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Application of Cross-Conjugated Heteroaromatic Betaines to the Synthesis of the Schizozygane Alkaloid (±)-Strempeliopine†

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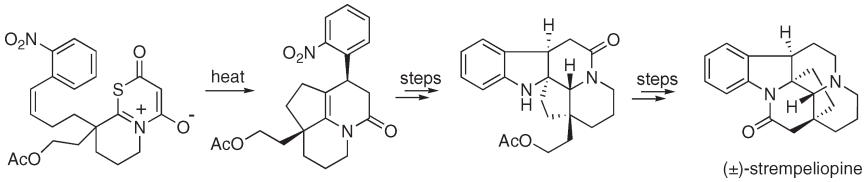

An efficient stereocontrolled route to the isoschizozygane alkaloid core has been developed utilizing an intramolecular 1,4-dipolar cycloaddition of a cross-conjugated heteroaromatic betaine. The resulting cycloadduct undergoes loss of COS, and further reduction delivers a 5*a*-azaacenaphthylene intermediate that was transformed into the isoschizozygane skeleton upon treatment with acid. A variation of this tactic was then employed for a synthesis of the hexacyclic framework of the shizozygane alkaloid (±)-strempeliopine. The key step of the synthesis corresponds to an intramolecular 1,4-dipolar cycloaddition of a heteroaromatic betaine across a tethered 4-((2-nitrophenyl)but-3-enyl) side chain. Catalytic reduction of the nitro group followed by reaction with NBS resulted in the formation of the required pentacyclic indoline framework of the target alkaloid. Closure of the final ring of the shizozygane skeleton was carried using an oxidative cyclization.

Introduction

The cyclopentaquinolizine and hexahydrojulolidine basic ring skeletons (i.e., **1** and **2**, respectively) are found in a variety of biologically active naturally occurring alkaloids, including the schizozygane and isoschizozygane alkaloids.[1] These compounds (Figure 1) represent a relatively small group of hexacyclic indoline alkaloids isolated from a variety of shrub species.[2] All but strempeliopine (**3**), an alkaloid of the Cuban species *Strempeliopsis strempelioides* K. Schum,[3] were isolated from the East-African monotypic shrub *Schizozygia coffaeoides* (Boj.) Baill.[4] This plant has been used as a traditional medicine for a variety of skin diseases, and some

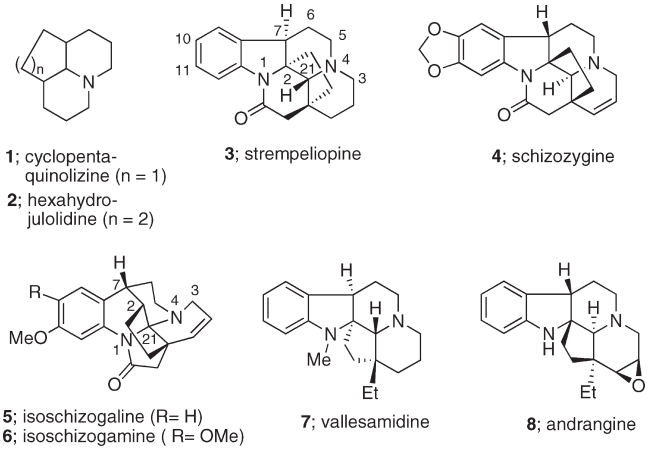

FIGURE 1

members of this family also exhibit antifungal and antimicrobial activity.[5] Although these compounds exhibit modest biological activity, the highly caged, hexacyclic core of the

† This paper is dedicated to the memory of Professor Nabi Magomedov of the University of Rochester who died tragically on February 7, 2006, in a multivehicle accident.

(1) Saxton, J. E. In *Indoles, Part 4, The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; John Wiley: New York, 1984; Chapter 9, pp 437−486.

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(4) Renner, U.; Fritz, H. *Helv. Chim. Acta* **1965**, *27*, 308.

(5) (a) Omino, E. A.; Kokwaro, J. O. *J. Etnopharmacol.* **1993**, *40*, 167. (b) Kariba, R. M.; Siboe, G. M.; Dossaji, S. F. *J. Etnopharmacol.* **2001**, *74*, 41. (c) Kariba, R. M.; Houghton, P. J.; Yenesew, A. *J. Nat. Prod.* **2002**, *65*, 566.

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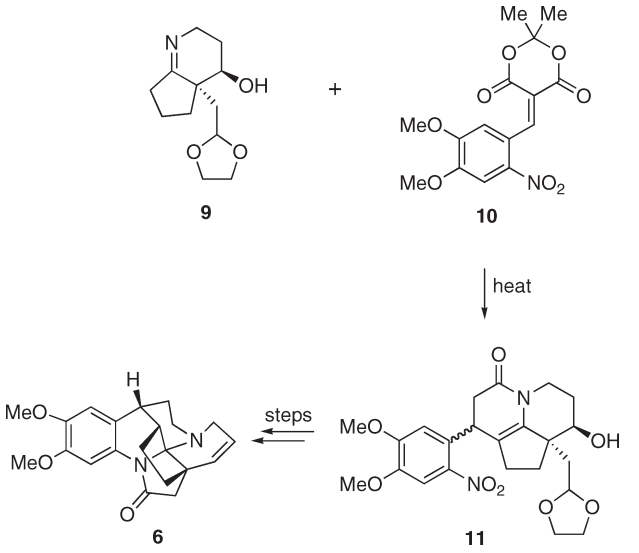
SCHEME 1

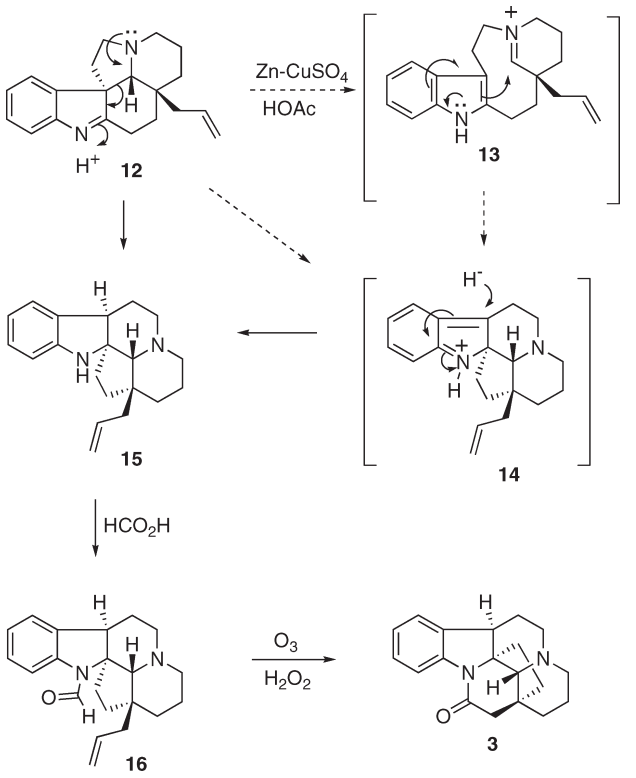


schizozyganes and isoschizozyganes has made this class of natural products attractive targets for total synthesis.[6] Originally, the isoschizozyganes (**5**/**6**) were reported to contain a vicinal diamino unit that is also present in strempeliopine (**3**) and schizozygine (**4**).[2b] However, the structure of isoschizogamine (**6**) was subsequently revised and shown to contain the N1−C_{21}−N_4 aminal core linkage.[7]

Heathcock and Hubbs[6b] were the first to report a concise total synthesis of isoschizogamine (**6**) based on a partial biosynthesis proposed by Hajicek.[7] This involved Michael addition of the enamine tautomer of imine **9** with the Meldrum acid derivative **10** followed by cyclization with concomitant loss of acetone and carbon dioxide to afford a good yield of a diastereomeric mixture of lactams **11** which was eventually converted into **6** (Scheme 1). More recently, Magomedev presented an alternate strategy to the cyclopenta[*b*]quinoline core using a formal hetero Diels−Alder reaction as well as another approach based on a cyclization reaction of an acylamidine intermediate.[8]

The unusual structure of the schizozygane alkaloids has also made them challenging targets for total synthesis. While the synthesis of *seco*-schizozygane and the related vallesamidine alkaloids has been previously reported,[9] only one synthesis of strempeliopine (**3**) has been described to date and is based on a reductive rearrangement of an indolenine (Scheme 2).[10] Thus, Zn−$CuSO_4$-mediated reduction of compound **12** in hot acetic acid led to the formation of the 2,3,3-trisubstituted

SCHEME 2



indoline **15**.[11] This reaction has been suggested to proceed via the intermediacy of iminium ion **13** and then **14**, which is ultimately reduced to give **15**.[6a] An alternative possibility would involve a 1,2-shift of **12** to give **14**. Hydride attack on the conjugated iminium ion would come from the least hindered bottom face to provide **15**. Compound **15** was then formylated to furnish **16** which was subsequently subjected to ozonolysis in the presence of H_2O_2 to afford (±)-strempeliopine (**3**) in 49% yield. More recently, a total synthesis of 15α-hydroxystrempeliopine was accomplished by using a related zinc-mediated reductive rearrangement as the key step of the synthesis.[6a]

It was postulated that the skeleton of the schizozyganes could be related biogenetically to the *Aspidosperma* alkaloids, and indeed, both groups of alkaloids can be found in the same plant species.[5c] A proposed biosynthesis of the schizozyganes from the *Aspidosperma* alkaloids and further conversion to the isoschizozyganes was postulated by Hájíček[7] and is shown in Scheme 3. Acid-catalyzed rearrangement of the aspidosperma skeleton (i.e., **17**) would lead to the ring-opened schizozygane skeleton **18**. Simple ring closure of **18** leads to the schizozygane skeleton while oxidation gives rise to iminium intermediate **19**. Addition of the indoline nitrogen to iminium **19** produces aziridine **20** and further reductive opening of **20** followed by cyclization would eventually afford the isoschizozygane core skeleton.

During the context of our own interest in this area, we conceived an alternate approach to assemble the cyclopenta-[*b*]quinoline core of these alkaloids. Our plan toward the schizozygane and isoschizozygane alkaloid core is based on an annulation strategy previously developed in our laboratories.[12]

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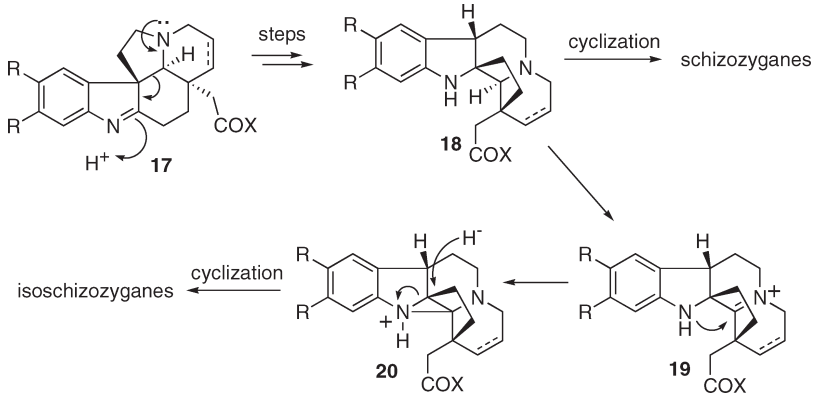
(11) (a) Hájíček, J.; Trojánek, J. *Tetrahedron Lett*. **1981**, *22*, 2927. (b) Hájíček, J.; Trojánek, J. *Tetrahedron Lett*. **1982**, *23*, 365. (c) Hájíček, J.; Trojánek, J. *Collect. Czech. Chem. Commun*. **1986**, *51*, 1731.
(12) Padwa, A.; Coats, S. J.; Semones, M. A. *Tetrahedron* **1995**, *51*, 6651.

SCHEME 3



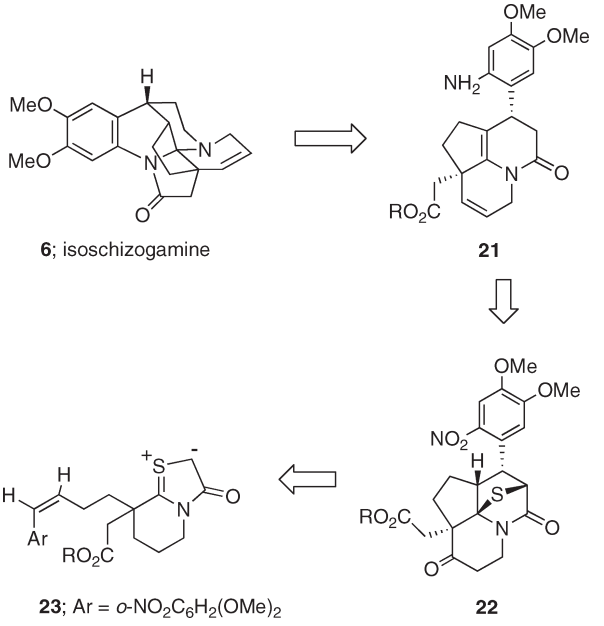
In this paper, we describe the details of our approach to this class of alkaloids which makes use of an intramolecular [1,4]-dipolar cycloaddition reaction of a cross-conjugated heteroaromatic betaine[13] to construct the novel hexacyclic skeleton of (±)-strempeliopine (**3**).

