Cycloaddition Reaction of Mesoionic Betaines as an Approach toward Trialkylindoline Alkaloids

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Intramolecular 1,4-dipolar cycloaddition of an anhydro-4-hydroxy-2-oxo-1,3-thiazium hydroxide across a tethered indole π-bond has been used for the construction of the pentacyclic skeleton of *epi*-16,17-dihydroeburnamenine. The reaction of 3-ethyl-3-(alkenyl)piperidinones with diketene and trimethylsilyl triflate in benzene at ambient temperature produced annulated pyridones in good yield. The initial reaction involved formation of a *N*-acetoacetylated amide which was further converted to the pyridone with TMSOTf. The overall process was found to proceed with complete stereospecificity. Treating a sample of 3-ethyl-3-[(*E*)-4-phenyl-3-butenyl]-2-piperidone with diketene and TMSOTf produced a cycloadduct in 63% yield whose stereochemistry was elucidated by a X-ray crystallographic study. The epimeric *Z*-isomer produced a different stereoisomer of the annulated dihydropyridone. The mechanism of the annulation involves a TMSOTf induced cyclization followed by proton removal and generation of a cross-conjugated heteroaromatic betaine. This 1,4-dipole undergoes a subsequent intramolecular dipolar cycloaddition across the neighboring π-bond, and the resulting cycloadduct is subsequently converted to the annulated lactam. A related annulation sequence leading to a key intermediate previously utilized in the synthesis of the (±)-vallesamidine has been developed which is based on the intramolecular dipolar cycloaddition of a mesoionic betaine intermediate.

The discovery of general methods for the synthesis of natural products continues to be a current research objective. This is particularly true for the synthesis of indole alkaloids, a group of compounds that have very different structures but that, due to their common biogenetic origin, possess some common structural features.[1] It is not surprising, therefore, that the construction of azapolycyclic ring systems continues to be of wide interest to researchers involved in developing new methods and reagents for organic synthesis.[2−10] Indeed, over the past few decades, an impressive number of effective protocols for the synthesis of trialkylindoline alkaloids have been developed, and many of these have also proven to be of value in work directed toward the synthesis of several different classes of alkaloids.[11−19]

Inter- and intramolecular dipolar cycloadditions have found wide application in the synthesis of a variety of heterocyclic systems, with those of the bimolecular 1,3-dipolar type being the most extensively studied.[20] In earlier papers we have described a convenient method for the preparation of *peri*-fused tricyclic heterocycles by a novel intramolecular 1,4-dipolar cycloaddition of thiazinium hydroxides of type **2** (Scheme 1).[21] These cross-conjugated heteroaromatic betaines contain a "*masked*" 1,4-dipole within their framework and are capable of

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(1) Cordell, G. A. In *The Alkaloids*; Manske, R. H. F., Rodrigo, G. R. A., Eds.; Academic Press: New York, 1979; Vol. 17, pp 199−384.

(2) Schultz, A. G.; Chiu, I. C. *J. Chem. Soc., Chem. Commun.* **1978**, 29. Schultz, A. G.; Holoboski, Smyth, M. S. *J. Am. Chem. Soc.* **1996**, *118*, 6210. Schultz, A. G.; Guzzo, P. R.; Nowak, D. M. *J. Org. Chem.* **1995**, *60*, 8044.

(3) Veenstra, S. J.; Speckamp, W. N. *J. Am. Chem. Soc.* **1981**, *103*, 4645. Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1047−1082.

(4) Hart, D. J. *J. Org. Chem.* **1981**, *46*, 367. Hart, D. J.; Kanai, K. *J. Org. Chem.* **1982**, *47*, 1555.

(5) Pearson, W. H.; Lin, K. C. *Tetrahedron Lett.* **1990**, *31*, 7571. Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 6783. Peason, W. H.; Walavalkar, R. *Tetrahedron* **1994**, *50*, 12293. Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5537.

(6) Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612. Arnold, H.; Overman, L. E.; Sharp, M. J.; Witschel, M. C. *Org. Synth.* **1991**, *70*, 111. Lin, N. H.; Overman, L. E.; Rabinowitz, M. H.; Roginson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062.

(7) Padwa, A.; Price, A. T. *J. Org. Chem.* **1995**, *60*, 6258. Marino, J. P., Jr.; Osterhout, M. H.; Padwa, A. *J. Org. Chem.* **1995**, *60*, 2704.

