmol) of acid chloride **15** at room temperature under N_2. The reaction mixture was stirred at room temperature for 30 min and heated at 90 °C for 1 h, and then 0.07 g (0.7 mmol) of triethylamine was added. The mixture was heated at reflux for an additional 2 h, cooled to room temperature, concentrated under reduced pressure, and chromatographed on a silica gel column to give 0.05 g (53%) of cycloadduct **26** as a white solid: mp 99−100 °C; IR (neat) 1700, 1448, 1360, and 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.77−1.87 (m, 1H), 1.99−2.16 (m, 4H), 2.32−2.39 (m, 1H), 2.42 (s, 3H), 2.48−2.62 (m, 3H), and 7.38−7.53 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.6, 26.1, 27.6, 31.6, 40.9, 50.1, 74.1, 84.2, 128.5, 128.6, 129.2, 134.7, and 176.5. Anal. Calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40. Found: C, 69.49; H, 6.64; N, 5.42.

9-Methyl-8-phenyl-11-thia-9-azatricyclo[6.2.1.0^{1,6}]-undecan-10-one (27). To a solution containing 0.05 g (0.3 mmol) of *N*-methylthiobenzamide in 10 mL of toluene was added 0.1 g (0.4 mmol) of acid chloride **14** in 5 mL of toluene. The mixture was stirred at 40 °C for 24 h, and then 0.09 g (0.8 mmol) of triethylamine was added and the solution heated at reflux for 2 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 0.05 g (52%) of **27** as a white solid: mp 94−95 °C; IR (neat) 1700, 1448, 1369, and 763 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31−1.45 (m, 2H), 1.67−1.83 (m, 3H), 1.96−2.05 (m, 2H), 2.13−2.23 (m, 2H), 2.29−2.37 (m, 1H), 2.43 (s, 3H), 2.62 (dd, 1H, J = 12 and 7.2 Hz), and 7.39−7.54 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4, 25.6, 25.7, 27.2, 31.6, 41.2, 43.1, 66.5, 81.7, 128.5, 128.7, 129.2, 134.7, and 177.4. Anal. Calcd for $C_{16}H_{19}NOS$: C, 70.29; H, 7.01; N, 5.12. Found: C, 70.21; H, 7.00; N, 5.05.

3-Aza-3-methyl-4-phenylbicyclo[4.3.0]non-4-en-2-one (28). A suspension of 1.2 g of Raney nickel in 10 mL of acteone was heated at reflux for 2 h. After being cooled to room temperature, the mixture was decanted, and 10 mL of ethanol and 0.12 g (0.46 mmol) of cycloadduct **26** were added. The resulting mixture was heated at reflux for 1 h, cooled to room temperature, filtered through Celite, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.08 g (80%) of **28** as a colorless oil: IR (neat) 1666, 1445, 1366, and 766 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.54−1.64 (m, 2H), 1.86−2.06 (m, 4H), 2.70 (q, 1H, J = 8.4 Hz), 2.83 (s, 3H), 2.86−2.88 (m, 1H), 4.87 (dd, 1H, J = 3.2 and 0.8 Hz), 7.16−7.20 (m, 2H), and 7.26−7.31 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1, 29.6, 32.3, 33.1, 37.3, 45.3, 112.0, 127.8, 128.1, 128.3, 136.6, 140.5, and 173.9; HRMS calcd for $C_{15}H_{17}NO$ 227.1310, found 227.1304.

3-Aza-3-methyl-4-phenylbicyclo[4.3.0]nonan-2-one (29). A solution containing 0.13 g (0.5 mmol) of cycloadduct **26**, 0.44

(51) Zhang, Z. J.; Padwa, A. *Heterocycles* **1994**, *37*, 41.

g (1.5 mmol) of tributyltin hydride, and 0.05 g of AIBN in 10 mL of anhydrous toluene was heated at reflux for 24 h. The mixture was cooled and concentrated under reduced pressure, and the residue was chromatographed on silica gel to give 0.09 g (81%) of **29** as a white solid: mp 107−108 °C; IR (KBr) 1639, 1389, 1323, and 764 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27−1.37 (m, 1H), 1.48−1.85 (m, 6H), 2.22−2.34 (m, 2H), 2.59 (s, 3H), 2.66−2.69 (m, 1H), 4.31 (dd, 1H, J = 11.4 and 4.0 Hz), 7.10−7.12 (m, 2H), 7.20−7.24 (m, 1H), and 7.26−7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.7, 29.8, 31.8, 32.8, 35.8, 37.6, 45.9, 64.3, 126.1, 126.6, 127.7, 128.6, 128.8, 141.9, and 174.2. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.36; N, 6.11. Found: C, 78.50; H, 8.33; N, 6.05.

3-Aza-3-methyl-4-phenylbicyclo[4.4.0]decan-2-one (30). A solution containing 0.09 g (0.3 mmol) of cycloadduct **27**, 0.3 mL (1.0 mmol) of tributyltin hydride, and 10 mg of AIBN in 10 mL of toluene was heated at reflux for 3 h. The mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel to give 0.06 g (75%) of **30** as a white solid: mp 141−142 °C; IR (KBr) 1661, 1451, and 760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00−1.88 (m, 10H), 1.99−2.04 (m, 1H), 2.36−2.40 (m, 1H), 2.59 (s, 3H), 4.28 (dd, 1H, J = 10.6 and 5.6 Hz), and 7.11−7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4, 26.1, 27.4, 32.9, 37.0, 41.7, 46.8, 64.2, 126.3, 127.6, 128.8, 142.8, and 173.1. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.87; H, 8.77; N, 5.69.

3,13-Diaza-21-thiahexacyclo[13.5.1.$0^{1,13}$.$0^{2,10}$.$0^{4,9}$.$0^{15,19}$]-henicosa-2(10),4(9),5,7-tetraen-14-one (32). A mixture of 0.6 g (3.1 mmol) of thioamide **31** in 40 mL of toluene was treated with 0.7 g (3.2 mmol) of acid chloride **15** at room temperature. After being stirred for 15 min at room temperature, the solution was heated at 100 °C for 1 h. The mixture was treated with 0.5 mL (3.6 mmol) of triethylamine, and heating was continued for an additional 1 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 0.64 g (62%) of **32** as a light yellow solid: mp 225−226 °C; IR (KBr) 3274, 1680, 1452, 1403, and 727 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ1.18−2.11 (m, 5H), 2.31−2.47 (m, 3H), 2.83−2.96 (m, 4H), 4.17 (dd, 1H, J = 6.7 and 1.5 Hz), 7.03 (t, 1H, J = 7.0 Hz), 7.13 (t, 1H, J = 7.0 Hz), 7.30 (d, 1H, J = 7.9 Hz), 7.45 (d, 1H, J = 7.9 Hz), and 9.90 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.1, 24.9, 27.1, 32.7, 32.8, 38.8, 46.3, 50.9, 77.0, 111.0, 112.4, 119.7, 120.7, 123.7, 127.1, 129.4, 137.8, and 176.7. Anal. Calcd for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.85; N, 9.03. Found: C, 69.51; H, 5.64; N, 9.24.