Results and Discussion

In an earlier paper,[14] we reported our approach to the isoschizozygane core utilizing dipolar cycloaddition chemistry developed in our laboratory. Our initial route was based on an intramolecular [3 + 2]-cycloaddition of a thiocarbonyl ylide across a tethered π-bond (Scheme 4).[15] We assumed that the hexacyclic skeleton of isoschizogamine (**6**) could be formed from a compound of type **21** by a sequence of enamide protonation, acyliminium ion cyclization, and lactamization. Enamide **21** may be generated by extrusion of sulfur from cycloadduct **22** followed by reduction of both the nitro and keto groups and a subsequent dehydration. The key cycloadduct **22** should be accessible from an intramolecular dipolar cycloaddition of the thioisomünchnone dipole **23**.

In order to test the feasibility of the retrosynthetic strategy outlined in Scheme 4, our initial efforts were focused on model substrates. Several *cis*-aryl alkenyl substituted piperidinethiones were prepared by Castro−Stevens coupling[16] of the acetylenic NH-lactams followed by nickel boride catalyzed hydrogenation of the alkynyl group[17] and subsequent conversion to the thiolactams using Lawesson's reagent.[18] Treatment of the simple phenyl-substituted thiolactam **24** with bromoacetyl chloride and triethylamine at 25 °C gave the desired cycloadduct **28** in 85% yield as a single diastereomer corresponding to *endo*-cycloaddition (Scheme 5). Assignment of the stereochemistry of cycloadduct **28** is based on its spectroscopic properties and also by analogy to related

SCHEME 4



cycloadditions using isomünchnones where X-ray data had been obtained.[19] Unfortunately, all of our attempts to induce an analogous reaction using the closely related *o*-nitro-substituted thioamide **25** failed to give any signs of an internal cycloadduct. Similar experiments were carried out using the related *o*-NHBoc and *o*-Br aryl piperidinethiones **26** and **27**. In both of these cases, no product attributable to intramolecular cycloaddition could be detected. Whereas the reaction of the *cis*-aryl alkenyl substituted piperidinethiones **25**−**27** failed to produce an internal cycloadduct, reaction in the presence of *N*-phenylmaleimide proved fruitful. This bimolecular cycloaddition occurred in 75−80% yield providing a 1:1 mixture of diastereomeric cycloadducts (i.e., **29**−**31**), thereby establishing that the expected 1,3-dipole was indeed being formed. Apparently, the presence of an ortho substituent on the aromatic ring of the dipole-derived thioamides **25**−**27** twists the thioisomünchnone far enough away from the tethered *cis*-alkenyl substituent in the preferred

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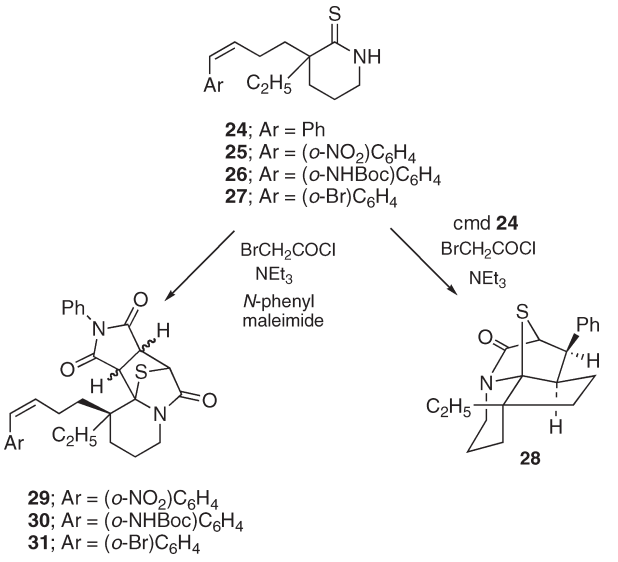
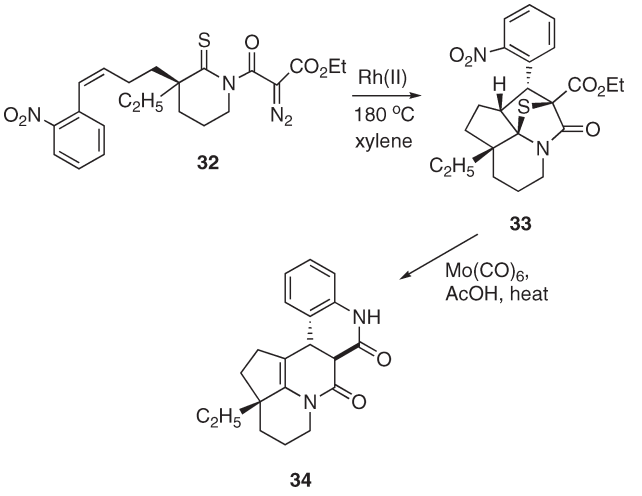
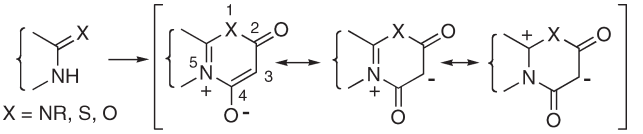
SCHEME 5



SCHEME 6



SCHEME 7



transition state, thereby preventing the intramolecular cycloaddition. This is not the case with the bimolecular cycloaddition, wherein the intermediate 1,3-dipole and the dipolarophile can be close in proximity without retardation of the cycloaddition process.

We thought that employing a more reactive dipole, especially one stable at a higher temperature, would help to alleviate this spatiality problem. The formation and dipolar trapping of thioisomünchnones via the interaction of rhodium carbenoids derived from diazo thioamides[20] has not been studied in as much detail as the isomünchnone system.[21] The advantage of using this method to generate the dipole is that the reaction can be carried out at much higher temperatures (i.e., 180 °C). Indeed, we were delighted to find that treatment of diazo thioamide **32** under Rh(II) catalysis did indeed provide cycloadduct **33** in 85% yield. However, our attempts to remove the sulfur atom by treating compound **33** with molybdenum hexacarbonyl in acetic acid following the protocol of Alper and Blais[22] only afforded pentacycle **34** in 83% yield (Scheme 6). This product arose by reduction of both the sulfur bridge and nitro group, and the resulting anilino group then underwent a subsequent lactamization reaction with the adjacent ester functionality.

In order to avoid the difficulties associated with the presence of the extra carbethoxy group in cycloadduct **33**, we decided to employ a 1,4-dipole (i.e., **35**) for formation of the structural backbone of the isoschizozygane alkaloids. In contrast with 1,3-dipoles, much less is known about the cycloaddition behavior of 1,4-dipoles whose transient existence was first postulated in 1967.[23] This class of reactive intermediates (Scheme 7), while of considerable theoretical interest, attracted little synthetic attention until the elements of a 1,4-dipole were incorporated into a cross-conjugated heteroaromatic betaine[13] by the cyclocondensation of an appropriately substituted monoprotic amidine or thioamide with a 1,3-bielectrophile derived from malonic acid.[24] Intramolecular 1,4-dipolar cycloadditions of these betaines,[25] or their tautomeric equivalents,[26] have resulted in ring annulations leading to bi- and tricyclic heterocycles[27] which were not readily accessible by normal cyclocondensation routes. The overall convenience of this method, the ease of access to starting materials, and the relatively high yields and purity of the products obtained suggested its application for the preparation of the isoschizoygane alkaloid core. It should be noted, however, that mesoionic dipoles constructed in a manner which allows for intramolecular cycloaddition often lead to cycloadducts that are difficult to convert into useful structures since subsequent elimination of a small stable fragment is not easily accomplished.[28] This can be avoided to some extent by using a suitably structured 1,4-dipole where the fragment being eliminated from the cycloadduct is, for example, cyanic acid,[29] carbon dioxide,[30] or carbonyl sulfide.[30] With this caveat in mind, we carried

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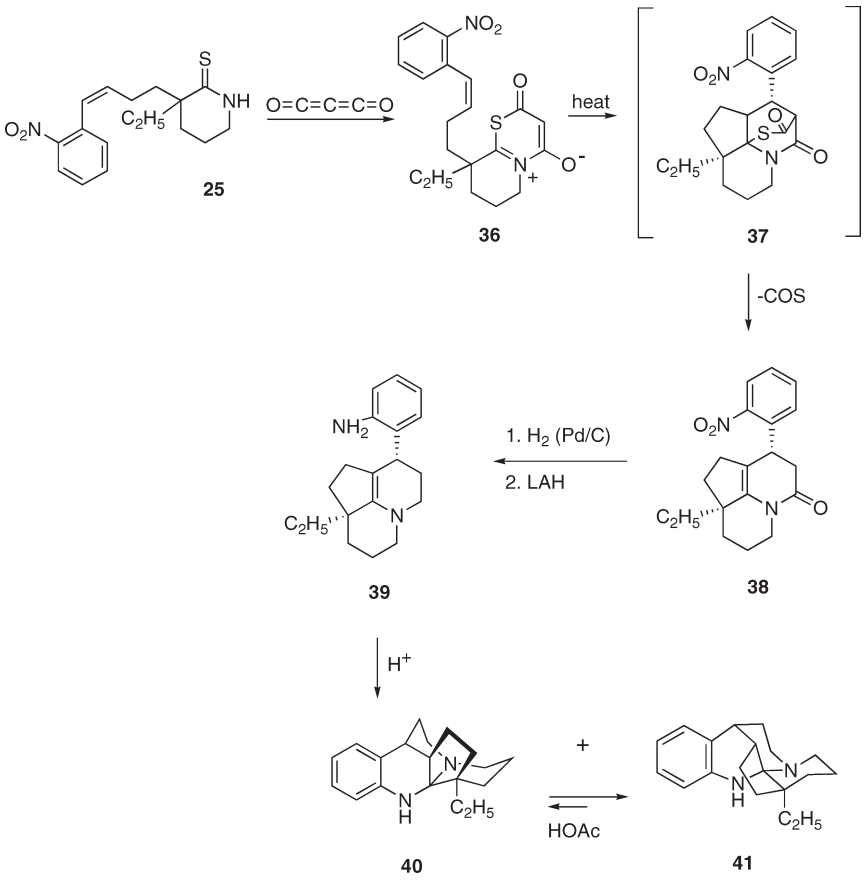
SCHEME 8



out a synthesis of 5*a*-aza-acenaphthylen-5-one **38** from the easily available thiolactam **25** (Scheme 8). Generation of the bright yellow isolable betaine **36** was accomplished by the reaction of **25** with carbon suboxide[31] at 25 °C for 5 h. Carbon suboxide is an extremely potent bis-electrophile that has found very limited use in the synthetic community. Presumably, the harsh conditions that were initially reported for its formation may have deterred its use.[31a] However, carbon suboxide can also be obtained from the zinc reduction of dibromomalonyl dichloride.[31b] This precursor, which is stable at low temperatures for extended periods of time, is easily scalable to multihundred gram scale. The carbon suboxide (bp = 7 °C) codistills with ether and is easily condensed with a dry ice/acetone condenser. Heating a sample of **36** at 120 °C for 3 h in toluene afforded **38** as a single diastereoisomer in 66% yield as a pale yellow solid whose formation is easily accounted for by extrusion of COS[32] from the originally formed cycloadduct **37** followed by a hydrogen shift. Catalytic reduction of the nitro functionality (H_2, Pd/C) in **38** to the corresponding amino group was followed by enamide reduction using LAH. The transient enamine **39** furnished a 3:2 mixture of diastereomeric aminals **40** and **41** when subjected to silica gel chromatography. The formation of the two observed diastereomers can be explained by protonation of the two diastereotopic faces of the double bond in the initially formed enamine **39**.[6b] Treatment of either isolated isomer with acetic acid resulted in an equilibrated 1:6 mixture of **40** and **41** with the major diastereomer possessing the correct core skeleton of the isoschizozygane family of alkaloids.