(8) Livinghouse, T.; Kercher, T. *J. Am. Chem. Soc.* **1996**, *118*, 4200. McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485. McGrane, P. L.; Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 549. McGrane, P. L.; Livinghouse, T. *J. Org. Chem.* **1992**, *57*, 1323.

(9) Comins, D. L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, *44*, 199 and references therein. Comins, D. L.; Morgan, L. A. *Tetrahedron Lett.* **1991**, *32*, 5919. Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *42*, 6299. Comins, D. L.; Al-awar, R. S. *J. Org. Chem.* **1995**, *60*, 711.

(10) Winkler, J. D.; Scott, R. D.; Willard, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 8971.

(11) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872.

(12) Ban, Y.; Sato, Y.; Inoue, I.; Nugai, M.; Terashima, M.; Yonemitsu, O.; Kanaoka, Y. *Tetrahedron Lett.* **1965**, 2261. Ban, Y.; Iijima, I. *Tetrahedron Lett.* **1969**, 2523.

(13) Stevens, R. V.; Fitzpatrick, M. J.; Kaplan, M.; Zimmerman, R. L. *J. Chem. Soc., Chem. Commun.* **1971**, 857.

(14) Martin, S. F.; Desai, S. R.; Philips, G. W.; Miller, A. C. *J. Am. Chem. Soc.* **1980**, *102*, 3294.

(15) Wu, P. L.; Chu, M.; Fowler, F. W. *J. Org. Chem.* **1988**, *53*, 963.

(16) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673.

(17) Overman, L. E.; Sworin, M.; Bass, L. S.; Clardy, J. *Tetrahedron* **1981**, *37*, 4041. Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685.

(18) Exon, C.; Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 4739. Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750. Magnus, P.; Pappalardo, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 212.

(19) Kuehne, M. E.; Earley, W. G. *Tetrahedron* **1983**, *39*, 3707. Kuehne, M. E.; Podhorez, D. E. *J. Org. Chem.* **1985**, *50*, 924. Kuehne, M. E.; Podhorez, D. E.; Mulamba, T.; Bornmaann, W. G. *J. Org. Chem.* **1987**, *52*, 347.

(20) For a general discussion see: *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vols. 1 and 2.

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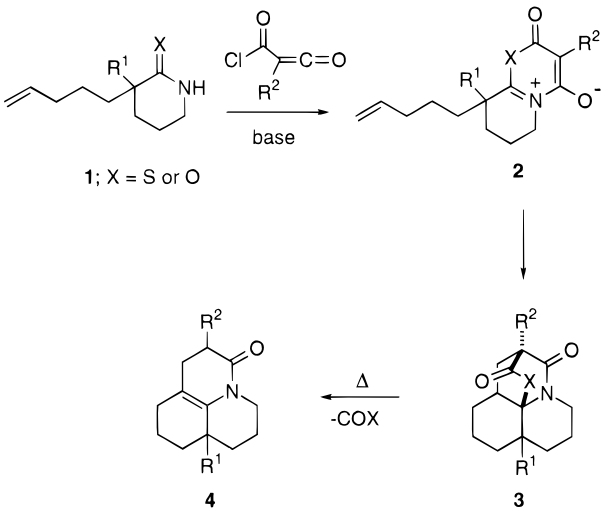
Scheme 1

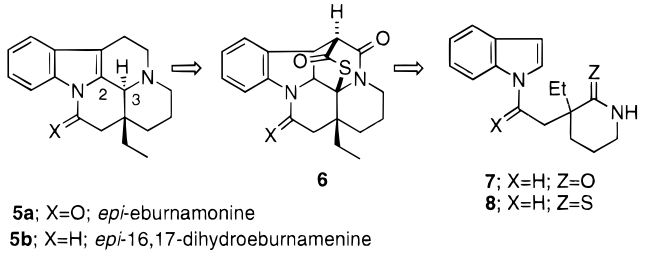


undergoing cycloaddition with π-bonds.[22] The overall convenience of this method, the ease of access to starting materials, and the relatively high yields obtained suggest its application toward the preparation of a number of polycyclic ring systems of interest in natural product chemistry. We had previously employed this methodology[21] for the synthesis of the hexahydrojulolidine ring skeleton found in many of the *Lycopodium* alkaloids.[23] In this paper, we report additional studies which further establish the synthetic utility of the intramolecular dipolar cycloaddition of mesoionic betaines for the construction of the core skeleton found in several indole alkaloids.[24]