3,13-Diaza-21-thiahexacyclo[13.5.1.$0^{1,13}$.$0^{2,10}$.$0^{4,9}$.$0^{15,19}$]-henicosa2(10),4(9),5,7-tetraen-14-one (33). To a stirred solution of 0.19 g (1 mmol) of the known thioamide **31**[52] in 15 mL of toluene was added 0.26 g (1 mmol) of acid chloride **14** at room temperature. After being stirred for 15 min at room temperature, the solution was heated at 100 °C for 1 h. To this mixture was added 0.14 mL (1.0 mmol) of triethylamine, and the solution was heated at reflux for an additional 2 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 0.24 g (75%) of cycloadduct **33** as a pale yellow solid: mp 200−201 °C; IR (KBr) 1680, 1445, 1403, 1260, and 734 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37−1.46 (m, 2H), 1.73−1.83 (m, 3H), 1.99−2.34 (m, 5H), 2.44−2.50 (m, 1H), 2.93−3.96 (m, 3H), 4.23−4.28 (m, 1H), 7.16 (t, 1H, J = 7.6 Hz), 7.25 (t, 1 H, J = 7.6 Hz), 7.38 (d, 1 H, J = 7.9 Hz), 7.55 (d, 1H, J = 7.9 Hz), and 8.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 22.5, 25.6, 25.9, 31.7, 37.3, 41.0, 47.9, 68.9, 73.5, 110.9, 111.3, 118.9, 120.1, 123.1, 128.4, 136.5, 150.0, and 175.8. Anal. Calcd for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.22; N, 8.64. Found: C, 70.29; H, 6.34; N, 8.57.

10,20-Diazapentacyclo[11.7.0.0^{2,10}.0^{4,8}.0^{14,19}]icosa-1(13),-14(19),15,17-tetraen-9-one (34). A 0.15 g (0.50 mmol) sample of cycloadduct **32** in 80 mL of ethanol was treated with 0.9 g of W-2 Raney nickel for 15 min at 50 °C. The mixture was filtered through a short pad of Celite, and the solvent was removed under reduced pressure. Chromatography of the residue on silica gel gave 0.12 g (85%) of **34** as a white solid: mp 222−224 °C; IR (KBr) 1602, 1438 and 734 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40−1.93 (m, 5H), 2.10−2.41 (m, 4H), 2.63−2.84 (m, 4H), 4.68 (d, 1H, J = 7.5 Hz), 4.95 (d, 1H, J = 9.9 Hz), 6.96−7.06 (m, 2H), 7.26 (d, 1H, J = 7.8 Hz), and 7.37 (d, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.4, 22.4, 29.4, 31.9, 33.4, 34.4, 39.5, 45.1, 53.7, 107.4, 110.5, 117.4, 118.5, 121.0, 125.9, 132.9, 136.2 and 173.2. Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.86; H, 7.20; N, 9.74.

(±)-Alloyohimban-21-one. A 0.1 g (0.3 mmol) sample of **33** was treated with 0.8 g of Raney nickel in 50 mL of EtOH. Standard workup afforded 0.08 g (90%) of (±)-alloyohimban-21-one[53] as a white solid: mp 240−242 °C; IR (KBr) 3253, 2925, 1602, 1438, and 727 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26−1.32 (m, 2H), 1.46−1.51 (m, 2H), 1.61−1.72 (m, 3H), 1.96−2.00 (m, 1H), 2.00−2.18 (m, 2H), 2.30 (dd, 1H, J = 8.4 and 4.0 Hz), 2.56 (dt, 1H, J = 11.8 and 5.2 Hz), 2.77−2.88 (m, 3H), 4.79 (t, 1H, J = 8.0 Hz), 5.15 (dd, 1H, J = 8.0 and 3.6 Hz), 7.14 (t, 1H, J = 8.0 Hz), 7.19 (t, 1H, J = 8.0 Hz), 7.35 (d, 1H, J = 7.6 Hz), 7.51 (d, 1H, J = 7.6 Hz), and 8.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9, 21.1, 25.6, 26.4, 29.7, 30.1, 30.5, 40.1, 43.2, 54.1, 108.9, 110.9, 118.3, 119.7, 122.0, 126.7, 133.7, 136.2, and 172.9. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.54; N, 9.52. Found: C, 77.48; H, 7.50; N, 9.32. Reduction of this amide with LAH according to the literature procedure[53] gave (±)-alloyohimbane (**11**) in 42% yield, whose spectral properties were identical in all respects with those listed in the literature.[34]

5-Benzyloxy-7-octenoic Acid. To a solution containing 5.2 g (40 mmol) of methyl 5-oxohexanoate[35] in 100 mL of CH_2Cl_2 was added 20 mL of a $TiCl_4$ solution (1.0 M in CH_2Cl_2) at −78 °C, followed by dropwise addition of 6.3 mL (40 mmol) of allyltrimethylsilane. After the addition was complete, the cold bath was removed, and the solution was warmed to room temperature and was stirred for 1 h. The mixture was poured onto 100 g of ice, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give 3.7 g (66%) of 5-allyl-δ-valerolactone as a colorless oil that was used in the next reaction without further purification: IR (neat) 1735, 1644, 1243 and 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41−1.50 (m, 1H), 1.74−1.88 (m, 3H), 2.25−2.53 (m, 4H), 4.25−4.30 (m, 1H), 5.02−5.09 (m, 2H), and 5.71−5.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2, 27.0, 29.3, 39.8, 79.6, 118.4, 132.5, and 171.6.

A mixture containing 3.7 g (26 mmol) of the above lactone, 6.1 g (109 mmol) of KOH, and 7.5 mL (65 mmol) of benzyl chloride in 100 mL of anhydrous toluene was heated at reflux for 20 h. The reaction was quenched with 100 mL of water, and the aqueous phase was washed twice with ether, acidified with HCl, and extracted with ether. The ether extracts were dried over Na_2SO_4 and concentrated under reduced pressure, and the residue was purified by flash silica gel chromatography to give 3.8 g (59%) of the title compound as a colorless oil: IR (neat) 3568−2521 (br), 1710, 1641, and 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.55−1.82 (m, 4H), 2.30−2.39 (m, 4H), 3.46−3.48 (m, 1H), 4.49 (d, 1H, J = 11.6 Hz), 4.59 (d, 1H, J = 11.6 Hz), 5.06−5.13 (m, 2H), 5.79−5.87 (m, 1H), and 7.26−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5, 33.0, 33.9, 38.1, 70.9, 77.9, 117.2, 127.5, 127.7, 128.3, 134.5, 138.5, and 179.8; HRMS calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1411.