With our success in forming the core skeleton of the isoschizozygane alkaloid core, we became interested in extending the 1,4-dipolar cycloaddition methodology toward a synthesis of strempeliopine (**3**). Our retrosynthetic analysis is outlined in Scheme 9. The proposed plan involves the formation and intramolecular cycloaddition of the cross-conjugated heteroaromatic betaine **42** followed by extrusion of COS to give **43**. This would be followed by reduction of the nitro group and a subsequent NBS bromination in order to generate the transient *N*-acyliminium ion necessary for closure to pentacycle **44**. The final product **3** was envisioned to be derived from an oxidative cyclization of the protected primary alcohol **44**. The required lactam **45** needed for the preparation of betaine **42** was synthesized by an initial alkylation of δ-valerolactam with 4-bromobutene followed by reaction with the TBS-protected iodoethanol[33] to form the dialkylated product as shown in Scheme 10. Installation of the alkyne functionality was accomplished using a two-step procedure which involved bromination with Br_2 followed by elimination with lithium diisopropylamide (LDA)

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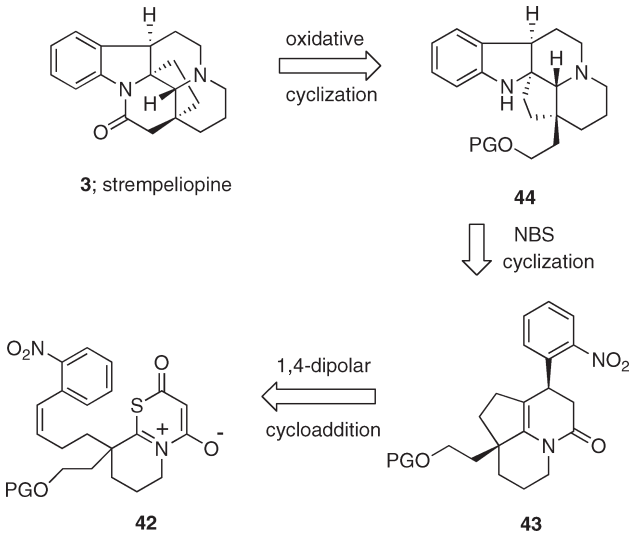
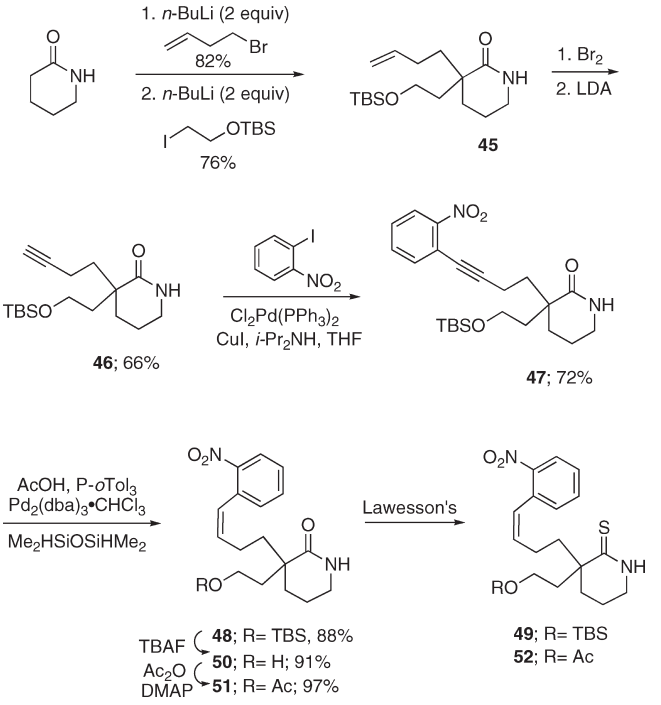
SCHEME 9



SCHEME 10



to produce alkyne **46** in 66% overall yield for the two-step sequence. Sonogashira coupling[34] of 1-iodo-2-nitrobenzene with **46** proceeded uneventfully to furnish the aromatic nitro functionality present in **47** in 72% yield. Conversion of **47** to the required *cis*-alkene **48** was carried out according to the method developed by Trost[35] using $Pd_2(dba)_3 \cdot CHCl_3$, AcOH, and 1,1,3,3-tetramethyldisiloxane to provide **48** in 88% yield as a 10:1 *Z*/*E* mixture. This four-step procedure for the installation of the alkenyl side chain was necessary as attempts to carry out the alkylkation with an alkynyl- or *cis*-alkenyl-substituted halide resulted in the exclusive formation of elimination products. Unfortunately, formation of the required thiolactam **49** from **48** using either Lawesson's reagent[18] or P_2S_5 under a variety of conditions resulted in poor conversion (< 15%), with the majority of the mass balance being decomposition products. Several TBS peaks in the crude ^{1}H NMR spectrum suggest loss of this protecting group. This problem was solved by a swap of the TBS group with an acetoxy group. Thus, treatment of **48** with tetrabutylammonium fluoride (TBAF) and then reprotection of the resulting alcohol with Ac_2O furnished acetate **51** in 89% overall yield for the two steps. Thiolactam formation using Lawesson's reagent proceeded uneventfully to provide **52** in 71% yield, thereby setting the stage for betaine formation and further cyclization.

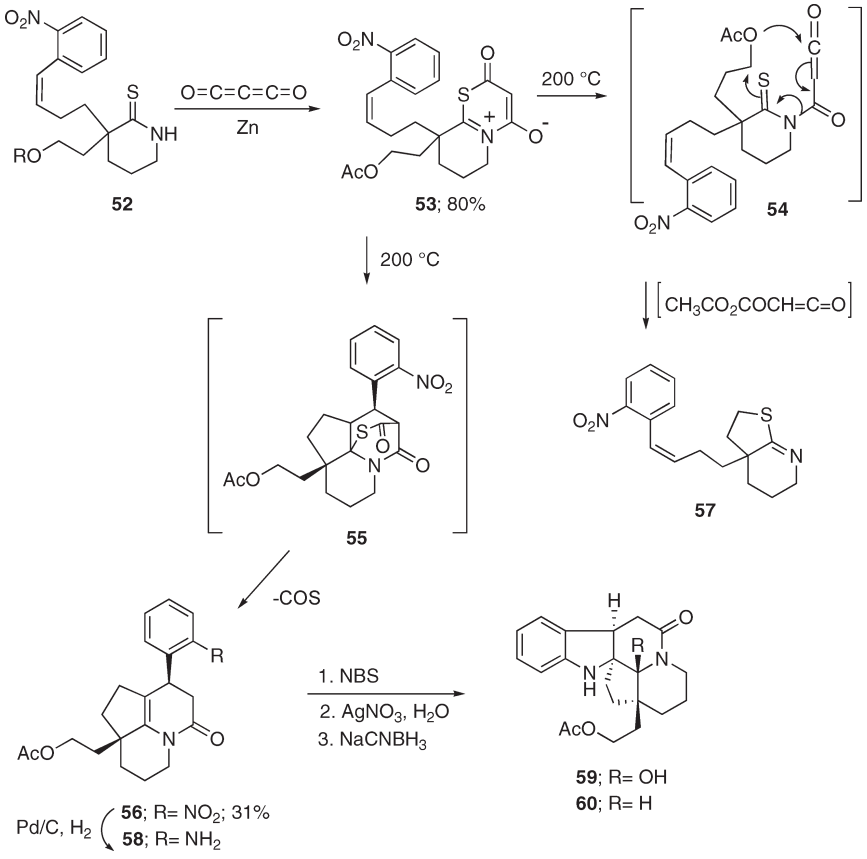
The isolable cross-conjugated heteroaromatic betaine **53** was obtained by treatment of thiolactam **52** with carbon suboxide (**33**)[31] as indicated in Scheme 11. Heating a sample of the bright yellow dipole **53** in a sealed tube in toluene at 200 °C for 1 h afforded tricycle **56** as a single diastereomer in 31% yield together with a similar amount of imine **57**. The formation of **57** can be explained by competitive loss of $CH_3CO_2COCH{=}C{=}O$ from betaine **53** by acetoxy elimination with concomitant cyclization onto the sulfur atom at the elevated reaction temperature. In our previous studies dealing with the generation of heteroaromatic betaines, the systems examined contained no potential leaving group attached to either of the side chains, and thus, products related to **57** were not encountered. All attempts to optimize the yield of **56** by heating the betaine dipole **53** for shorter periods of times, using lower reaction temperatures or varying the reaction solvent, were fruitless. Even though the yield of the cycloaddition step was less than optimum, we were able to obtain enough material to continue on with the planned synthesis of (±)-strempeliopine (**3**).

Catalytic reduction of the nitro functionality in **56** with Pd/C and H_2 provided the labile aniline derivative **58** that was subsequently used to construct the indoline core. The air and acid sensitivity of aniline **58** made it difficult to handle and purify so it was used without purification in the next step. Formation of the pentacyclic skeleton of the alkaloid skeleton was carried out by treating aniline **58** with NBS. This reaction afforded an unstable bromide that was not isolated but was immediately converted to hydroxy amide **59** (of unknown stereochemistry) by stirring it with $AgNO_3$ in aqueous methanol. Presumably, the overall reaction proceeds by electrophilic attack of NBS on the enamide double bond to initially produce a transient *N*-acyliminium ion that reacts further with the aniline nitrogen atom to produce the pentacyclic skeleton **59** after hydrolysis. Reduction of **59** with $NaBH_3CN$ in aqueous acetic acid provided indoline **60** as a single diastereomer. The stereostructure of **60** was rigorously established by X-ray analysis (see the Supporting Information for an ORTEP structure), thereby confirming that addition of hydride had occurred to the less hindered convex face of the intermediate *N*-acyliminium ion.

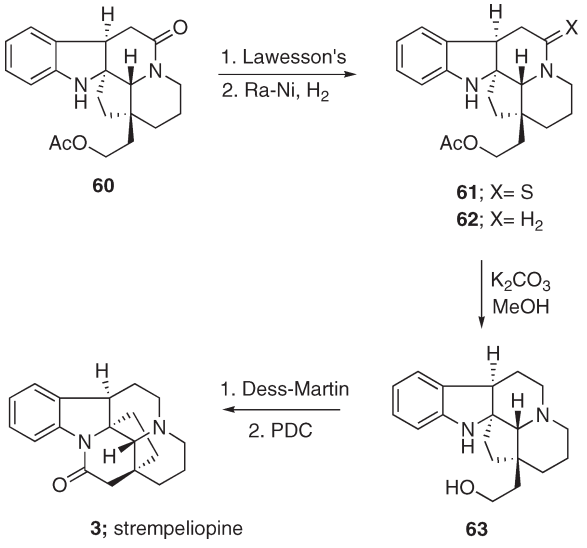
With the construction of the pentacyclic core accomplished, only a few steps remained to complete the synthesis of strempeliopine (**3**) (Scheme 12). Lactam reduction was best carried out by first converting **60** to the corresponding thiolactam **61** with Lawesson's reagent. A subsequent reduction with Ra−Ni gave indoline **62** in 60% yield for the two-step sequence. Acetate deprotection with potassium

(34) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.
(35) Trost, B. M.; Braslau, R. *Tetrahedron Lett.* **1989**, *30*, 4657.

SCHEME 11



SCHEME 12



carbonate provided the free alcohol **63** setting the stage for the final oxidative ring closure. Thus, oxidation of **63** with the Dess−Martin periodinane[36] afforded an intermediate aldehyde which was in equilibrium with the corresponding hemiaminal. Further oxidation of the crude mixture with PDC provided (±)-strempeliopine (**3**), the ^{1}H NMR spectrum of which was identical to that previously reported.[11c]

In summary, (±)-strempeliopinie (**3**) was readily synthesized from δ-valerolactam with the key reaction being an intramolecular 1,4-dipolar cycloaddition of a cross-conjugated heteroaromatic betaine. We also discovered that certain of these heteroaromatic betaines not only are stable at room temperature but also can be isolated by silica gel column chromatography. Formation of the core indoline skeleton of strempeliopinie from the dipolar cycloadduct was accomplished by reduction of the nitro group followed by an NBS-induced cyclization of the resulting aniline derivative onto the enamide π-bond. Completion of the synthesis was achieved by an oxidative cyclization to form the hexacyclic alkaloid. We believe that the chemistry described herein will be useful for the preparation of a variety of other alkaloids.

Experimental Section

3- But-3-enyl-3-ethylpiperidin-2-one. To a solution containing 3.0 g (30.0 mmol) of δ-valerolactam in 100 mL of THF at −78 °C was added a solution of 26.6 mL (2.5 M, 66.0 mmol) of *n*-BuLi in hexane. The reaction mixture was allowed to warm to 0 °C and was stirred at that temperature for 1 h. The resulting solution was cooled to −78 °C, and 4.5 g (33 mmol) of 4-bromo-1-butene was added. The solution was slowly warmed to room temperature and was stirred overnight. The reaction mixture was quenched by the addition of a saturated solution of ammonium chloride and extracted with EtOAc, and the combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dried under high

(36) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

vacuum, and the crude product was used without purification in the next step.

To a solution containing the above product in 100 mL of THF at −78 °C was added 26.6 mL (2.5 M, 66.0 mmol) of *n*-BuLi in hexane. The reaction mixture was allowed to warm to 0 °C and was stirred at that temperature for 1 h. The solution was cooled to −78 °C, and 5.1 g (33 mmol) of iodoethane was added. The solution was slowly warmed to room temperature and was stirred overnight. The reaction mixture was quenched by the addition of a saturated solution of ammonium chloride and extracted with EtOAc, and the combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography provided the title compound (4.6 g, 84%) as a colorless oil: IR (neat) 3282, 3209, 2940, and 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, 3H, $J = 7.6$ Hz), 1.46−1.56 (m, 2H), 1.64−1.82 (m, 6H), 1.97−2.14 (m, 2H), 3.26 (td, 2H, $J = 6.0$ and 2.0 Hz), 4.91 (dd, 1H, $J = 10.0$ and 0.8 Hz), 5.00 (dd, 1H, $J = 17.2$ and 1.6 Hz), 5.79 (ddt, 1H, $J = 17.2$, 10.0, and 6.4 Hz), and 5.87 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.6, 19.8, 28.7 29.0, 31.1, 37.4, 42.6, 44.6, 114.3, 138.8, and 177.0; HRMS calcd for $C_{11}H_{19}NO$ 181.1467, found 181.1465.