Results and Discussion

Eburnamenine Class of Alkaloids. *Vinca* alkaloids comprise a large group of biologically active, naturally occurring bases, isolated from several plants of the *Vinca* species.[25] Among this class of natural products, the pentacyclic array found in the indole alkaloid eburnamonine has received considerable attention over the years.[26,27] Most of the strategies used for its synthesis involve the construction of the C_2-C_3 carbon−carbon

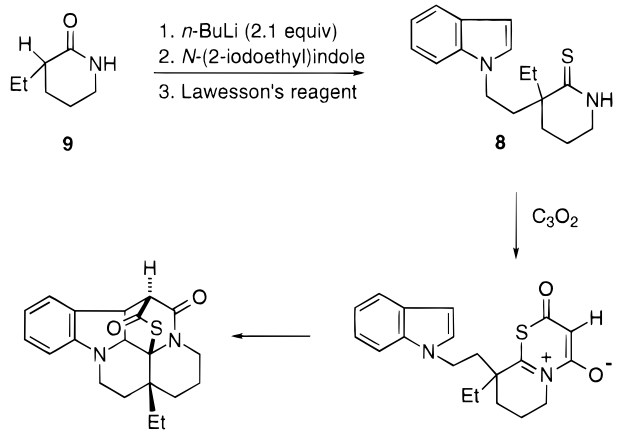
Scheme 2



5a; X=O; *epi*-eburnamonine
5b; X=H; *epi*-16,17-dihydroeburnamenine

bond via either a Pictet−Spengler or Bischler−Napieralski cyclization.[28] As a consequence, the majority of these syntheses have also led to *epi*-eburnamonine (**5a**) which possesses the trans ring fusion. Our own strategy for the synthesis of the pentacyclic indoloquinolizidine moiety found in *epi*-16,17-dihydroeburnamenine[29] (**5b**) is outlined in the retrosynthetic pathway depicted in Scheme 2. The basic approach involves an intramolecular 1,4-dipolar cycloaddition of thiazinium betaine **10** (vide infra) to construct the key cycloadduct **6**.[21,24] Cycloaddition of betaine **10** across the pendent indole π-system would be expected to lead to the pentacyclic skeleton found in **5**.

We began our investigation by treating 3-ethyl-2-piperidone (**9**) in THF with 2.1 equiv of *n*-butyllithium at 0 °C. Alkylation took place on the nitrogen atom when *N*-(2-iodoethyl)indole was added, affording amide **7** in 80% overall yield. Interestingly, the amide dianion underwent smooth alkylation without the need for an additional cosolvent (i.e., HMPA) which is often necessary to facilitate alkylation. Conversion of **7** to thiolactam **8** was carried out using Lawesson's reagent.[31] Treatment of **8** with carbon suboxide[32] at 25 °C furnished the 1,4-dipolar cycloadduct **6** as a single diastereomer in 95% yield. The reaction of **10** across the indolyl π-bond



represents a rare example of this heteroaromatic ring functioning as a dipolarophile in 1,3-dipolar cycloaddition

(21) Potts, K. T.; Rochanapruk, T.; Coats, S. J.; Hadjiarapoglou, L.; Padwa, A. *J. Org. Chem.* **1993**, *58*, 5040. Potts, K. T.; Rochanapruk, T.; Padwa, A.; Coats, S. J.; Hadjiarapoglou, L. *J. Org. Chem.* **1995**, *60*, 3795. Padwa, A.; Coats, S. J.; Harring, S. R.; Hadjiarapoglou, L.; Semones, M. A. *Synthesis* **1995**, 973. Padwa, A.; Coats, S. J.; Semones, M. A. *Tetrahedron* **1995**, *24*, 6651.

(22) Ollis, W. D.; Stanforth, S. P.; Ramsden, C. A. *Tetrahedron* **1985**, *41*, 2239.

(23) Ayer, W. A.; Trifonov, L. S. *The Alkaloids*; Cordell, G. A., Brossi, A., Eds.; Academic Press: San Diego, 1994; Vol. 45, pp 233−274.

(24) For a preliminary report of this work, see: Padwa, A.; Semones, M. A. *Tetrahedron Lett.* **1996**, *37*, 335.

(25) Atta-ur, Rahman; Sultana, M. *Heterocycles* **1984**, *22*, 841.