2-Bromo-5-benzyloxyoct-7-enoyl Chloride (35). To a 3.7 g (15.0 mmol) sample of the above acid in 5 mL of THF and 5 mL of HMPA at −15 °C was added 30 mL of an LDA solution (1.0 M in THF). After being stirred at −15 °C for 2 h, the solution was cooled to −78 °C, and 12.6 g (38 mmol) of carbon tetrabromide in 10 mL of THF was added. The resulting mixture was stirred at −78 °C for 2 h and then quenched with brine. The solution was acidified and filtered through a short

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pad of Celite. The mixture was extracted with ether, dried over Na_2SO_4, and concentrated under reduced pressure, and the residue was purified by silica gel chromatography to give 3.0 g (60%) of 2-bromo-5-benzyloxy-7-octenoic acid as a pale oil: IR (neat) 3592−2348 (br), 1717, 1641, and 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.60−2.44 (m, 6H), 3.49−3.52 (m, 1H), 4.22 (m, 1H), 4.47−4.62 (m, 2H), 5.09−5.15 (m, 2H), 5.79−5.86 (m, 1H), 7.29−7.38 (m, 5H), and 8.66 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.5, 31.1, 37.9, 45.6, 65.3, 70.9, 117.6, 127.1, 127.8, 128.4, 134.1, 138.2, and 175.0; HRMS calcd for $C_{15}H_{19}BrO_3$ 326.0518, found 326.0521.

A solution containing 2.9 g (8.9 mmol) of the above bromoacid and 1.2 mL (13 mmol) of oxalyl chloride in 40 mL of benzene was heated at reflux for 2 h. The mixture was concentrated under reduced pressure to give 3.0 g (99%) of **35** as a pale yellow oil that was immediately used in the next step without further purification: IR (neat) 1783, 1641, 1451, and 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.60−2.44 (m, 6H), 3.49−3.54 (m, 1H), 4.22 (m, 1H), 4.46−4.64 (m, 2H), 5.11−5.16 (m, 2H), 5.81−5.86 (m, 1H), and 7.26−7.44 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.6, 30.8, 37.8, 54.3, 70.3, 70.9, 117.6, 127.7, 128.3, 128.8, 133.9, 138.1, and 170.1.

17-Benzyloxy-3,19-*epi*-thioyohimbane (36). The reaction of 1.0 g (5.0 mmol) of thioamide **31** and 1.7 g (5.0 mmol) of the above acid chloride in the presence of 1 mL (7.2 mmol) of triethylamine afforded 1.2 g (57%) of cycloadduct **36** as a pale yellow solid after silica gel chromatography: mp 259−260 °C; IR (KBr) 3280, 1679, 1398, and 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.53−1.57 (m, 1H), 1.86−1.95 (m, 1H), 2.18−2.48 (m, 7H), 2.90−3.06 (m, 3H), 3.42−3.48 (m, 1H), 4.18−4.23 (m, 1H), 4.55−4.63 (AB, 2H, J = 18.6 and 11.6 Hz), 7.13 (t, 1H, J = 7.4 Hz), 7.20−7.37 (m, 7H), 7.51 (d, 1H, J = 7.4 Hz), and 8.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8, 24.0, 28.5, 37.4, 37.5, 40.8, 47.7, 67.9, 70.2, 73.9, 76.4, 110.8, 111.3, 118.8, 120.0, 123.1, 126.2, 127.7, 127.9, 128.4, 136.6, 138.3, and 175.3. Anal. Calcd for $C_{26}H_{26}N_2O_2S$: C, 72.53; H, 6.09; N, 6.51. Found: C, 72.38; H, 6.14; N, 6.42.

17-Benzyloxy-3,14-didehydroyohimbane (37). The reaction of 0.3 g (0.7 mmol) of **36** with W-Raney nickel according to the procedure used above afforded a mixture of two stereoisomers. The minor diastereomer **37a** contained 0.08 g (27%) of a white solid: mp 257−258 °C; IR (KBr) 3304, 1641, 1394, 1221, and 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24−1.37 (m, 4H), 1.98−2.04 (m, 1H), 2.23−2.37 (m, 3H), 2.78−2.82 (m, 1H), 2.85−2.90 (m, 1H), 3.09 (t, 1H, J = 12.0 Hz), 3.37−3.42 (m, 1H), 4.53 (q, 2H, J = 12.0 Hz), 4.92−4.97 (m, 1H), 5.23 (d, 1H, J = 4.8 Hz), 7.04 (t, 1H, J = 7.2 Hz), 7.15 (t, 1H, J = 7.2 Hz), 7.21−7.31 (m, 6H), 7.44 (d, 1H, J = 7.2 Hz) and 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 24.3, 31.4, 34.0, 38.0, 39.5, 44.6, 70.3, 76.5, 104.4, 111.0, 112.3, 119.0, 120.1, 123.6, 126.6, 127.5, 127.7, 128.4, 130.4, 137.1, 138.7, and 171.3. Anal. Calcd for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.11; H, 6.46; N, 6.94.

The major diasteromer **37b** contained 0.15 g (55%) of a clear oil: IR (KBr) 3303, 1669, 1641, 1401, 1227, and 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31−1.41 (m, 2H), 1.48−1.58 (m, 1H), 1.84−1.94 (m, 2H), 2.44−2.48 (m, 2H), 2.61 (q, 1H, J = 4.8 Hz), 2.75−2.86 (m, 2H), 3.33−3.43 (m, 2H), 4.46 (q, 2H, J = 12.0 Hz), 4.61 (brs, 1H), 5.45 (d, 1H, J = 7.0 Hz), 7.03 (dt, 1H, J = 8.0 and 0.8 Hz), 7.11−7.27 (m, 7H), 7.42 (d, 1H, J = 8.0 Hz), and 8.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6, 22.6, 28.5, 31.7, 34.1, 39.4, 40.8, 69.6, 76.0, 103.3, 110.9, 111.8, 118.9, 119.9, 123.4, 126.9, 127.4, 127.9, 128.3, 129.7, 137.1, 138.8, and 170.6; HRMS calcd for $C_{26}H_{26}N_2O_2$ 398.1994, found 398.1995.