3- But-3-ynyl-3-ethylpiperidin-2-one. To a solution containing 4.3 g (23.7 mmol) of the above amide in 100 mL of CCl_4 at room temperature was added 3.8 g (24 mmol) of bromine dropwise. The reaction mixture was stirred for 1 h at 25 °C, and then the solvent was removed under reduced pressure. The residue was dried under high vacuum, and the product was used without any purification for the next step. To a solution containing 16.8 g (166 mmol) of diisopropylamine in 150 mL of THF at 0 °C was added 66 mL (2.5 M, 166 mmol) of *n*-BuLi in hexane. The resulting mixture was stirred at 0 °C for 1 h and was then cooled to −78 °C and added to a solution of the above dibromide in 50 mL of THF. The solution was allowed to warm slowly to room temperature and was stirred for an additional 8 h. The mixture was quenched by the addition of a saturated solution of ammonium chloride and extracted with EtOAc, and the combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 3.0 g (71%) of the title compound as a yellow pale solid: mp 80−82 °C; IR (CH_2Cl_2) 3276, 3235, 2874, and 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, 3H, $J = 7.6$ Hz), 1.53 (sext, 1H, $J = 7.6$ Hz), 1.67−1.85 (m, 6H), 1.90−1.99 (m, 2H), 2.21−2.28 (m, 2H), 3.28 (td, 2H, J = 5.6 and 2.8 Hz), and 5.77 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.4, 13.9, 19.5, 29.0, 30.4, 36.8, 42.5, 44.3, 68.1, 84.6, and 176.4. Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.59; H, 9.66; N, 7.78.

3- Ethyl-3-[4-phenylbut-3-ynyl]piperidin-2-one. To a solution containing 1.4 g (7.8 mmol) of the above alkyne and 2.0 g (9.4 mmol) of iodobenzene in 10 mL of THF at room temperature were added 0.14 g (0.2 mmol) of dichlorobis(triphenylphosphine)palladium(II), 0.07 g (0.4 mmol) of copper iodide, and 5 mL of diisopropylamine. The resulting mixture was stirred for 12 h and was filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography to provide 1.99 g (95%) of the title compound as a white solid: mp 94−95 °C; IR (CH_2Cl_2) 1651,1483, 751, and 685 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H, $J = 7.4$ Hz), 1.54 (sext, 1H, $J = 7.2$ Hz), 1.69−1.84 (m, 6H), 2.00 (m, 1H), 2.44 (ddd, 2H, $J = 11.6$, 6.4, and 3.6 Hz), 3.34 (m, 2H), 6.68 (brs, 1H), 7.23 (m, 2H), and 7.33 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.3, 14.8, 19.5, 28.2, 30.5, 36.8, 42.3, 44.2, 80.3, 90.1, 123.7, 127.3, 128.0, 131.2, and 176.4. Anal. Calcd for $C_{17}H_{21}NO$: C, 79.95; H, 8.29; N, 5.49. Found: C, 79.73; H, 8.20; N, 5.31.

3- Ethyl-3-[(*Z*)-4-phenylbut-3-enyl]piperidin-2-one. To a solution containing 0.04 g (0.16 mmol) of nickel acetate tetrahydrate in 10 mL of ethanol at room temperature was added 6 mg (0.16 mmol) of sodium borohydride. After the mixture was stirred for 15 min at rt, 0.02 g (0.3 mmol) of ethylenediamine was added. After an additional 5 min of agitation, a solution containing 0.6 g (2.0 mmol) of the above alkyne in 5 mL of ethanol was added. The reaction mixture was stirred at room temperature for 24 h under a hydrogen atmosphere (1 atm), and then the solvent was removed under reduced pressure. To the resulting residue was added 10 mL of a saturated solution of ammonium chloride. The mixture was extracted with EtOAc, and the combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 0.57 g (96%) of the expected *Z*-olefin as a colorless oil: IR (neat) 1651, 1490, and 693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 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), 5.85 (brs, 1H), 6.35 (d, 1H, $J = 11.4$ Hz), and 7.13−7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) 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, 132.4, 137.3 and 176.9.

3-Ethyl-3-[(*Z*)-4-phenylbut-3-enyl]piperidin-2-thione (24). A solution containing 0.4 g (1.0 mmol) of the above *Z*-amide and 0.23 g (0.6 mmol) of Lawesson's reagent in 7 mL of toluene was heated at reflux for 1 h. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. Purification of the residue by silica gel chromatography provided 0.36 g (93%) of thioamide **24** as a colorless oil: IR (neat) 1549, 1439, 1351, 1073, and 693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 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), and 9.30 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 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, and 210.7. Anal. Calcd for $C_{17}H_{23}NS$: C, 74.68; H, 8.49; N, 5.13. Found: C, 74.77; H, 8.25; N, 5.07.

Preparation of Cycloadduct 28. To a solution containing 0.15 g (0.38 mmol) of the above thioamide **24** in 7 mL of xylene at room temperature was added a solution of bromoacetyl chloride in xylene (2 mL). The solution was allowed to stir overnight at 25 °C and was then heated to reflux, and triethylamine (0.15 g) in xylene (2 mL) was added. The solution was heated for an additional 1 h at reflux and allowed to cool to rt. The mixture was filtered through a Celite pad and concentrated under reduced pressure, and the residue was chromatographed on a silica gel column to give cycloadduct **28** in 85% as a white solid: mp 173−174 °C; IR (neat) 1690, 1452, 1353, 1267, and 704 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 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 ($CDCl_3$, 100 MHz) 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, and 177.5. Anal. Calcd for $C_{19}H_{23}NOS$: C, 72.81; H, 7.48; N, 4.47. Found: C, 72.72; H, 7.33; N, 4.25.

3-Ethyl-3-[4-(2-nitrophenyl)but-3-ynyl]piperidin-2-one. To a solution containing 1.4 g (7.8 mmol) of 3-but-3-ynyl-3-ethylpiperidin-2-one and 2.3 g (9.4 mmol) of 1-iodo-2-nitrobenzene in 10 mL of THF at room temperature were added 0.14 g (0.2 mmol) of dichlorobis(triphenylphosphine)palladium(II), 0.07 g (0.4 mmol) of copper iodide, and 5 mL of diisopropylamine. The resulting mixture was stirred for 12 h at 25 °C and was filtered through a Celite pad. The filtrate was concentrated, and the residue was purified by silica gel chromatography to provide 1.99 g (85%) of the title compound as a yellow solid: mp 90−91 °C; IR (CH_2Cl_2) 3284, 2942, 2230, and 1654 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, 3H, $J = 7.2$ Hz), 1.56 (sext, 1H, $J = 7.2$ Hz), 1.68−1.88 (m, 6H), 1.98−2.10 (m, 1H), 2.52 (ddd, 2H,

J = 9.6, 6.4, and 4.0 Hz), 3.20−3.34 (m, 2H), 6.31 (brs, 1H), 7.37 (td, 1H, J = 8.0 and 1.6 Hz), 7.50 (td, 1H, J = 8.0 and 1.6 Hz), 7.55 (dd, 1H, J = 8.0 and 1.6 Hz), and 7.94 (dd, 1H, J = 8.0 and 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.7, 15.7, 19.9, 29.4, 30.9, 36.7, 42.9, 44.7, 76.1, 99.4, 119.4, 124.6, 128.1, 132.8, 135.0, 150.2, and 176.6. Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.69; H, 6.73; N, 9.19.

3-Ethyl-3-[(*Z*)-4-(2-nitrophenyl)but-3-enyl]piperidin-2-one. To a solution containing 1.85 g (6.2 mmol) of the above alkyne in 50 mL of benzene at 25 °C were added 0.14 g (0.16 mmol) of tris-(dibenzylideneacetone)dipalladium(0),[35] 0.09 g (0.32 mmol) of tri-*o*-tolylphosphine, and 0.37 g (6.16 mmol) of acetic acid. After the mixture was stirred at rt for 1 min, 0.83 g (6.2 mmol) of 1,1,3,3-tetramethyldisiloxane was added dropwise over 15 min. The reaction mixture was stirred for an additional 1 h and was then quenched by the addition of water. The resulting mixture was extracted with EtOAc, and the combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 1.6 g (83%) of the title compound as a pale yellow solid: mp 88−91 °C; IR (CH_2Cl_2) 3279, 2940, 1654, and 1522 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82 (t, 3H, J = 7.6 Hz), 1.44 (sext, 1H, J = 6.4 Hz), 1.48−1.58 (m, 2H), 1.59−1.82 (m, 5H), 2.00−2.17 (m, 2H), 3.14−3.21 (m, 2H), 5.78 (dt, 1H, J = 12.0 and 7.6 Hz), 6.22 (brs, 1H), 6.66 (d, 1H, J = 12.0 Hz), 7.36 (d, 1H, J = 7.2 Hz), 7.37 (t, 1H, J = 7.2 Hz), 7.55 (td, 1H, J = 7.2 and 1.2 Hz), and 8.00 (dd, 1H, J = 7.2 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.5, 19.6, 23.6, 28.9, 30.9, 37.7, 42.5, 44.5, 124.4, 125.1, 127.6, 131.8, 132.6, 132.7, 134.3, 148.1, and 176.7. Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.79; H, 7.33; N, 9.01.

3-Ethyl-3-[(*Z*)-4-(2-nitrophenyl)but-3-enyl]piperidine-2-thione (25). A solution containing 1.5 g (5.1 mmol) of the above amide and 1.1 g (2.8 mol) of Lawesson's reagent in 10 mL of toluene was heated at reflux for 1 h. The resulting mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was subjected to silica gel to give 1.4 g (87%) of thioamide **25** as a pale yellow solid: mp 146−148 °C; IR (CH_2Cl_2) 3166, 3066, 2959, and 1521 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, 3H, J = 7.2 Hz), 1.50−1.84 (m, 6H), 1.92 (sext, 1H, J = 6.4 Hz), 2.00−2.22 (m, 3H), 3.12−3.28 (m, 2H), 5.80 (dt, 1H, J = 11.2 and 7.2 Hz), 6.67 (d, 1H, J = 11.2 Hz), 7.38 (t, 1H, J = 8.0 Hz), 7.44 (d, 1H, J = 7.6 Hz), 7.56 (t, 1H, J = 7.6 Hz), 7.97 (d, 1H, J = 8.0 Hz), and 8.80 (brs, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 8.5, 19.4, 23.8, 27.3, 35.3, 41.4, 45.2, 48.6, 124.4, 125.4, 127.7, 132.1, 132.6, 132.9, 134.1, 148.1, and 210.7; HRMS calcd for $C_{17}H_{22}N_2O_2S$ 318.1402, found 318.1400.

Preparation of Bimolecular Cycloadduct 29. To a solution containing 0.07 g (0.2 mmol) of thioamide **25** in 7 mL of xylene at room temperature was added a solution of bromoacetyl chloride in xylene (1.0 M, 0.2 mL, 0.2 mmol). The reaction mixture was stirred for 3 h at 25 °C, and then a solution of triethylamine in xylene (1.0 M, 0.4 mL, 0.4 mmol) and 0.04 g (0.22 mmol) of *N*-phenylmaleimide was added. After being stirred for 15 min at 25 °C, the resulting mixture was heated at reflux for 5 h. After the mixture was cooled to room temperature, water was added, and the mixture was extracted with EtOAc. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography provided 0.08 g (75%) of an inseparable 1.2:1 mixture of the diastereomeric cycloadducts of **29** as a yellow oil: IR (neat) 2957, 2922, 1718, and 1522 cm^{-1}; (major) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.70 (t, 3H, J = 7.2 Hz), 1.30−1.80 (m, 7H), 1.90−2.20 (m, 2H), 2.53−2.64 (m, 2H), 3.58−3.67 (m, 2H), 3.84−3.92 (m, 1H), 4.26 (d, 1H, J = 1.6 Hz), 5.64 (ddd, 1H, J = 11.6, 9.2, and 5.6 Hz), 6.64 (d, 1H, J = 11.6 Hz), 7.20 (td, 1H, J = 8.0 and 1.2 Hz), 7.30 (d, 1H, J = 7.6 Hz), 7.36−7.56 (m, 6H), and 7.99 (dd, 1H, J = 7.6 and 1.2 Hz); (minor) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80 (t, 3H, J = 7.2 Hz), 1.30−1.80 (m, 7H), 1.90−2.20 (m, 2H), 2.40 (sext, 1H, J = 7.6 Hz), 2.53−2.64 (m, 1H), 3.58−3.67 (m, 2H), 3.84−3.92 (m, 1H), 4.29 (d, 1H, J = 1.6 Hz), 5.79 (dt, 1H, J = 11.2 and 7.6 Hz), 6.73 (d, 1H, J = 11.2 Hz), 7.20 (td, 1H, J = 8.0 and 1.2 Hz), 7.30 (d, 1H, J = 7.6 Hz), 7.36−7.56 (m, 6H), and 8.00 (dd, 1H, J = 8.4 and 1.2 Hz).