(26) Eburnamine-Vincamine Alkaloids: Lounasmaa, M.; Tolvanen, A. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1992; Vol. 42. p 1. Taylor, W. I. *Alkaloids* **1968**, *11*, 125. Hesse, M. *Indolalkaloide in Tabellen*, Supplement; Springer-Verlag: New York, 1968; p 45. Bruneton, J.; Bouquet, A.; Cave, A. *Phytochemistry* **1973**, *12*, 1475.

(27) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1965**, *87*, 1580.

(28) Buzas, A.; Herrison, C.; Lavielle, G. *C. R. Acad. Sci. Ser. C* **1976**, *283*, 763. Novak, L.; Rohaly, J.; Szantay, C. *Heterocycles* **1977**, *6*, 1149. Wenkert, E.; Hudlicky, T.; Showalter, H. D. *J. Am. Chem. Soc.* **1978**, *100*, 4893. Wenkert, E.; Hudlicky, T. *J. Org. Chem.* **1988**, *53*, 1953. Bolsing, E.; Klatte, G.; Rosentreter, U.; Winterfeldt, E. *Chem. Ber.* **1979**, *112*, 1902. Irie, K.; Ban, Y. *Heterocycles* **1981**, *15*, 201. Imanishi, T.; Miyasha, K.; Nakai, A.; Inoue, M.; Hanaoka, M. *Chem. Pharm. Bull.* **1982**, *30*, 1521.

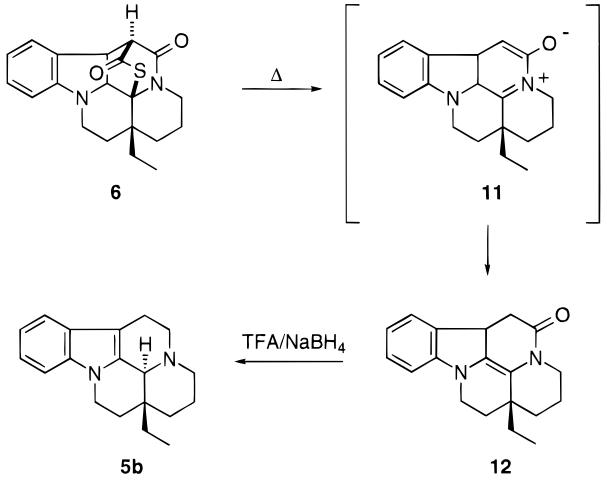
(29) Coffen, E. L.; Katonak, D. A.; Wong, F. *J. Am. Chem. Soc.* **1974**, *96*, 3966. Rahman, A.; Zaman, K.; Perveen, S.; Rehman, H.; Muzaffar, A.; Choudhary, M. I.; Pervin, A. *Phytochemistry* **1991**, *30*, 1285.

(30) Meyers, A. I.; Kunnen, K. B.; Still, W. C. *J. Am. Chem. Soc.* **1987**, *109*, 4405. Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. *Synthesis* **1977**, 509. Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 1688.

(31) Lawesson, S. O.; Shabana, R.; Scheibye, S.; Clausen, K.; Oleseh, S. O. *Nouv. J. Chem.* **1980**, *47*, 4. Lawesson, S. O.; Thompson, I.; Clausen, K.; Scheibye, S. *Org. Synth.* **1990**, *7*, 372.

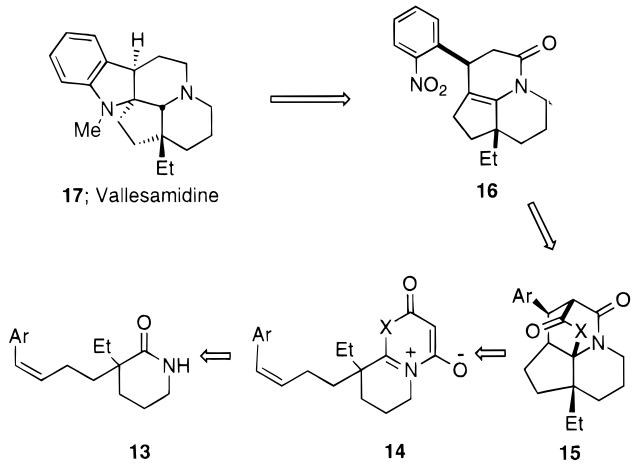
(32) Kappe, T.; Ziegler, E. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 491. Hopff, H.; Hegar, G. *Helv. Chim. Acta* **1961**, *44*, 2016. Staudinger, H.; Beresa, S. *Ber.* **1908**, *41*, 4461.