Preparation of Indolo[1,2-*a*]-octahydro-1-thia-3a-azacyclopenta[*d*]naphthylen-3-one (43). To a solution containing 3.0 g (12 mmol) of 3-(2-indol-1-yl)ethylpiperidin-2-one[22] in 50 mL of toluene was added 2.5 g (6 mmol) of Lawesson's reagent, 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 2.0 g (63%) of 3-(2-indol-1-yl)ethylpiperidine-2-thione (**41**) as a light yellow solid: mp 79−80 °C; IR (neat) 1577, 1551, and 1472 cm^{-1}; 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, 1H, J = 3.0 Hz), 7.45−7.48 (m, 1H), 7.63−7.66 (m, 1H), and 9.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.5, 25.6, 35.3, 43.7, 44.2, 44.3, 101.1, 109.0, 118.5, 120.7, 121.3, 127.6, 128.4, 135.8, and 205.5. Anal. Calcd for $C_{15}H_{18}N_2S$: C, 69.72; H, 7.02; N, 10.84; S, 12.41. Found: C, 69.81; H, 7.02; N, 10.79; S, 12.51.

To a solution containing 0.2 g (0.8 mmol) of **41** in 20 mL of dry CH_2Cl_2 was added 0.07 mL (0.9 mmol) of bromoacetyl chloride under N_2, and the mixture was stirred at 25 °C for 1.5 h. The solution was treated with 0.2 mL (1.5 mmol) of triethylamine 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 0.15 g (65%) of **43** as a white solid: mp 151−152 °C; IR (neat) 1685, 1470, and 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), and 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, and 170.3. Anal. Calcd for $C_{17}H_{18}N_2OS$: C, 68.43; H, 6.08; N, 9.39; S, 10.73. Found: C, 68.24; H, 6.08; N, 9.41; S, 10.82.

10,17-Diaza-20-thiahexacyclo[11.7.0^{1,17}.0^{2,10}.0^{3,19}.0^{4,9}]icosa-2(3),4(9),5,7-tetraen-18-one (44). To a solution of 1.9 g (6.3 mmol) of *N*,*S*-ketal **43** in 45 mL of MeOH and 15 mL of dioxane at 0 °C was added 1.8 g (8.2 mmol) of sodium periodate as a solution in 20 mL of water. After being warmed to room temperature, the mixture was allowed to stir for 24 h. Water was added, and the mixture was extracted with chloroform. The organic extracts were dried, and the solvent was removed under reduced pressure. Flash silica gel chromatography of the residue gave 1.4 g (71%) of indolo[1,2-*a*]octahydro-1-thiaoxy-3a-azacyclopenta[*d*]naphthylen-3-one as a pale yellow solid: mp 179−181 °C; IR (KBr) 2926, 1684, 1059, and 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.60−1.70 (m, 2H), 1.75−1.80 (m, 1H), 1.90−1.95 (m, 1H), 2.17 (d, 1H, J = 14.8 Hz), 2.54−2.69 (m, 2H), 2.75 (t, 1H, J = 12.4 Hz), 3.38 (dd, 1H, J = 4.4 and 17.2 Hz), 3.89−3.96 (m, 2H), 4.00−4.32 (m, 2H), 6.25 (s, 1H), 7.15 (t, 1H, J = 8.0 Hz), 7.28 (t, 1H, J = 8.4 Hz), 7.34 (d, 1H, J = 8.4 Hz), and 7.54 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.3, 24.4, 24.5, 29.5, 37.5, 40.3, 51.3, 79.9, 102.0, 109.7, 120.7, 120.8, 123.0, 127.3, 128.8, 137.7, and 167.3. Anal. Calcd for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.91. Found: C, 64.89; H, 5.79; N, 8.91

To a solution containing 5 mL (54 mmol) acetic anhydride and 50 mg (0.3 mmol) of *p*-toluenesulfonic acid in 90 mL of toluene at reflux was slowly added 0.85 g (2.7 mmol) of the above sulfoxide. After being stirred for 1 h, the solution was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by silica gel chromato-graphy to give 0.7 g (92%) of **44** as a yellow solid: mp 231−233 °C; IR (KBr) 2927, 1651, and 1140 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.91−1.96 (m, 2H), 2.39 (t, 2H, J = 6.8 Hz), 2.61 (brs, 3H), 3.64 (brs, 2H), 4.00 (brs, 3H), 7.07−7.11 (m, 1H), 7.22−7.25 (m, 2H), and 7.45 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4, 29.1, 29.2, 38.0, 40.0, 42.8, 106.0, 108.9, 119.0, 119.9, 122.4, 123.3, 126.7, 126.9, 127.3, 135.5, and 169.6. Anal. Calcd for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45. Found: C, 68.90; H, 5.48; N, 9.49.

3-[2-(3,4-Dimethoxyphenyl)ethyl]pyrrolidine-2-thione (45). To a solution of 1 mL (7 mmol) of diisopropylamine in 10 mL of THF at 0 °C was added 3 mL (7.5 mmol) of 2.5 M *n*-butyllithium. The solution was allowed to stir at 0 °C for 30 min and was cooled to −78 °C. To this solution was added a solution of 1.2 g (6.2 mmol) of *N*-*tert*-butyldimethylsilylpyrrolidin-2-one[54] in 10 mL of THF. The reaction mixture was allowed to warm to 25 °C over a period of 1 h and was recooled to −78 °C. A 2.0 g (7 mmol) sample of 3,4-dimethox-

yphenethyl iodide[55] was added, and the reaction was allowed to warm to 25 °C over a period of 2 h. The mixture was quenched with a saturated solution of NH_4Cl and extracted with ethyl acetate. The combined organic extracts were concentrated under reduced pressure, and the residue was taken up in 10 mL of THF. A large excess of a 1.5 M tetrabutylammonium fluoride solution in THF was added at room temperature, and the mixture was allowed to stir at 25 °C for 2 h. The mixture was concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 1.05 g (68%) of 3-[2-(3,4-dimethoxyphenyl)ethyl]-pyrrolidin-2-one as a white solid: mp 76−77 °C; IR (CH_2Cl_2) 1655, 1510, and 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.64−1.68 (m, 1H), 1.82−1.87 (m, 1H), 2.19−2.22 (m, 1H), 2.31−2.38 (m, 2H), 2.64−2.74 (m, 2H), 3.31−3.63 (m, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 5.53 (brs, 1H), and 6.73−6.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 33.1, 34.5, 47.1, 52.3, 55.7, 55.8, 111.0, 111.6, 121.3, 134.2, 147.0, 148.3, and 175.3. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.43; H, 7.69; N, 5.62. Found: C, 67.78; H, 7.41; N, 5.53.