3- [4-(2-Aminophenyl)but-3-ynyl]-3-ethylpiperidin-2-one. To a solution containing 0.5 g (2.8 mmol) of 3-but-3-ynyl-3-ethylpiperidin-2-one and 0.73 g (3.4 mmol) of 2-iodoaniline in 5 mL of THF at room temperature were added 0.05 g (0.07 mmol) of dichlorobis(triphenylphosphine)palladium(II), 0.03 g (0.14 mmol) of copper iodide, and 2.5 mL of diisopropylamine. The resulting mixture was stirred for 12 h and filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 0.61 g (81%) of the title compound as a colorless oil: IR (neat) 3149, 2952, and 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, 3H, J = 7.6 Hz), 1.55 (sext, 1H, J = 7.2 Hz), 1.70−1.85 (m, 6H), 2.03−2.14 (m, 1H), 2.44−2.62 (m, 2H), 3.20−3.34 (m, 2H), 4.18 (brs, 2H), 6.10 (brs, 1H), 6.60−6.68 (m, 2H), 7.05 (td, 1H, J = 7.8 and 1.6 Hz), 7.20 (dd, 1H, J = 7.8 and 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.5, 15.3, 19.7, 29.0, 31.0, 37.0, 42.6, 44.4,77.4, 95.2, 108.7, 114.1, 117.6, 128.8, 131.9, 147.8, and 176.5; HRMS calcd for $C_{17}H_{22}N_2O$ 270.1732, found 270.1730.

[2-[4-(3-Ethyl-2-oxopiperidin-3-yl)but-1-enyl]phenyl]carbamic Acid *tert*-Butyl Ester. To a solution containing 0.04 g (0.16 mmol) of nickel acetate tetrahydrate in 10 mL of ethanol at room temperature was added 6 mg (0.16 mmol) of sodium borohydride. After the mixture was stirred for 15 min at rt, 0.02 g (0.3 mmol) of ethylenediamine was added. After an additional 5 min of agitation, a solution containing 0.56 g (2.1 mmol) of the above compound in 5 mL of ethanol was added. The reaction mixture was stirred at room temperature for 24 h under a hydrogen atmosphere (1 atm), and then the solvent was removed under reduced pressure. To the resulting residue was added 10 mL of a saturated solution of ammonium chloride. The mixture was extracted with EtOAc, and the combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 0.49 g (87%) of the expected olefin as a colorless oil: IR (neat) 3346, 3209, 2940, and 1651 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (t, 3H, J = 7.6 Hz), 1.38−1.84 (m, 8H), 2.00−2.24 (m, 2H), 3.10−3.22 (m, 2H), 3.70 (brs, 2H), 5.72 (dt, 1H, J = 11.2 and 6.8 Hz), 6.23 (d, 1H, J = 11.2 Hz), 6.33 (s, 1H), 6.66 (d, 1H, J = 8.0 Hz), 6.69 (t, 1H, J = 7.2 Hz), 6.98−7.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.6, 19.7, 23.5, 28.6, 31.0, 37.9, 42.5, 44.7, 115.0, 117.9, 123.0, 124.9, 127.9, 129.5, 134.4, 143.9 and 177.0.

To a solution containing 0.31 g (1.1 mmol) of the above olefin in 5 mL of methanol at room temperature were added 0.37 g (1.7 mmol) of di-*tert*-butyl dicarbonate and 1 g of potassium hydroxide. The reaction mixture was stirred for 7 days at 25 °C. After removal of the solvent under reduced pressure, 10 mL of water was added, the mixture was extracted with EtOAc, and the combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 0.39 g (77%) of the title compound as a colorless oil: IR (neat) 3209, 2950, and 1651 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80 (t, 3H, J = 7.6 Hz), 1.36−1.46 (m, 12H), 1.46−1.70 (m, 4H), 1.76 (ddd, 1H, J = 13.2, 12.0, and 4.8 Hz), 1.70−2.14 (m, 2H), 3.04−3.21 (m, 2H), 5.82 (dt, 1H, J = 11.2 and 7.2 Hz), 6.25 (d, 1H, J = 11.2 Hz), 6.45 (s, 1H), 6.52 (s, 1H), 6.95 (td, 1H, J = 8.0 and 1.2 Hz), 7.05 (d, 1H, J = 8.0 Hz), 7.19 (td, 1H, J = 8.0 and 1.2 Hz), and 7.95 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.5, 19.6, 23.5, 28.2, 28.6, 30.9, 37.5, 42.4, 44.5, 80.2, 119.0, 122.4, 124.3, 126.4, 127.7, 129.1, 135.7, 136.3, 152.6, and 176.8; HRMS calcd for $C_{22}H_{32}N_2O_3$ 372.2413, found 372.2409.

[2-[(*Z*)-4-(3-Ethyl-2-thioxopiperidin-3-yl)but-1-enyl]phenyl]-carbamic Acid *tert*-Butyl Ester (26). A solution containing 0.39 g (1.0 mmol) of the above *Z*-amide and 0.23 g (0.6 mmol) of Lawesson's reagent in 7 mL of toluene was heated at reflux for 1 h. The resulting mixture was cooled to room temperature, and the solvent was removed under reduced pressure. Purification of the residue by silica gel chromatography provided 0.35 g (85%) of thioamide **26** as a pale yellow oil: IR (neat) 2953, 1694, 1594, and 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, 3H, J = 7.6 Hz), 1.52 (s, 9H), 1.56−1.82 (m, 6H), 1.95 (sext, 1H, J = 7.2 Hz), 2.00−2.15 (m, 2H), 3.12−3.28 (m, 2H), 5.84−5.94 (m, 1H), 6.30 (d, 1H, J = 11.2 Hz), 6.50 (s, 1H), 7.00 (td, 1H, J = 8.0 and 1.2 Hz), 7.10 (d, 1H, J = 8.0 Hz), 7.24 (td, 1H, J = 8.0 and 1.2 Hz), 8.01 (d, 1H, J = 8.0 Hz), and 8.24 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.6, 19.3, 23.7, 27.1, 28.3, 35.0, 41.4, 45.2, 48.7, 80.4, 118.9, 122.4, 124.4, 126.3, 127.8, 129.2, 135.8, 136.4, 152.7, and 210.9; HRMS calcd for $C_{22}H_{32}N_2O_2S$ 388.2184, found 388.2180.

Preparation of Bimolecular Cycloadduct 30. To a solution containing 0.12 g (0.3 mmol) of thioamide **26** in 7 mL of xylene at room temperature was added a solution of bromoacetyl chloride in xylene (1.0 M, 0.31 mL, 0.31 mmol). The reaction mixture was stirred for 3 h, and then a solution of triethylamine in xylene (1.0 M, 0.6 mL, 0.6 mmol) and 0.06 g (0.34 mmol) of *N*-phenylmaleimide was added. After being stirred for 15 min at 25 °C, the mixture was heated at reflux for 5 h. After the mixture was cooled to room temperature, water was added, and the mixture was extracted with EtOAc. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 0.13 g (77%) of *Z*-**30** as an inseparable 1.8:1 mixture of diastereomeric cycloadducts as a yellow oil: IR (neat) 2952, 2916, 1720, and 1514 cm^{-1}; (major) ^1H NMR ($CDCl_3$, 400 MHz) δ 0.68 (t, 3H, J = 7.6 Hz), 1.30−1.80 (m, 7H), 1.49 (s, 9H), 1.94−2.22 (m, 2H), 2.48−2.62 (m, 2H), 3.56−3.65 (m, 2H), 3.82−3.91 (m, 1H), 4.26 (d, 1H, J = 1.6 Hz), 5.67 (ddd, 1H, J = 11.6, 9.2, and 5.6 Hz), 6.24 (d, 1H, J = 11.6 Hz), 6.41 (s, 1H), 6.97 (td, 1H, J = 7.6 and 1.2 Hz), 7.05 (d, 1H, J = 8.0 Hz), 7.15−7.26 (m, 3H), 7.37−7.50 (m, 3H), and 8.00 (d, 1H, J = 7.6 Hz); (minor) ^1H NMR ($CDCl_3$, 400 MHz) δ 0.79 (t, 3H, J = 7.6 Hz), 1.30−1.80 (m, 7H), 1.50 (s, 9H), 1.94−2.22 (m, 2H), 2.38 (sext, 1H, J = 7.6 Hz), 2.48−2.62 (m, 1H), 3.56−3.65 (m, 2H), 3.82−3.91 (m, 1H), 4.28 (d, 1H, J = 1.2 Hz), 5.87 (dt, 1H, J = 11.2 and 7.2 Hz), 6.35 (d, 1H, J = 11.2 Hz), 6.46 (s, 1H), 6.97 (td, 1H, J = 7.6 and 1.2 Hz), 7.05 (d, 1H, J = 8.0 Hz), 7.15−7.26 (m, 3H), 7.37−7.50 (m, 3H), and 8.00 (d, 1H, J = 7.6 Hz).

3-[4-(2-Bromophenyl)but-3-ynyl]-3-ethylpiperidin-2-one. To a solution containing 0.5 g (2.8 mmol) of 3-but-3-ynyl-3-ethylpiperidin-2-one and 0.9 g (3.4 mmol) of 1-bromo-2-iodobenzene in 5 mL of THF at room temperature were added 0.05 g (0.07 mmol) of dichlorobis(triphenylphosphine)palladium(II), 0.03 g (0.14 mmol) of copper iodide, and 2.5 mL of diisopropylamine. The resulting mixture was stirred for 12 h and then filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give 0.74 g (79%) of the title compound as a colorless oil: IR (CH_2Cl_2) 3199, 2943, 1655, and 1469 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, 3H, J = 7.6 Hz), 1.55 (sext, 1H, J = 6.8 Hz), 1.72−1.89 (m, 6H), 2.05 (ddd, 2H, J = 13.6, 9.6, and 6.4 Hz), 2.51 (ddd, 2H, J = 9.6, 6.8, and 3.2 Hz), 3.20−3.32 (m, 2H), 6.32 (brs, 1H), 7.09 (td, 1H, J = 8.0 and 1.2 Hz), 7.20 (t, 1H, J = 8.0 Hz), 7.39 (dd, 1H, J = 8.0 and 1.2 Hz), and 7.53 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.5, 15.2, 19.7, 29.0, 30.6, 36.7, 42.6, 44.5, 79.2, 95.4, 125.3, 125.9, 126.8, 128.6, 132.2, 133.3, and 176.4; HRMS calcd for $C_{17}H_{20}BrNO$ 333.0729, found 333.0726.

3- [4-(2-Bromophenyl)but-3-enyl]-3-ethylpiperidin-2-one. To a solution containing 0.73 g (2.2 mmol) of the above compound in 25 mL of benzene at room temperature were added 0.05 g (0.055 mmol) of tris(dibenzylideneacetone)dipalladium(0), 0.03 g (0.11 mmol) of tri-*o*-tolylphosphine and 0.13 g (2.2 mmol) of acetic acid. After the mixture was stirred for 1 min, 0.29 g (2.2 mmol) of 1,1,3,3-tetramethyldisiloxane was added dropwise over 15 min. The reaction mixture was stirred for an additional 1 h and was then quenched by the addition of water. The resulting mixture was extracted with EtOAc, and the combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 0.6 g (81%) of an inseparable 3:1:1 mixture of *cis*, *trans*, as well as the saturated piperidones: IR (CH_2Cl_2) 3279, 2940, 1654, and 1522 cm^{-1}; *cis* (major) product: ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, 3H, J = 7.6 Hz), 1.49 (sext, 1H, J = 6.8 Hz), 1.54−1.90 (m, 7H), 2.10−2.24 (m, 2H), 3.16−3.28 (m, 2H), 5.69 (brs, 1H), 5.75 (dt, 1H, J = 11.2 and 7.6 Hz), 6.43 (d, 1H, J = 11.2 Hz), 7.09 (td, 1H, J = 7.2 and 1.2 Hz), 7.22−7.34 (m, 2H), and 7.56 (d, 1H, J = 8.0 Hz).

3-[4-(2-Bromophenyl)but-3-enyl]-3-ethylpiperidine-2-thione (27). A solution containing 0.21 g (0.62 mmol) of the above mixture and 0.14 g (0.34 mmol) of Lawesson's reagent in 3 mL of toluene was heated at reflux for 1 h. The resulting mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography to give 0.17 g (78%) of a 3:1:1 mixture of three inseparable thioamides as a colorless oil: IR (CH_2Cl_2) 3134, 3067, 2959, and 1592 cm^{-1}; *cis* product (**27**) ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 3H, J = 7.2 Hz), 1.56−1.83 (m, 6H), 1.97 (sext, 1H, J = 6.0 Hz), 2.10−2.22 (m, 3H), 3.16−3.28 (m, 2H), 5.75 (dt, 1H, J = 11.6 and 7.2 Hz), 6.44 (d, 1H, J = 11.6 Hz), 7.10 (td, 1H, J = 8.0 and 1.2 Hz), 7.24−7.36 (m, 2H), 7.56 (d, 1H, J = 8.0 Hz), and 8.40 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.6, 19.3, 23.5, 27.2, 35.0, 41.5, 45.1, 48.6, 123.8, 126.9, 128.2, 128.6, 130.6, 132.4, 133.5, 137.3, and 210.5.