chemistry.[33,34] When cycloadduct **6** was heated at 210 °C for 10 min, it underwent loss of COS[35] and gave rise to enamide **12** in 98% yield. More than likely, this transformation proceeds by deprotonation of the initially formed 1,4-dipole **11**. When **12** was subjected to reduction using excess trifluoroacetic acid/$NaBH_4$ in dioxane,[36] *epi*-16,17-dihydroeburnamenine (**5b**) was obtained in 90% yield. The stereochemistry of the ring junction was determined by an X-ray crystallographic study.[37] A likely scenario for the one-pot reduction of **12** → **5** involves protonation of the enamide, aromatization to generate the indole, followed by amide reduction. The *trans*-stereochemistry can be rationalized as being the consequence of a steric effect by the angular ethyl group which directs protonation to the less hindered face of the molecule.[27]



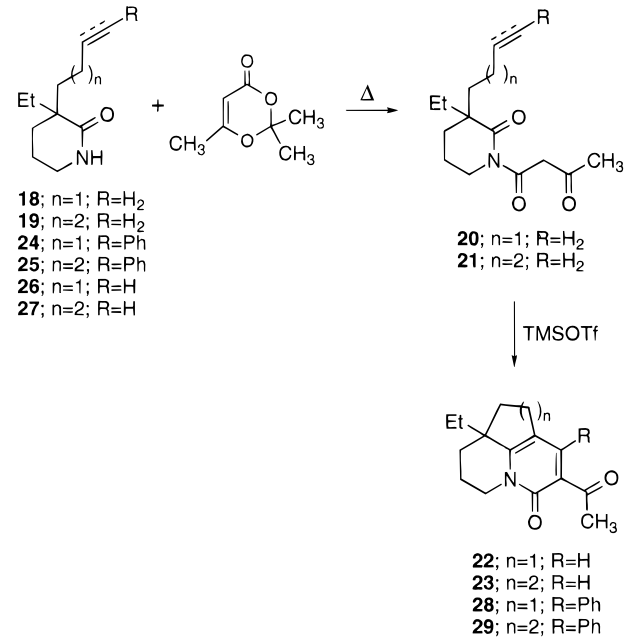
2,2,3-Trialkylindoline Class of Alkaloids. To further illustrate the viability of employing the intramolecular dipolar cycloaddition of cross-conjugated betaines as a practical strategy for the synthesis of alkaloids, we have explored the utility of this reaction in the context of a total synthesis of a 2,2,3-trialkyl-substituted indoline alkaloid. A particularly attractive target for such an investigation was vallesamidine (**17**).[38] Vallesamidine was isolated in 1965 from *Vallesia dichotoma*, and its molecular structure and absolute configuration were determined by Djerassi in 1968.[38] It was first synthesized by Levy in 1971[39] and later by Heathcock in 1989.[40] Our initial approach to vallesamidine is adumbrated in the retrosynthetic format depicted in Scheme 3 and

Scheme 3



features the intramolecular 1,4-dipolar cycloaddition of a mesoionic betaine (**14**; X = O or S) to furnish **16** after extrusion of CO_2 or COS from the initially formed cycloadduct **15**. Since **16** has previously been converted to vallesamidine by Heathcock,[40] its preparation would constitute a formal total synthesis of this structurally unique alkaloid.

Model Studies Using Cross-Conjugated Heteroaromatic Betaines. At the outset, our principal concern was whether mesoionic betaines such as **14** would undergo intramolecular dipolar cycloaddition.[21] We therefore initiated a simple model study, in which we discovered that the reaction of a 3,3-disubstituted cyclic amide with diketene in the presence of TMSOTf is a convenient method for generating the equivalent of a cross-conjugated heteroaromatic betaine dipole.[41,42] Thus, stirring a sample of 3-ethyl-3-(buten-4-yl)piperidinone (**18**) and diketene with 0.13 equiv of trimethylsilyl triflate in benzene at 25 °C initially produced the *N*-acetoacetylated



(33) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 16. Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990.

(34) Hassner, A.; Murthy, K. S. K.; Padwa, A.; Chioacchio, U.; Dean, D. C.; Schoffstall, A. M. *J. Org. Chem.* **1989**, *54*, 5277. Dehaen, W.; Hassner, A. *J. Org. Chem.* **1991**, *56*, 896.