To a solution of 1.0 g (4.0 mmol) of the above amide in 40 mL of toluene was added 0.8 g (2.0 mmol) of Lawesson's reagent. The mixture was heated at reflux for 4 h and was cooled to room temperature. The solution was concentrated under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography to give 0.97 g (91%) of **45** as a white solid: mp 125−126 °C; IR (CH_2Cl_2) 3310, 1517, and 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.65−1.74 (m, 1H), 1.83−1.93 (m, 1H), 2.35−2.43 (m, 1H), 2.45−2.54 (m, 1H), 2.58−2.65 (m, 1H), 2.70−2.78 (m, 2H), 3.50−3.61 (m, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 6.74−6.80 (m, 3H), and 8.72 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 32.9, 34.9, 47.2, 51.5, 55.7, 55.8, 111.0, 111.6, 120.1, 133.8, 147.1, 148.7, and 209.0. Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.37; H, 7.22; N, 5.28. Found: C, 63.42; H, 7.14; N, 5.23.

3-[2-(3,4-Dimethoxyphenyl)ethyl]piperidine-2-thione (46). To a solution of 0.9 mL (6.3 mmol) of diisopropylamine in 10 mL of THF at 0 °C was added 2.7 mL (7 mmol) of 2.5 M *n*-butyllithium. The solution was allowed to stir at 0 °C for 30 min and was cooled to −78 °C. To this mixture was added a solution of 1.0 g (6 mmol) of *N*-trimethylsilylvalerolactam[56] in 5 mL of THF. The reaction mixture was allowed to warm to room temperature over a period of 1 h and was recooled to −78 °C. A 2.0 g (7 mmol) sample of 3,4-dimethoxyphenethyl iodide[55] was added, and the solution was allowed to warm to room temperature over a period of 2 h. The mixture was quenched with a saturated solution of NH_4Cl and extracted with ethyl acetate. The combined organic extracts were concentrated under reduced pressure, and the resulting residue was dissolved in 10 mL of THF. An excess of a 1.5 M tetrabutylammonium fluoride solution in THF was added at room temperature, and the mixture was allowed to stir for 2 h. The solution was concentrated under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography to give 1.2 g (79%) of 3-[2-(3,4-dimethoxyphenyl)-ethyl]piperidin-2-one as a white solid: mp 75−76 °C; IR (CH_2Cl_2) 1652, 1510, and 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.79−1.90 (m, 4H), 2.02−2.10 (m, 2H), 2.57−2.66 (m, 3H), 3.34 (brs, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 6.33 (brs, 1H), and 6.73−6.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 29.8, 30.3, 40.9, 42.6, 44.7, 55.7, 55.8, 111.0, 111.6, 119.9, 134.9, 146.9, 148.7, and 176.4. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.40; H, 8.04; N, 5.32. Found: C, 68.46; H, 7.98; N, 5.29.

To a solution of 0.5 g (2 mmol) of the above amide in 10 mL of toluene was added 0.4 g (1 mmol) of Lawesson's reagent. The mixture was heated at reflux for 2 h and cooled to room temperature. The crude reaction mixture was concentrated under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography to give 0.4 g (87%) of **46** as a white solid: mp 98−99 °C; IR (CH_2Cl_2) 1561, 1359, and 1325 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.63−1.97 (m, 5H), 2.55−2.81 (m, 4H), 3.34−3.36 (m, 2H), 3.86 (s, 3H), 3.89 (s, 3H), 6.76−6.81 (m, 3H), and 8.31 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 24.7, 32.6, 36.8, 44.9, 45.7, 55.8, 55.9, 111.1, 111.6, 120.2, 134.1, and 208.0. Anal. Calcd for $C_{15}H_{21}NO_2S$: C, 64.49; H, 7.58; N, 5.02. Found: C, 64.58; H, 7.63; N, 4.93.

6,7-Dimethoxy-2,2a,3,4-tetrahydro-1*H*-9-thia-11a-azapentaleno[6a,1a]naphthalen-11-one (47). To a solution of 1.0 g (3.7 mmol) of thioamide **45** in 30 mL of CH_2Cl_2 at room temperature was added 0.4 mL (4.2 mmol) of bromoacetyl chloride, and the mixture was heated at reflux for 2 h. The reaction mixture was cooled to 0 °C, quenched with water, and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 1.0 g (88%) of **47** as a white solid: mp 153−154 °C; IR (CH_2Cl_2) 1680, 1510, and 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.80−1.91 (m, 2H), 2.08−2.25 (m, 2H), 2.52−2.59 (m, 1H), 2.65−2.83 (m, 2H), 2.95−3.01(m, 1H), 3.75 (d, 1H, J = 15.6 Hz), 3.80−3.85 (m, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 4.23 (d, 1H, J = 15.6 Hz), 6.51 (s, 1H), and 6.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 23.8, 27.1, 36.6, 42.1, 46.0, 55.7, 55.9, 74.6, 109.3, 110.3, 127.9, 129.3, 148.2, 148.9, and 172.0. Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.28; N, 4.59. Found: C, 62.89; H, 6.23; N, 4.58.

14-Aza-4,5-dimethoxy-17-thiatetracyclo[8.7.0.0^{1,14}.0^{2,7}]-heptadeca-2(7),3,5-trien-15-one (48). To a solution of 0.3 g (1.0 mmol) of thioamide **46** in 5 mL of CH_2Cl_2 at room temperature was added 0.1 mL (1.2 mmol) of bromoacetyl chloride, and the mixture was heated at reflux for 2 h. The solution was cooled to 0 °C, quenched with water, and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 0.3 g (95%) of **48** as a colorless solid: mp 138−139 °C; IR (CH_2Cl_2) 1676, 1401, and 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.51−1.72 (m, 4H), 1.79−1.86 (m, 1H), 2.11−2.17 (m, 1H), 2.26−2.35 (m, 1H), 2.55−2.85 (m, 3H), 3.71 (d, 1H, J = 15.6 Hz), 3.81 (s, 3H), 3.84 (d, 1H, J = 15.6 Hz), 3.85 (s, 3H), 4.20−4.25 (m, 1H), 6.54 (s, 1H), and 6.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 24.7, 25.0, 25.9, 33.2, 40.2, 43.8, 55.8, 56.1, 72.1, 107.4, 111.1, 127.7, 128.7, 148.6, 148.9, and 170.3. Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.89; H, 6.65; N, 4.31.