Preparation of Bimolecular Cycloadduct 31. To a solution containing 0.14 g (0.38 mmol) of the mixture of the above thioamides in 7 mL of xylene at room temperature was added a solution of bromoacetyl chloride in xylene (1.0 M, 0.38 mL, 0.38 mmol). The mixture was stirred for 3 h, and then a solution of triethylamine in xylene (1.0 M, 0.76 mL, 0.76 mmol) and 0.07 g (0.42 mmol) of *N*-phenylmaleimide was added. The resulting mixture was heated at reflux for 5 h with stirring. After the mixture was cooled to room temperature, water was added, and the mixture was extracted with EtOAc. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography gave 0.18 g (81%) of a mixture of diastereomeric cycloadducts as a pale yellow oil. After crystallization, one major isomer of cycloadduct **31** could be obtained: mp 141−144 °C; IR (KBr) 2951, 1713, and 1383 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.82 (t, 3H, J = 7.2 Hz), 1.41 (sext, 1H, J = 7.6 Hz), 1.51−1.70 (m, 4H), 1.74−1.85 (m, 2H), 1.92−2.14 (m, 2H), 2.41 (sext, 1H, J = 7.6 Hz), 2.55−2.68 (m, 1H), 3.58−3.63 (m, 2H), 3.84−3.92 (m, 1H), 4.28 (d, 1H, J = 1.6 Hz), 5.74 (dt, 1H, J = 11.2 and 7.2 Hz), 6.46 (d, 1H, J = 11.2 Hz), 7.10 (td, 1H, J = 7.6 and 2.0 Hz), 7.18−7.26 (m, 4H), 7.37−7.49 (m, 3H), and 7.57 (dd, 1H, J = 8.0 and 0.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.2, 18.1, 22.3, 26.6, 29.8, 34.4, 38.8, 41.0, 50.4, 50.5, 50.8, 91.0, 123.9, 126.3, 126.9, 128.4, 129.1, 129.3, 129.4, 130.3, 131.6, 132.58, 132.63, 137.4, 172.8, 173.0, and 174.7; HRMS calcd for $C_{29}H_{29}BrN_2O_3S$ 564.1083, found 564.1078.

Preparation of 2-Diazo-3-[3-ethyl-3-[4-(2-nitrophenyl)but-3-enyl]-2-thioxopiperidin-1-yl]-3-oxopropionic Acid Ethyl Ester (32). To a solution containing 0.79 g (2.5 mmol) of thioamide **25** in 30 mL of CH_2Cl_2 was added 1.0 mL (7.4 mmol) of triethylamine and then 0.66 g (3.7 mmol) of ethyl 2-diazomalonyl chloride.[37]

(37) Marino, J. P. Jr.; Osterhout, M. H.; Price, A. T.; Sheehan, S. M.; Padwa, A. *Tetrahedron Lett.* **1994**, *35*, 849.

The resulting mixture was stirred at room temperature for 10 min, and the reaction mixture was quenched by the addition of 30 mL of a saturated solution of $NaHCO_3$. The solution was extracted with 150 mL of CH_2Cl_2, and the organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by silica gel chromatography gave 0.82 g (72%) of diazothioamide **32** as a colorless oil which was immediately used in the next step without purification.

Preparation of Cycloadduct 33. A mixture of 0.81 g (1.8 mmol) of **32** and 0.02 g (0.04 mmol) of rhodium acetate(II) dimer in 10 mL of xylene was heated at reflux for 3 h. The reaction mixture was then cooled to room temperature and was rapidly passed through a Celite pad. Concentration of the solution under reduced pressure followed by silica gel chromatography gave 0.63 g (85%) of cycloadduct **33** as white solid: mp 195−196 °C; IR (CH_2Cl_2) 2967, 1734, and 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, 3H, J = 7.2 Hz), 0.96 (t, 3H, J = 7.2 Hz), 1.16−1.42 (m, 3H), 1.46−1.53 (m, 1H), 1.56−1.76 (m, 3H), 1.87 (ddd, 1H, J = 13.2, 11.2, and 2.0 Hz), 1.95−2.08 (m, 2H), 2.84−2.94 (m, 1H), 3.45 (dt, 1H, J = 11.6 and 8.0 Hz), 3.70−3.78 (m, 1H), 4.03−4.17 (m, 3H), 7.38 (td, 1H, J = 7.6 and 1.2 Hz), 7.52 (td, 1H, J = 7.6 and 1.2 Hz), 7.88 (dd, 1H, J = 7.6 and 1.2 Hz), and 7.93 (dd, 1H, J = 7.6 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.5, 13.7, 18.9, 25.1, 30.0, 30.6, 37.6, 40.4, 40.7, 46.4, 55.9, 62.2, 73.1, 92.0, 124.8, 127.6, 128.1, 132.4, 133.0, 150.2, 166.4, and 173.2; HRMS calcd for $C_{22}H_{26}N_2O_5S$:430.1562, found 430.1564.

2*a*-Ethyl-1,2,2*a*,3,4,5,8,12*b*-octahydro-6*aH*-5*a*,8-diazabenzo-[*l*]aceanthrylene-6,7-dione (34). A sample containing 0.21 g (0.49 mmol) of **33** and 0.9 g (3.4 mmol) of $Mo(CO)_6$ in 7 mL of AcOH was heated at reflux overnight. The reaction mixture was poured into a 3 N NaOH solution. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.12 g (83%) of lactam **34** as a pale yellow solid: mp 194−195 °C; IR (CH_2Cl_2) 3230, 2926, and 1694 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.62 (t, 3H, J = 7.2 Hz), 1.15−1.30 (m, 2H), 1.31−1.50 (m, 2H), 1.63−1.79 (m, 3H), 1.82−1.96 (m, 2H), 2.99 (td, 1H, J = 12.4 and 5.2 Hz), 3.65 (d, 1H, J = 5.6 Hz), 4.06 (d, 1H, J = 5.6 Hz), 4.15−4.22 (m, 1H), 6.86 (d, 1H, J = 7.6 Hz), 7.00 (t, 1H, J = 7.6 Hz), 7.13−7.23 (m, 2H), and 9.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.5, 19.3, 26.6, 28.1, 32.4, 35.5, 36.5, 41.2, 45.7, 50.3, 114.1, 116.0, 121.7, 123.3, 128.2, 128.6, 135.9, 142.8, 166.7, and 168.0; HRMS calcd for $C_{20}H_{22}N_2O_2$ 322.1681, found 322.1680.

9-Ethyl-4-hydroxy-9-[4-(2-nitrophenyl)but-3-enyl]-2-oxo-6,7,8,9-tetrahydro-2*H*-pyrido[2,1-*b*][1,3]thiazin-5-ylium (36). To a solution containing 0.32 g (1.0 mmol) of thioamide **25** was added carbon suboxide, prepared from 0.15 g of zinc dust and 0.27 g of dibromomalonyl dichloride at −78 °C. The resulting mixture was warmed to room temperature and was stirred at 25 °C for 5 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 0.28 g (72%) of **36** as a bright yellow oil: IR (neat) 2966, 1635, and 1521 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, 3H, J = 7.2 Hz), 1.72−1.82 (m, 2H), 1.82−2.00 (m, 8H), 2.04−2.13 (m, 1H), 4.05 (dt, 1H, J = 15.6 and 6.4 Hz), 4.17 (dt, 1H, J = 15.6 and 6.4 Hz), 5.21 (s, 1H), 5.72 (dt, 1H, J = 11.2 and 6.8 Hz), 6.76 (d, 1H, J = 7.6 Hz), 7.23 (d, 1H, J = 7.6 Hz), 7.47 (td, 1H, J = 7.6 and 1.2 Hz), 7.59 (td, 1H, J = 7.6 and 1.2 Hz), and 8.01 (dd, 1H, J = 7.6 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.5, 19.0, 23.3, 28.2, 36.8, 42.6, 47.9, 49.6, 88.0, 124.7, 127.6, 128.6, 130.9, 131.3, 131.8, 133.1, 148.1, 161.5, 166.4, and 194.2; HRMS calcd for $C_{20}H_{22}N_2O_4S$ 386.1300, found 386.1297.

8*a*-Ethyl-3-(2-nitrophenyl)-1,2,3,4,6,7,8,8*a*-octahydro-5*a*-azaacenaphthylen-5-one (38). A mixture containing 0.28 g (0.72 mmol) of dipole **36** in 15 mL of toluene in a sealed tube was placed in a preheated oil bath at 120 °C for 3 h. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography to give 0.18 g (66%) of **38** as a pale yellow solid: mp 134−136 °C; IR (neat) 2942, 1683, and 1321 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, 3H, J = 7.2 Hz), 1.19−1.30 (m, 1H), 1.44−1.65 (m, 3H), 1.69−1.82 (m, 3H), 1.91−2.02 (m, 2H), 2.04−2.15 (m, 1H), 2.67 (t, 1H, J = 14.8 Hz), 2.95 (dd, 1H, J = 14.8 and 6.0 Hz), 3.07 (dt, 1H, J = 12.8 and 8.0 Hz), 3.96 (dt, 1H, J = 12.8 and 4.4 Hz), 4.34 (dd, 1H, J = 14.8 and 6.0 Hz), 7.26−7.41 (m, 2H), 7.59 (td, 1H, J = 7.6 and 1.2 Hz), and 7.79 (dd, 1H, J = 7.6 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.1, 19.3, 27.5, 28.3, 31.8, 34.7, 36.0, 40.9, 41.0, 45.8, 114.5, 124.3, 127.5, 129.9, 132.8, 136.8, 143.4, 150.1, and 169.6. Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.84; H, 6.80; N, 8.45.

Preparation of Aminals 40 and 41. A mixture containing 0.027 g (0.08 mmol) of lactam **38** and 0.03 g of Pd/C was stirred under a hydrogen atmosphere (4 atm) for 15 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was taken up in 5 mL of THF, and this solution was treated with 0.065 g (1.7 mmol) of LAH at 0 °C. The mixture was heated at reflux for 20 h and was then cooled to room temperature. To this mixture were added 65 μL of water, 65 μL of 15% of NaOH, and 195 μL of water followed by the addition of 1 g of anhydrous Na_2SO_4, and the mixture was filtered. The solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography to give 0.01 g (48%) of the undesired aminal diasteromer **40** as a pale yellow oil: IR (neat) 3433, 2920, and 1321 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.78 (t, 3H, J = 7.6 Hz), 1.10 (td, 1H, J = 13.6 and 4.8 Hz), 1.24−1.41 (m, 3H), 1.44−1.52 (m, 1H), 1.56−1.62 (m, 2H), 1.64−1.73 (m, 1H), 1.80 (qt, 1H, J = 13.2 and 4.8 Hz), 1.97−2.14 (m, 2H), 2.24−2.52 (m, 6H), 2.93 (d, 1H, J = 3.2 Hz), 4.51 (brs, 1H), 6.52 (d, 1H, J = 8.0 Hz), 6.56 (td, 1H, J = 7.2 and 1.2 Hz), 6.91 (dd, 1H, J = 7.6 and 1.2 Hz), and 6.97 (td, 1H, J = 7.6 and 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.3, 21.2, 21.8, 27.7, 28.0, 28.8, 29.4, 35.4, 41.2, 46.3, 46.6, 48.3, 75.3, 112.1, 116.1, 126.9, 127.2, 128.6, and 146.9; HRMS calcd for $C_{19}H_{26}N_2$ 282.2096. found 282.2091.

The second fraction from the above chromatographic separation contained 0.008 g (35%) of the desired aminal diasteromer **41** as a white solid: mp 122−124 °C; IR (neat) 3420, 2939, and 1311 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, 3H, J = 7.6 Hz), 1.02−1.15 (m, 1H), 1.18−1.70 (m, 8H), 1.74−1.80 (m, 1H), 1.81−1.88 (m, 1H), 2.13 (tt, 1H, J = 13.2 and 4.0 Hz), 2.41 (dd, 1H, J = 14.4 and 3.2 Hz), 2.68−2.74 (m, 1H), 2.78−2.87 (m, 1H), 2.98 (dt, 1H, J = 12.0 and 3.6 Hz), 3.00−3.04 (m, 1H), 3.13 (dt, 1H, J = 14.0 and 3.6 Hz), 4.14 (brs, 1H), 6.45 (d, 1H, J = 8.0 Hz), 6.60 (td, 1H, J = 8.0 and 0.8 Hz), 6.93 (dd, 1H, J = 8.0 and 1.2 Hz), and 7.01 (td, 1H, J = 8.0 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.3, 22.0, 22.6, 23.5, 28.0, 30.4, 33.8, 34.7, 45.1, 45.9, 48.9, 76.0, 111.9, 116.8, 122.4, 127.4, 129.0, and 144.7; HRMS calcd for $C_{19}H_{26}N_2$ 282.2096, found 282.2094.

A 0.02 g sample containing either aminal **40** or **41** was dissolved in 1 mL of acetic acid at room temperature. The solution was stirred for 2 h at rt and was then poured into 10 mL of a saturated sodium bicarbonate solution and extracted with CH_2Cl_2. The solution was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was analyzed by ^1H NMR spectroscopy ($CDCl_3$, 400 MHz) which indicated a 1:6 mixture of aminals **40** (minor) and **41** (major).