(35) Carbonyl sulfide was identified by trapping in an alcoholic solution of piperidine where it formed the corresponding salt; see: Seibert, W. *Angew. Chem.* **1959**, *71*, 194.

(36) Umino, N.; Iwakuma, T.; Itoh, N. *Tetrahedron Lett.* **1976**, *10*, 763.

(37) The authors have deposited coordinates for structures **5**, **31**, **33**, **34**, **42a**, and **42b** with the Cambridge Data Centre. The coordinates can be obtained from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

(38) Walser, A.; Djerassi, C. *Helv. Chim. Acta* **1965**, *48*, 391. Brown, S. H.; Djerassi, C.; Simpson, P. G. *J. Am. Chem. Soc.* **1968**, *90*, 2445.

(39) Levy, J.; Mauperin, P.; Doe, M.; Le Men, J. *Tetrahedron Lett.* **1971**, 1003.

(40) Dickman, D. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 1528. Heathcock, C. H.; Norman, M. H.; Dickman, D. A. *J. Org. Chem.* **1990**, *55*, 798.

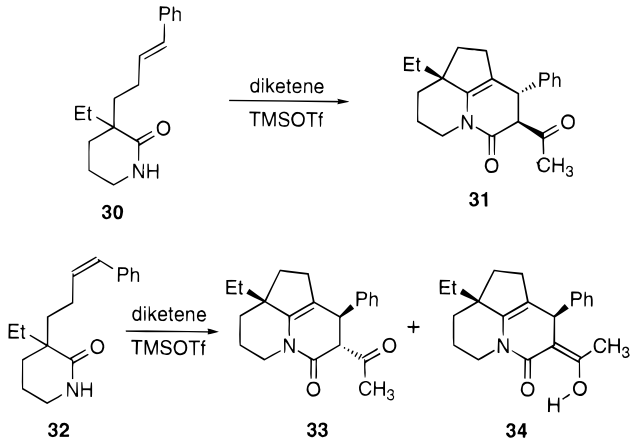
(41) Friedrichsen, W.; Kappe, T. *Heterocycles* **1982**, *19*, 1083. Ollis, W. D.; Stanforth, S. P.; Ramsden, C. A. *Tetrahedron* **1985**, *41*, 2239.

(42) For a preliminary report, see: Padwa, A.; Harring, S. R.; Semones, M. A. *J. Org. Chem.* **1995**, *60*, 2952.

amide **20** which was further converted to pyridone **22** (53% yield) under the reaction conditions. An independent synthesis of **20** was also carried out by heating a sample of **18** with 2,2,6-trimethyl-4*H*-1,3-dioxen-4-one in xylene at 140 °C.[43] Treatment of a pure sample of **20** with TMSOTf in benzene cleanly afforded pyridone **22**, with no signs of the initially formed dihydropyridone (vide infra), which we assume is oxidized to the thermodynamically more stable pyridone.

Control of ring size in the final product of the cycloaddition by variation of the dipolarophilic chain length was of appreciable interest. Introduction of a five-carbon chain was readily achieved by treating 3-ethylpiperidinone (**9**) with 2 equiv of *n*-butyllithium followed by reaction with 5-bromopentene to give lactam **19**. Treatment of lactam **19** with diketene and TMSOTf (0.13 equiv) in benzene afforded pyridone **23** (26%) together with some of the *N*-acetoacetylated product **21**. Entry to the [6.6.5] and [6.6.6]pyridone ring systems was also possible using the corresponding alkynyl-substituted amides **24**−**27**. Thus, the reaction of **24** or **25** with diketene and TMSOTf in benzene at 25 °C gave pyridones **28** and **29** in 50% and 65% yield, respectively. It should also be noted that the reaction of the alkynyl-substituted lactams **26** and **27** afforded the same pyridones (**22** and **23**) as was obtained from lactams **18** and **19** in 53% yield.