7,8-Dimethoxy-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indole (51). To a solution of 0.1 g (0.3 mmol) of **47** in 5 mL of EtOH was added 1 mmol of excess of Raney nickel. The reaction mixture was heated at 80 °C for 12 h and was cooled to room temperature. The mixture was filtered through Celite and concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 0.07 g (91%) of **51** as a clear oil: IR (CH_2Cl_2) 1603, 1503, and 1270 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.55−1.65 (m, 2H), 2.25−2.32 (m, 2H), 2.80−2.86 (m, 2H), 2.95−2.99 (m, 1H), 3.66−3.75 (m, 1H), 3.84 (s, 3H), 3.91 (s, 3H), 4.10−4.16 (m, 1H), 6.66 (s, 1H), and 7.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8, 29.9, 31.1, 46.7, 55.8, 55.9, 59.1, 107.1, 110.6, 122.8, 134.6, 147.7, 151.2, and 174.0. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.69; H, 7.41; N, 6.06. Found: C, 72.71; H, 7.40; N, 5.99.

6,7-Dimethoxy-1,2,3,4-tetrahydro-4-azaphenanthrene (52). To a solution of 0.1 g (0.3 mmol) of **48** in 5 mL of EtOH was added a 1 mmol excess of Raney nickel. The reaction mixture was heated at 80 °C for 5 h and was cooled to room temperature. The mixture was filtered through Celite and concentrated under reduced pressure. The resulting crude residue was subjected to flash silica gel chromatography to give 0.07 g (90%) of **52** as a colorless oil: IR (CH_2Cl_2) 3424, 1489, and 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.01−2.06 (m, 2H), 2.90 (t, 2H, J = 6.4 Hz), 3.49 (t, 2H, J = 5.6 Hz) 3.98 (s, 3H), 3.99 (s, 3H), 6.96 (s, 1H), 7.00 (d, 1H, J = 8.4 Hz), and 7.06−7.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 27.3, 42.7, 55.7, 55.9, 99.2, 107.3, 116.1, 116.8, 118.8, 126.8, 128.5,

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137.3, 148.7, and 148.9. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.05; N, 5.76. Found: C, 74.01; H, 6.93; N, 5.72.

3-Phenethylpiperidine-2-thione (53). To a solution of 0.9 mL (6.4 mmol) of diisopropylamine in 10 mL of THF at 0 °C was added 2.8 mL (7.0 mmol) of 2.5 M *n*-butyllithium. The solution was allowed to stir at 0 °C for 30 min and was cooled to −78 °C. To this mixture was added a solution of 1.0 g (5.8 mmol) of *N*-trimethylsilylvalerolactam[56] in 5 mL of THF. The reaction mixture was allowed to warm to room temperature over a period of 1 h and was recooled to −78 °C. A 1.0 mL (7.0 mmol) sample of phenethyl iodide[55] was added, and the reaction mixture was allowed to warm to room temperature over a period of 2 h. The mixture was quenched with a saturated solution of NH_4Cl and extracted with ethyl acetate. The combined organic extracts were concentrated under reduced pressure and the resulting residue was dissolved in 10 mL of THF. An excess of 1.5 M tetrabutylammonium fluoride solution in THF was added at room temperature, and the mixture was allowed to stir for 2 h. The reaction mixture was concentrated under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography to give 0.9 g (77%) of 3-phenethylpiperidin-2-one as a white solid: mp 99−100 °C; IR (CH_2Cl_2) 1559, 1360, and 1331 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50−2.04 (m, 5H), 2.21−2.33 (m, 2H), 2.60−2.79 (m, 2H), 3.25−3.32 (m, 2H), 5.92 (brs, 1H), and 7.12−7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 26.3, 33.2, 33.3, 40.5, 42.4, 125.8, 128.3, 128.4, 141.9, and 174.7. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.80; H, 8.43; N, 6.89. Found: C, 76.91; H, 8.46; N, 6.94.

To a solution of 0.8 g (4.0 mmol) of the above amide in 40 mL of toluene was added 0.8 g (2.0 mmol) of Lawesson's reagent. The mixture was heated at reflux for 4 h and cooled to room temperature. The crude mixture was concentrated under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography to give 0.8 g (89%) of thioamide **53** as a white solid: mp 90−91 °C; IR (CH_2Cl_2) 1560, 1360, and 1325 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.62−1.69 (m, 1H), 1.74−1.82 (m, 1H), 1.87−1.98 (m, 3H), 2.54−2.71 (m, 3H), 2.77−2.84 (m, 1H), 3.28−3.36 (m, 2H), 7.16−7.20 (m, 1H), 7.23−7.30 (m, 4H), and 8.97 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 24.6, 33.1, 36.6, 44.7, 45.8, 125.8, 128.4, 128.5, 141.5, and 207.2. Anal. Calcd for $C_{13}H_{17}NS$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.13; H, 7.85; N, 6.33.

14-Azathiatetracyclo[8.7.0.0^{1,14}.0^{2,7}]heptadeca-2(7),3,5-trien-15-one (54). To a solution of 0.2 g (0.9 mmol) of thioamide **53** in 5 mL of CH_2Cl_2 was added 0.1 mL (1.1 mmol) of bromoacetyl chloride at room temperature. After the mixture was stirred for 10 min, 0.4 g (2.7 mmol) of $AlCl_3$ was added in one portion, and the reaction was heated at reflux for 2 h. The mixture was cooled to 0 °C, quenched with water, and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give a 2:1 mixture of two compounds. The major product obtained contained 0.08 g (31%) of *N,S*-ketal **54** as a clear oil that exhibited the following spectral properties: IR (CH_2Cl_2) 1674, 1396, and 1268 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43−1.74 (m, 4H), 1.83−1.89 (m, 1H), 2.16−2.33 (m, 2H), 2.52−2.58 (m, 1H), 2.75−2.91 (m, 2H), 3.69 (d, 1H, J = 15.6 Hz), 3.84 (d, 1H, J = 15.6 Hz), 4.20−4.25 (m, 1H), 7.09−7.14 (m, 2H), and 7.18−7.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 24.6, 24.7, 26.1, 33.0, 39.9, 43.9, 71.6, 125.0, 127.2, 127.8, 129.5, 134.8, 137.4, and 170.2; HRMS calcd for $C_{15}H_{17}NOS$ 259.1030, found 259.1028.