3-(But-3-enyl)-3-(2-(*tert*-butyldimethylsilyloxy)ethyl)piperidin-2-one (45). To a solution of 5.0 g (50.4 mmol) of δ-valerolactam in THF (175 mL) cooled to −78 °C was added 44.4 mL (2.5 M solution in hexane, 111 mmol) of *n*-BuLi dropwise over 10 min. After being stirred at −78 °C for 15 min, the reaction mixture was allowed to warm to 0 °C and was stirred for an additional 1 h at that temperature. The resulting mixture was cooled to −78 °C, and 5.6 mL (55 mmol) of 4-bromobutene was added. The

solution was slowly warmed to rt over 2 h and was further stirred for 15 h. The reaction mixture was quenched by the addition of a saturated aqueous ammonium chloride solution and was extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give 7.3 g of the expected alkylated lactam that was used in the next step without further purification.

To a solution containing 4.54 g (29.6 mmol) of the above lactam in THF (115 mL) cooled to −78 °C was added 26.0 mL (2.5 M solution in hexane, 65.2 mmol) of *n*-BuLi dropwise over 10 min. After being stirred at −78 °C for 15 min, the reaction mixture was allowed to warm to 0 °C and was stirred at that temperature for an additional 1 h. The resulting mixture was cooled to −78 °C, and 5.65 g (19.8 mmol) of *tert*-butyl(2-iodoethoxy)dimethylsilane[33] in THF (10 mL) was added. The solution was slowly warmed to rt over 2 h and was stirred for an additional 15 h. The reaction mixture was quenched by the addition of a saturated aqueous ammonium chloride solution and was extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column silica gel chromatography gave the title compound (4.67 g, 76%) as a clear oil: IR (neat) 3291, 3211, 3077, 2930, 2857, 1660, and 1471 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.86 (s, 9H), 1.51−1.58 (m, 1H), 1.69−1.86 (m, 6H), 1.90−2.13 (m, 3H), 3.23−3.26 (m, 2H), 3.70 (t, 2H, J = 7.0 Hz), 4.89−5.02 (m, 2H), 5.73−5.83 (m, 1H), and 6.55 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.2, 18.4, 19.9, 26.1, 28.8, 30.3, 37.9, 40.9, 42.8, 43.5, 60.0, 114.6, 138.8, and 176.8.

3-(But-3-ynyl)-3-(2-(*tert*-butyldimethylsilyloxy)ethyl)piperidin-2-one (46). To a solution of 1.09 g (3.5 mmol) of **45** in CCl_4 (17 mL) at rt was added 0.18 mL (3.5 mmol) of Br_2 dropwise. The reaction mixture was stirred at rt for 1 h, and then the solvent was removed under reduced pressure. The residue was dried under high vacuum, and the residue was used without further purification in the next step. To a solution containing 3.4 mL (24 mmol) of diisopropylamine in THF (20 mL) cooled to 0 °C was added 9.8 mL (2.5 M solution in hexane, 24 mmol) of *n*-BuLi dropwise over 5 min. The resulting solution was stirred at 0 °C for 30 min and was then cooled to −78 °C. To the resulting mixture was added a solution of the above dibromide in THF (5 mL). The solution was allowed to slowly warm to rt over 2 h and was stirred for an additional 15 h. The dark solution was quenched by the addition of a saturated aqueous ammonium chloride solution and extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column silica gel chromatography gave alkyne **46** (0.71 g, 66% over the two steps) as a white solid: mp 87−89 °C; IR ($CDCl_3$) 3225, 2857, 1652, 1254, 1094, and 836 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ −0.02 (s, 3H), −0.01 (s, 3H), 0.82 (s, 9H), 1.63−1.95 (m, 9H), 2.11−2.25 (m, 2H), 3.19−3.21 (m, 2H), 3.65 (t, 2H, J = 7.0 Hz), and 7.08 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.3, 14.0, 18.3, 19.5, 26.0, 30.2, 37.4, 40.2, 42.5, 43.2, 59.7, 68.3, 84.6 and 176.2.

3-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-3-(4-(2-nitrophenyl)but-3-ynyl)piperidin-2-one (47). To a solution containing 1.0 g (3.4 mmol) of alkyne **46** and 1.0 g (4.03 mmol) of 1-iodo-2-nitrobenzene in diisopropylamine (13 mL) and THF (26 mL) at rt were added 71 mg (0.1 mmol) of dichlorobis(triphenylphosphine)-palladium(II) and 38 mg (0.2 mmol) of CuI. The resulting mixture was stirred at rt for 15 h and was then filtered through a Celite pad eluting with EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column silica gel chromatography to provide **47** (1.15 g, 79%) as a yellow solid: mp 102−104 °C; IR ($CDCl_3$) 3288, 2230, 1659, and 1527 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.86 (s, 9H), 1.72−2.10 (m, 8H), 2.46−2.59 (m, 2H), 3.24−3.29 (m, 2H), 3.70−3.73 (m, 2H), 6.65 (brs, 1H), 7.34−7.39 (m, 1H), 7.47−7.55 (m, 2H), and 7.93 (dd, 1H, J = 8.2 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.3, −5.2, 15.6, 18.3, 19.6, 26.0, 30.3, 37.0, 40.4, 42.7, 43.4, 59.7, 76.1, 99.2, 119.3, 124.5, 128.0, 132.7, 134.9, 150.0, and 175.1; HRMS calcd for $C_{23}H_{34}N_2O_4Si$ 431.2366, found 431.2358.

(*Z*)-3-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-3-(4-(2-nitrophenyl)-but-3-enyl)piperidin-2-one (48). To a solution of 0.37 g (0.86 mmol) of alkyne **47**, 22 mg (0.021 mmol) of $Pd_2(dba)_3 \cdot CHCl_3$, and 26 mg (0.086 mmol) of P(*o*-tolyl)$_3$ in benzene (9 mL) at rt were added 53 μL (0.86 mmol) of AcOH and 0.15 mL (0.86 mmol) of 1,1,3,3-tetramethyldisiloxane. The reaction mixture was stirred at rt for 2 h, then poured into H_2O, and extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column silica gel chromatography gave alkene **48** (0.33 g, 88%) as a yellow oil as a 9:1 mixture of *Z*/*E* isomers: IR (neat) 3392, 3290, 2857, 1658, and 1524 cm^{-1}; *Z*-isomer **48:** ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 6H), 0.84 (s, 9H), 1.53−2.17 (m, 8H), 3.13−3.22 (m, 2H), 3.66 (t, 2H, J = 7.0 Hz), 5.77 (dt, 1H, J = 11.3 and 7.4 Hz), 6.42 (brs, 1H), 6.66 (d, 1H, J = 11.3 Hz), 7.35−7.39 (m, 2H), 7.53−7.57 (m, 1H), and 7.97 (d, 1H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.3, −5.2, 18.3, 19.7, 23.7, 26.0, 30.0, 38.2, 40.7, 42.7, 43.6, 59.8, 124.6, 125.4, 127.9, 132.0, 132.8, 132.9, 134.3, 148.3, and 176.5.

(*Z*)-3-(2-Hydroxyethyl)-3-(4-(2-nitrophenyl)but-3-enyl)-piperidin-2-one (50). A solution of 0.33 g (0.76 mmol) of alkene **48** in THF (8 mL) was cooled to 0 °C. To this solution was added 1.1 mL (1.0 M in THF, 1.1 mmol) of TBAF dropwise over 5 min, and the resulting mixture was stirred at 0 °C for 30 min. The reaction mixture was then warmed to rt and was stirred for an additional 3 h. The dark brown solution was poured into a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column silica gel chromatography gave alcohol **50** (0.21 g, 87%) as a light yellow solid: mp 106 − 108 °C; IR (neat) 3397, 2948, 2871, 1644, and 1522 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56−1.85 (m, 7H), 1.88−1.96 (m, 1H), 2.04−2.10 (m, 2H), 3.19−3.31 (m, 2H), 3.55−3.64 (m, 2H), 3.77−3.85 (m, 1H), 5.81 (dt, 1H, J = 11.4 and 7.4 Hz), 6.00 (brs, 1H), 6.71 (d, 1H, J = 11.4 Hz), 7.37 (d, 1H, J = 7.4 Hz), 7.42 (m, 1H), 7.59 (dt, 1H, J = 7.8 and 1.2 Hz), and 8.01 (dd, 1H, J = 8.2 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 23.2, 31.3, 36.8, 40.5, 42.7, 43.4, 58.9, 124.6, 125.8, 128.0, 131.9, 132.6, 132.9, 133.8, 148.3, and 178.1; HRMS calcd for $C_{17}H_{22}N_2O_4$ 319.1658, found 319.1651.

(*Z*)-2-(3-(4-(2-Nitrophenyl)but-3-enyl)-2-oxopiperidin-3-yl)-ethyl Acetate (51). A solution of 0.43 g (1.4 mmol) of alcohol **50** in CH_2Cl_2 (15 mL) was cooled to 0 °C. To this solution was added 0.38 mL (2.7 mmol) of NEt_3 followed by 17 mg (0.14 mmol) of DMAP and then 0.14 mL (1.5 mmol) of Ac_2O. The resulting mixture was stirred at 0 °C for 1 h, then poured into H_2O, and extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column silica gel chromatography afforded the title compound (0.48 g, 98%) as a clear oil: IR (neat) 3433, 3402, 2947, 2870, 1737, 1656, and 1522 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.59−1.86 (m, 7H), 1.98−2.21 (m, 3H), 2.01 (s, 3H), 3.17−3.30 (m, 2H), 4.07−4.19 (m, 2H), 5.79 (dt, 1H, J = 11.4 and 7.4 Hz), 6.63 (brs, 1H), 6.69 (d, 1H, J = 11.4 Hz), 7.37 (d, 1H, J = 7.4 Hz), 7.41 (dt, 1H, J = 8.2 and 0.8 Hz), 7.59 (dt, 1H, J = 7.4 and 1.2 Hz), and 8.01 (dd, 1H, J = 8.2 and 1.2 Hz) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.6, 21.2, 23.6, 30.1, 36.5, 38.2, 42.6, 43.3, 61.4, 124.7, 125.7, 128.0, 132.0, 132.7, 133.0, 134.0, 148.4, 171.2, and 175.9.

(*Z*)-2-(3-(4-(2-Nitrophenyl)but-3-enyl)-2-thioxopiperidin-3-yl)-ethyl Acetate (52). A solution of 0.65 g (1.8 mmol) of acetate **51** and 0.44 g (1.1 mmol) of Lawesson's reagent in toluene (20 mL)

was heated at reflux for 2 h. After being cooled to rt, the solvent was removed under reduced pressure. The yellow residue that remained was purified by flash column silica gel chromatography to give the *Z*-substituted thiolactam **52** (0.48 g, 71%) as a light yellow oil: IR (neat) 3306, 3176, 3065, 1737, 1523, 1348, and 1239 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.61−1.94 (m, 7H), 2.01 (s, 3H), 2.07−2.18 (m, 2H), 2.29−2.36 (m, 1H), 3.15−3.27 (m, 2H), 4.07−4.25 (m, 2H), 5.74−5.81 (m, 1H), 6.69 (d, 1H, J = 11.4 Hz), 7.38−7.42 (m, 2H), 7.57 (dt, 1H, J = 7.4 and 1.2 Hz), 7.98 (dd, 1H, J = 8.6 and 1.2 Hz), and 9.15 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3, 21.2, 23.7, 28.5, 40.3, 41.9, 45.3, 47.4, 61.3, 124.6, 125.9, 128.0, 132.1, 132.7, 133.1, 133.7, 148.3, 171.2 and 209.1; HRMS calcd for $[C_{19}H_{25}N_2O_4S + H^+]$ 377.1535, found 377.1530.

(*Z*)-9-(2-Acetoxyethyl)-9-(4-(2-nitrophenyl)but-3-enyl)-2-oxo-6,7,8,9-tetrahydro-2*H*-pyrido[2,1-*b*][1,3]thiazin-5-ium-4-olate (53). To a solution containing 0.12 g (0.32 mmol) of thioamide **52** in CH_2Cl_2 (5.5 mL) at −78 °C was added carbon suboxide, prepared from 0.19 g (2.9 mmol) of zinc dust and 0.67 g (2.2 mmol) of dibromomalonyl dichloride in refluxing Et_2O (11 mL) for 20 min. The resulting yellow solution was stirred for an additional 45 min at rt. The solvent was removed under reduced pressure, and the resulting mixture was purified by flash column silica gel chromatography to give dipole **53** (0.11 g, 80%) as a bright yellow oil: IR (neat) 2954, 1738, 1646, and 1522 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.81−2.05 (m, 8H), 1.98 (s, 3H), 2.07−2.16 (m, 1H), 2.33 (ddd, 1H, J = 14.9, 8.6, and 6.3 Hz), 3.94−4.01 (m, 1H), 4.03−4.16 (m, 2H), 4.26 (ddd, 1H, J = 11.7, 6.7, and 5.1 Hz), 5.23 (s, 1H), 5.73 (dt, 1H, J = 11.3 and 7.4 Hz), 6.79 (d, 1H, J = 11.3 Hz), 7.26 (d, 1H, J = 7.4 Hz), 7.48 (dt, 1H, J = 8.2 and 1.2 Hz), 7.62 (dt, 1H, J = 7.4 and 1.2 Hz), and 8.03 (dd, 1H, J = 8.2 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3, 20.8, 23.3, 29.0, 42.2, 43.8, 47.9, 48.1, 59.6, 88.0, 125.0, 128.2, 128.9, 130.7, 131.5, 131.9, 133.4, 148.3, 161.6, 166.2, 170.6, and 193.7.