8-Phenethyl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyridin-3-one (55). The minor fraction isolated from the above column chromatography contained 0.03 g (14%) of **55** as a yellow solid: mp 84−85 °C; IR (CH_2Cl_2) 1687, 1652, and 1389 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.80−1.86 (m, 2H), 2.11 (t, 2H, J = 6.4 Hz), 2.29 (t, 2H, J = 7.6 Hz), 2.72 (t, 2H, J = 7.8 Hz), 3.57 (t, 2H, J = 6.4 Hz), 3.70 (s, 2H), 7.18−7.21 (m, 3H), and 7.26−7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 26.8, 32.6, 33.6, 35.1, 41.4, 109.3, 125.9, 127.0, 128.3, 128.4, 141.4, and 169.5. Anal. Calcd for $C_{15}H_{17}NOS$: C, 69.47; H, 6.61; N, 5.40. Found: C, 69.44; H, 6.62; N, 5.36.

Methyl 3,7-Dimethyloct-6-enethionic Acid Amide (56). To a solution containing 3 mL (16 mmol) of citronellic acid in 30 mL of CH_2Cl_2 was added 3.2 g (20 mmol) of 1,1′-carbonyldiimidazole. The reaction mixture was allowed to stir for 1 h, after which time the mixture was cannulated into a solution of 10 mL of 40% methylamine in 20 mL of CH_2Cl_2 at 0 °C. The solution was allowed to warm to room temperature over a period of 4 h and was diluted with 50 mL of water. The product was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give 0.3 g (98%) of *N*-methyl 3,7-dimethyloct-6-enamide as a thick oil. This material was dissolved in 50 mL, of toluene and 3.2 g (8.0 mmol) of Lawesson's reagent was added. The mixture was heated at reflux for 2 h and cooled to 25 °C, and the solvent was removed under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 2.6 g (82%) of thioamide **56** as a clear oil: IR (CH_2Cl_2) 1538, 1453, and 1368 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 6.4 Hz), 1.17−1.25 (m, 1H), 1.31−1.42 (m, 1H), 1.60 (s, 3H), 1.68 (s, 3H), 1.91−2.09 (m, 2H), 2.12−2.22 (m, 1H), 2.39−2.45 (m, 1H), 2.65−2.70 (m, 1H), 3.16 (d, 3H, J = 4.8 Hz), 5.08 (t, 1H, J = 7.2 Hz), and 7.88 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 18.7, 25.3, 25.5, 32.7, 33.4, 36.4, 54.3, 124.1, 131.4, and 205.4. Anal. Calcd for $C_{11}H_{21}NS$: C, 66.29; H, 10.63; N, 7.03. Found: C, 66.15; H, 10.71; N, 7.18.

6-Isopropenyl-4,9-dimethyl-1-thia-4-azaspiro[4.5]decan-3-one (58). To a solution of 0.5 g (2.5 mmol) of **56** in 20 mL of CH_2Cl_2 at room temperature was added 0.3 mL (3.0 mmol) of bromoacetyl chloride, and the mixture was heated at reflux for 2 h. The solution was concentrated under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography to give 0.38 g (63%) of the major diasteromer of **58** as a colorless solid: mp 124−125 °C; IR (CH_2Cl_2) 1673, 1453 and 1389 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, 3H, J = 5.6 Hz), 1.64−1.83 (m, 10H), 2.33−2.37 (m, 1H), 2.87 (s, 3H), 3.30 (d, 1H, J = 15.6 Hz), 3.41 (d, 1H, J = 15.6 Hz), and 4.89 (d, 2H, J = 17.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 22.8, 28.2, 28.8, 29.5, 32.7, 34.0, 48.4, 49.2, 76.5, 115.2, 144.1, and 171.3. Anal. Calcd for $C_{13}H_{21}NO_1S$: C, 65.24; H, 8.85; N, 5.86. Found: C, 65.33; H, 8.91; N, 5.80. The stereochemistry of **58** is not known.

5,6,9-Trimethoxy-11b*H*-1-thia-3a-azacyclopenta[*l*]-phenanthren-3-one (62). To a solution of 0.5 g (1.6 mmol) of thioamide **60**[57] in 30 mL of CH_2Cl_2 at room temperature was added 0.2 mL (2.0 mmol) of bromoacetyl chloride, and the mixture was heated at reflux for 2 h. The solution was concentrated under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography to give 0.4 g (77%) of **62** as a yellow solid: mp 200−202 °C; IR (CH_2Cl_2) 1666, 1595 and 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 4.58 (s, 2H), 6.77−6.94 (m, 5H), and 7.27−7.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.6, 55.6, 56.1, 56.2, 110.4, 111.3, 115.0, 119.8, 119.9, 128.3, 130.3, 149.8, 150.2, 161.9, 163.4, 167.8, and 183.2. Anal. Calcd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08. Found: C, 63.08; H, 5.02; N, 4.11.

1-(2,3,9-Trimethoxy-6*H*-phenanthridin-5-yl)ethanone (63). To a solution of 0.2 g (0.6 mmol) of **62** in 5 mL of EtOH at room temperature was added a 3 equiv excess of Raney nickel. The reaction mixture was heated at 80 °C for 5 h and was allowed to cool to room temperature. The mixture was filtered through Celite and concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 0.2 g (83%) of **63** as a pale yellow oil: IR (CH_2Cl_2) 1648, 1511 and 1205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.51 (s, 3H), 3.75 (s, 3H), 3.76 (s, 3H), 3.85 (s, 3H), 6.69−6.71 (m, 2H), 6.76−6.78 (m, 2H), 6.83−6.86 (m, 1H), 7.18 (s, 1H), and 7.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 55.6, 56.1, 56.2, 101.2, 110.6, 111.3, 114.8, 120.0, 120.3, 128.7, 130.1, 149.7, 150.0, 162.1, 163.0, 165.8, and 170.3; HRMS calcd for $C_{18}H_{19}NO_4$ 313.1314, found 313.1315.

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8,9-Dimethoxy-10b-methyl-6,10b-dihydro-5*H*-thiazolo-[2,3-*a*]isoquinolin-3-one (65). To a solution of 0.5 g (2 mmol) of thioamide **64**[49] in 10 mL of CH_2Cl_2 at room temperature was added 0.2 mL (2.4 mmol) of bromoacetyl chloride, and the mixture was stirred at room temperature for 18 h. The solution was concentrated under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography to give 0.6 g (98%) of **65** as a white solid: mp 129−130 °C; IR (CH_2Cl_2) 1673, 1510, and 1140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.95 (s, 3H), 2.66−2.71 (m, 1H), 2.91−2.98 (m, 1H), 3.14−3.17 (m, 1H), 3.63 (d, 1H, J = 15.6 Hz), 3.80−3.85 (m, 1H), 3.84 (s, 3H), 3.89 (s, 3H), 4.40−4.51 (m, 1H), 6.56 (s, 1H), and 6.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 32.4, 34.0, 36.7, 55.8, 56.0, 68.0, 107.7, 111.2, 123.6, 132.1, 148.2, 148.4, and 169.1. Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.06; H, 6.09; N, 4.98.