2-(1-(2-Nitrophenyl)-3-oxo-2,3,5,6,7,7*a*,8,9-octahydro-1*H*-cyclopenta[*ij*]-quinolizin-7a-yl)ethyl Acetate (56). A solution of 0.52 g (1.2 mmol) of dipole **53** in toluene (11 mL) in a sealed tube was placed in a preheated oil bath at 200 °C for 1 h. The dark mixture was cooled to rt, and the solvent was removed under reduced pressure. The residue was purified by flash column silica gel chromatography to give tricycle **56** (0.14 g, 31%) as a yellow solid: mp 118−121 °C; IR ($CDCl_3$) 2939, 2859, 1737, 1673, and 1525 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37−1.29 (m, 1H), 1.60−1.68 (m, 1H), 1.78−1.87 (m, 4H), 1.91−2.00 (m, 2H), 2.02−2.17 (m, 2H), 2.09 (s, 3H), 2.69 (dd, 1H, J = 14.9 and 14.5 Hz), 2.95 (dd, 1H, J = 15.4 and 5.7 Hz), 3.01−3.09 (m,1H), 4.01 (dt, 1H, J = 12.9 and 3.9 Hz), 4.10−4.22 (m, 2H), 4.34−4.39 (m, 1H), 7.35−7.42 (m, 2H), 7.62 (dt, 1H, J = 7.8 and 1.2 Hz), and 7.80 (dd, 1H, J = 7.8 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.5, 21.2, 28.4, 33.1, 33.3, 34.9, 37.0, 40.1, 41.2, 44.7, 61.8, 115.9, 124.5, 127.9, 130.0, 133.2, 136.6, 142.6, 150.3, 169.8, and 171.3; HRMS calcd for $C_{21}H_{24}N_2O_5$ 385.1763, found 385.1756.

2-(2*a*′-Hydroxy-7-oxo-2,2*a*,2*a*′,3,4,5,7,8,8*a*,13-decahydro-1*H*-cyclopenta[*ij*]-indolo[2,3-*a*]quinolizin-2a-yl)ethyl Acetate (59). A mixture of 28 mg (0.073 mmol) of tricycle **56**, 28 mg of 10% Pd/C in EtOH (2.2 mL), and THF (1 mL) was stirred under an H_2 atmosphere (4 atm) at rt for 15 h. The reaction mixture was filtered through a pad of Celite with EtOAc. The solvent was removed under reduced pressure, and the crude aniline **58** was used in the next step without purification. To the above aniline **58** in CH_2Cl_2 (5 mL) at rt was added 6 mg (0.03 mmol) of *N*-bromosuccinimide in one portion. The orange mixture was stirred at rt for 20 min, and then the solvent was removed under reduced pressure without heating. The crude bromide was used immediately in the next step without purification.

To the above bromide in MeOH (0.5 mL) at rt was added a solution of 13 mg (0.078 mmol) of $AgNO_3$ in H_2O (6 mL) and MeOH (1.5 mL). The reaction mixture was stirred at rt for 1 h and was then poured into brine (20 mL) and extracted with $CHCl_3$. The combined organic mixture was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Purification of the residue by flash column chromatography on deactivated (2% NEt_3) silica gel gave the title compound **59** (5.7 mg, 21% over three steps) as a light yellow oil; IR (CH_2Cl_2) 3313, 2951, 1734, 1647, 1403, and 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.49−1.75 (m, 6H), 1.86−2.01 (m, 3H), 2.06 (s, 3H), 2.13−2.22 (m, 1H), 2.31 (ddd, 1H, J = 15.7, 13.3, and 0.8 Hz), 2.53 (dd, 1H, J = 15.7 and 5.1 Hz), 2.79−2.86 (m, 1H), 3.25 (dd,1H, J = 13.3 and 4.7 Hz), 3.89 (s, 1H), 4.13−4.24 (m, 2H), 4.41−4.46 (m, 1H), 4.81 (s, 1H), 6.79 (d, 1H, J = 7.8 Hz), 6.88 (dt, 1H, J = 7.4 and 0.8 Hz), and 7.08−7.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.8, 21.4, 29.1, 29.2, 34.0, 36.9, 39.1, 39.5, 48.0, 48.4, 61.7, 76.4, 91.6, 111.8, 121.8, 124.4, 128.6, 130.7, 147.7, 171.4, and 174.4.

2-(7-Oxo-2,2*a*,2*a*′,3,4,5,7,8,8*a*,13-decahydro-1*H*-cyclopenta-[*ij*]indolo[2,3-*a*]quinolizin-2*a*-yl)ethyl Acetate (60). To a stirred solution of 9.0 mg (0.024 mmol) of pentacycle **59** in AcOH (2 mL) and H_2O (1.0 mL) at rt was added 24 mg (0.38 mmol) of $NaBH_3CN$ in one portion. The reaction mixture was stirred at rt for 30 min and then heated at 50 °C for an additional 2 h. The reaction mixture was cooled to rt and was then carefully poured into a saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Purification of the residue by flash column silica gel chromatography gave **60** (5.9 mg, 69%) as a white solid: mp 143−144 °C; IR (neat) 3360, 2924, 2854, 1738, 1645, and 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.57−1.72 (m, 6H), 1.81−2.07 (m, 5H), 2.09 (s, 3H), 2.42 (dd, 1H, J = 15.6 and 12.0 Hz), 2.51−2.58 (m, 2H), 3.22 (dd, 1H, J = 11.7 and 4.7 Hz), 3.43 (s, 1H), 4.16−4.29 (m, 2H), 4.43−4.48 (m, 1H), 6.66 (d, 1H, J = 7.8 Hz), 6.76 (t, 1H, J = 7.2 Hz), and 7.06−7.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 21.3, 30.5, 34.2, 36.7, 38.7, 39.1, 40.2, 44.0, 47.0, 61.3, 70.3, 76.0, 110.0, 119.6, 124.3, 128.4, 130.4, 149.0, 171.4, and 172.7; HRMS Calcd for $C_{21}H_{26}N_2O_3$ 355.2022, found 355.2015.

2-(2,2*a*,2*a*′,3,4,5,7,8,8*a*,13-Decahydro-1*H*-cyclopenta[*ij*]indolo[2,3-*a*]quinolizin-2*a*-yl)ethyl Acetate (62). A solution of 27 mg (0.07 mmol) of pentacycle **60** and 17 mg (0.04 mmol) of Lawesson's reagent in toluene (2 mL) was heated at reflux for 2 h. The reaction mixture was cooled to rt, and the solvent was removed under reduced pressure. The dark yellow residue was passed through a short plug of silica gel to give (26 mg, 93%) of **61** as a yellow oil that was used without further purification in the next reaction. To a stirred suspension of Ra−Ni under N_2 in THF (1 mL) was added a solution of 9.8 mg (0.026 mmol) of the above thiolactam **61** in THF (1.5 mL) at rt. After the heterogeneous mixture was stirred under a H_2 balloon for 1.5 h, the reaction mixture was filtered through Celite. The solvent was removed under reduced pressure. Purification of the residue by preparative TLC on silica gel gave the title compound **62** (5.6 mg, 64%) as a colorless oil: IR (neat) 3411, 1732, 1608, 1463, and 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44−1.50 (m, 3H), 1.54−1.62 (m, 2H), 1.72−1.84 (m, 1H), 1.87−2.04 (m, 7H), 2.07−2.13 (m, 1H), 2.08 (s, 3H), 2.20−2.29 (m, 1H), 2.52−2.57 (m, 1H), 2.66−2.71 (m, 1H), 3.24 (t, 1H, J = 4.3 Hz), 4.04 (dt, 1H, J = 10.6 and 5.5 Hz), 4.31 (dt, 1H, J = 10.6 and 5.5 Hz), 4.47 (brs, 1H), 6.65 (d, 1H, J = 7.4 Hz), 6.72 (t, 1H, J = 7.4 Hz), and 6.99−7.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.5, 21.3, 24.9, 30.1, 35.0, 35.8, 39.2, 44.1, 45.0, 50.7, 53.3, 61.8, 75.2, 75.3, 109.2, 118.6, 122.9, 127.6, 131.6, 150.2, and 171.6; HRMS calcd for $C_{21}H_{28}N_2O_2$ 341.2229, found 341.2222.

2-(2,2*a*,2*a*′,3,4,5,7,8,8*a*,13-Decahydro-1*H*-cyclopenta[*ij*]indolo[2,3-*a*]quinolizin-2*a*-yl)ethanol (63). To a solution containing 5.6 mg (0.016 mmol) of **62** in MeOH (1 mL) at 0 °C was added 4.5 mg (0.033 mmol) of K_2CO_3. After the mixture was stirred for

2 h at 0 °C, the solution was warmed to rt, and stirred for an additional 1 h. The mixture was diluted with Et_2O, poured into H_2O, and extracted with Et_2O and EtOAc. The combined organic extracts were dried over anhydrous Mg_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by preparative TLC on silica gel gave alcohol **63** (4.9 mg, 99%) as a colorless oil: IR (neat) 3343, 2929, 2854, 1608, and 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39−1.64 (m, 6H), 1.73−1.83 (m, 1H), 1.91−2.12 (m, 9H), 2.23−2.31 (m, 1H), 2.53−2.57 (m, 1H), 2.66−2.70 (m, 1H), 3.28−3.29 (m, 1H), 3.75−3.87 (m, 2H), 6.63 (d, 1H, J = 7.4 Hz), 6.76−6.80 (m, 1H), and 7.01−7.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 25.1, 30.7, 35.0, 36.1, 43.3, 44.4, 45.3, 50.7, 53.2, 59.7, 75.0, 75.2, 110.6, 119.7, 123.0, 127.7, 133.0, and 149.6.

(±)-Strempeliopine (3). To a stirred solution of 4.4 mg (0.015 mmol) of alcohol **63** in CH_2Cl_2 (1 mL) at rt was added 13 mg (0.03 mmol) of Dess−Martin periodinane. After being stirred at rt for 45 min, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2, and washed with H_2O. The organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was quickly passed through a silica gel plug eluting with a 20:1 CH_2Cl_2/MeOH mixture with 2% NEt_3. The solvent was removed under reduced pressure, and the crude aldehyde was used without further purification in the next reaction.

To the above compound in CH_2Cl_2 (1 mL) at rt was added 7 mg (0.02 mmol) of PDC in one portion. After the mixture was stirred at rt for 1 h, a saturated aqueous $NaHCO_3$ solution (1 mL) was added, and the mixture was stirred for an additional 15 min at rt. The reaction mixture was then filtered through Celite with CH_2Cl_2, washed with a saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by preparative TLC on silica gel gave (1.8 mg, 29%) of (±)-strempeliopine (**3**)[11c] as a white solid: mp 151−153 °C; IR (neat) 2919, 2850, 1660, 1599, 1479, 1392, and 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.30 (dd, 1H, J = 13.3 and 4.6 Hz), 1.46−1.50 (m, 1H), 1.57−1.62 (m, 1H), 1.72−1.75 (m, 1H), 1.82−1.89 (m, 1H), 1.94−1.99 (m, 1H), 2.02−2.06 (m, 2H), 2.07−2.12 (m, 1H), 2.23 (ddd, 1H, J = 11.9, 11.9, and 6.0 Hz), 2.26−2.32 (m, 3H), 2.46 (dd, 1H, J = 17.9 and 1.7 Hz), 2.63 (d, 1H, J = 17.9 Hz), 2.84−2.88 (m, 1H), 2.97 (ddd, 1H, J = 13.7, 7.8, and 6.0 Hz), 3.25 (dd, 1H, J = 7.3 and 6.9 Hz), 7.04−7.07 (m, 1H), 7.16 (d, 1H, J = 7.3 Hz), 7.21−7.24 (m, 1H), and 8.05 (d, 1H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.0, 26.4, 31.5, 32.0, 39.0, 42.1, 43.2, 50.5, 50.8, 54.3, 69.8, 72.4, 116.0, 123.8, 124.1, 124.2, 128.2, 145.0, and 169.3; HRMS calcd for $[C_{19}H_{23}N_2O + H^+]$ 295.1810, found 295.1804.

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Supporting Information Available: ^1H and ^{13}C NMR data of various key compounds lacking CHN analyses together with an ORTEP drawing for compound **60** as well as the corresponding CIF file. Atomic coordinates for compound **60** will be deposited with the Cambridge Crystallographic Data Centre. This material is available free of charge via the Internet at http://pubs.acs.org.