1-(6,7-Dimethoxy-1-methylene-3,4-dihydro-1*H*-isoquinolin-2-yl)ethanone (66). To a solution of 0.1 g (0.4 mmol) of **65** in 5 mL of EtOH at room temperature was added a 3 equiv excess of Raney nickel. The reaction mixture was heated at reflux for 15 h and was cooled to room temperature. The mixture was filtered through Celite and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.06 g (71%) of **66** as a white solid: mp 106−107 °C (lit.[49] mp 106−107 °C); IR (CH_2Cl_2) 1681, 1510, and 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.83 (t, 2H, J = 6.0 Hz), 3.88 (s, 3H), 3.92 (s, 3H), 3.98 (t, 2H, J = 6.0 Hz), 4.97 (brs, 1H), 5.61 (brs, 1H), 6.60 (s, 1H), and 7.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 28.3, 41.4, 55.7, 55.8, 104.0, 106.5, 111.0, 123.5, 127.8, 142.9, 147.5, 149.6, and 169.1. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.98; H, 6.93; N, 5.67. Found: C, 67.79; H, 6.87; N, 5.55.

2-(3,4-Dimethoxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)-ethyl]thioacetamide (68). To a solution of 5.0 g (25 mmol) of (3,4-dimethoxyphenyl)acetic acid in 50 mL of benzene was added 6.7 mL (76 mmol) of oxalyl chloride, which contained 2 drops of DMF. The solution was allowed to stir for 2 h at room temperature, after which time the excess oxalyl chloride was removed under reduced pressure. The crude acid chloride was taken up in 50 mL of CH_2Cl_2 and was cannulated into a solution containing 4.3 mL (25 mmol) of 3,4-dimethoxyphenethylamine in 150 mL of CH_2Cl_2 at 0 °C. The mixture was allowed to warm to room temperature over a period of 2 h and was quenched with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford 8.0 g (87%) of 2-(3,4-dimethoxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide as a thick oil. This material was dissolved in 50 mL of toluene, and 4.5 g (11 mmol) of Lawesson's reagent was added. The reaction mixture was heated at reflux for 5 h and cooled to room temperature, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 7.9 g (83%) of **68** as a light amber oil: IR (CH_2Cl_2) 1510, 1261, and 1232 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.78 (t, 2H, J = 6.4 Hz), 3.78 (s, 3H), 3.82−3.88 (m, 2H), 3.83 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 4.03 (s, 2H), 6.40 (d, 1H, J = 8.0 Hz), 6.58 (m, 4H), 6.79 (d, 1H, J = 8.0 Hz), and 7.02 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.0, 44.6, 52.7, 55.7, 55.8, 110.9, 111.0, 111.2, 111.3, 120.3, 121.9, 126.4, 129.9, 147.7, 148.6, 149.1, 149.4, and 201.9. Anal. Calcd for $C_{20}H_{25}NO_4S$: C, 63.97; H, 6.72; N, 3.73. Found: C, 63.85; H, 6.68; N, 3.71.

2-(3,4-Dimethoxybenzylidene)-3-[2-(3,4-dimethoxyphenyl)ethyl]thiazolidin-4-one (69). To a solution of 0.5 g (1.3 mmol) of **68** in 15 mL of toluene at room temperature was added 0.1 mL (1.6 mmol) of bromoacetyl chloride, and the mixture was heated at reflux for 18 h. The solution was concentrated under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography to give 0.5 g (84%) of **69** as a pale yellow oil: IR (CH_2Cl_2) 1688, 1510 and 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.96 (t, 2H, J = 7.6 Hz), 3.76−3.98 (m, 16H), 6.00 (s, 1H), and 6.78−6.92 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0, 32.3, 44.2, 55.8, 55.9, 102.2, 110.9, 111.2, 111.9, 112.0, 120.3, 120.7, 128.4, 130.3, 135.1, 147.2, 147.8, 148.7, 148.9, and 170.2. Anal. Calcd for $C_{22}H_{25}N\,O_5S$: C, 63.59; H, 6.07; N, 3.37. Found: C, 63.71; H, 6.04; N, 3.30.

10b-(3,4-Dimethoxybenzyl)-8,9-dimethoxy-6,10b-dihydro-5*H*-thiazolo[2,3-*a*]isoquinolin-3-one (70). To a solution of 0.15 g (0.35 mmol) of **69** in 3 mL of CH_2Cl_2 was added 0.3 mL (3.6 mmol) of trifluoroacetic acid, and the mixture was allowed to stir at room temperature for 2 days. The solution was quenched with water and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 0.14 g (93%) of **70** as a colorless oil: IR (CH_2Cl_2) 1674, 1510, and 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.59 (d, 1H, J = 14.8 Hz), 2.72−2.77 (m, 1H), 2.93−3.02 (m, 1H), 3.13−3.23 (m, 2H), 3.41 (d, 1H, J = 14.8 Hz), 3.86−3.92 (m, 13H), 4.47−4.51 (m, 1H), 6.61 (s, 1H), 6.64 (s, 1H), 6.71−6.73 (m, 1H), 6.79 (s, 1H), and 6.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 34.5, 37.0, 48.5, 55.7, 55.8, 55.9, 56.2, 71.5, 107.9, 110.6, 111.3, 114.1, 123.2, 124.0, 127.1, 131.3, 148.2, 148.4, 148.5, and 170.0. Anal. Calcd for $C_{22}H_{25}NO_5S$: C, 63.59; H, 6.07; N, 3.37. Found: C, 63.51; H, 6.04; N, 3.24.

***N*-Acetyltetrahydropapaveroline (71).** To a solution of 0.1 g (0.2 mmol) of **70** in 5 mL of EtOH at room temperature was added a 3 equiv excess of Raney nickel. The reaction mixture was heated at reflux for 15 h and was cooled to room temperature. The solution was filtered through Celite and then concentrated under reduced pressure. The resulting crude residue was subjected to flash silica gel chromatography to give 0.06 g (68%) of **71** as a white solid: mp 135−136 °C (lit.[49] 135−136 °C). Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.54; H, 7.06; N, 3.64. Found: C, 68.43; H, 6.97; N, 3.41. This compound was taken on to tetrahydropapaverine (**72**) according to the method of Kitamura and co-workers.[49]

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Supporting Information Available: ^1H and ^{13}C NMR spectra for new compounds lacking elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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