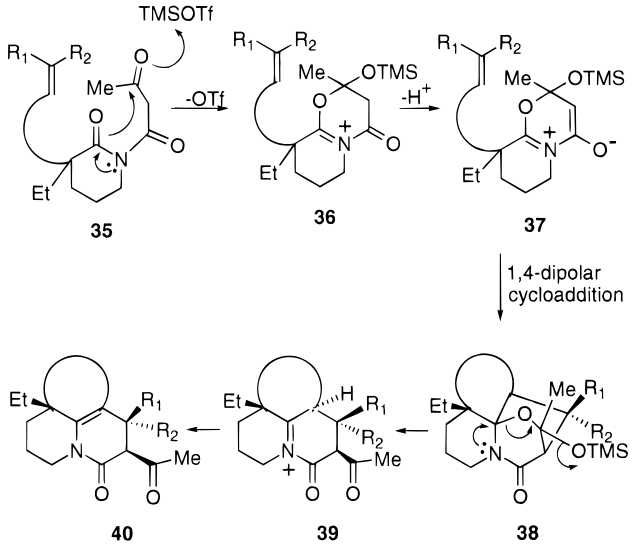
Another aspect of the cycloaddition worth noting was the complete stereospecificity of the process. Treating a sample of the *E*-isomer of lactam **30** with diketene and TMSOTf in benzene produced cycloadduct **31** in 63% yield. The stereochemistry of the substituent groups was established by an X-ray crystallographic study of the 2,4-dinitrophenyl hydrazone derivative.[37] Reaction of the *Z*-isomer of lactam **32**, on the other hand, gave rise to a 2:1-mixture of cycloadducts **33** and **34** in 93% overall yield. The two tautomers were separated by silica gel



chromatography and their structures were unequivocally assigned by single-crystal X-ray diffractometry.[37] Cycloadducts **33** and **34** were readily interconverted upon standing in solution.

Although trimethylsilyl triflate is known to catalyze some carbon−carbon bond forming reactions,[44,45] its use in generating zwitterionic species capable of undergoing

Scheme 4

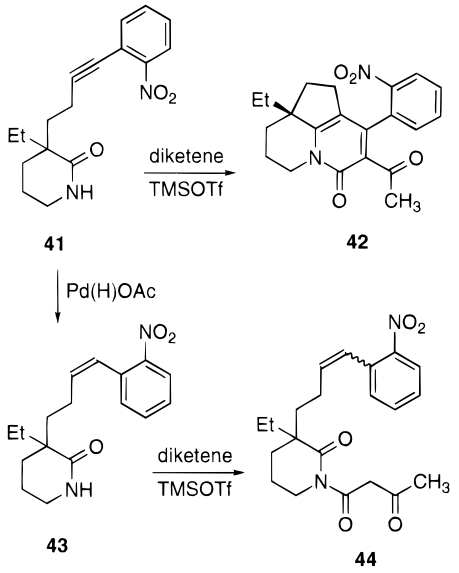


dipolar cycloaddition has been reported only for 1,3-dipoles.[46] The present reaction involves the intramolecular cycloaddition of a 1,4-dipole synthon formed from the reaction of an *N*-acetoacetylated alkenyl amide in the presence of TMSOTf. In our initial studies, $BF_3{\cdot}OEt_2$ was utilized as the Lewis acid promoter for the annulation reaction. Subsequent studies demonstrated that these annulation reactions were capricious with variable yields of product being obtained. In addition, 1 full equiv of the Lewis acid was required, causing subsequent problems during workup. To overcome these difficulties, a survey of diverse Lewis acids was carried out. Among the many Lewis acids tried, trimethylsilyl triflate gave the highest yield of the annulated product. The virtually non-nucleophilic character of the triflate anion allows for the desired acid−base chemistry to occur without competitive trapping by the counterion.[47]

The mechanism of this unusual annulation reaction has not been unequivocally established, but one reasonable possibility is outlined in Scheme 4. Here it is proposed that cyclization of the starting *N*-acetoacetylated amide (i.e., **35**) occurs in the presence of TMSOTf to give the cyclized acyl iminium ion **36**. Removal of the acidic proton generates the cross-conjugated heteroaromatic betaine **37** which undergoes a subsequent intramolecular 1,4-dipolar cycloaddition. The resulting cycloadduct **38** proceeds on to the annulated product **40** via nitrogen assisted C−O bond cleavage and ejection of $TMSO^-$, followed by a proton shift. The observed stereochemistry of the annulation product **31**, derived from lactam **30**, is perfectly consistent with this mechanism. On the other hand, the stereoisomer derived from lactam **32** is expected to have all three substituent groups on the same side of the tricyclic skeleton, but this isomer was not found. To account for the stereochemistry actually encountered, we assume that the initially produced diastereomer is readily epimerized to the thermodynamically more stable isomer. Indeed, the isolation of **34** as a distinct tautomer from this reaction lends support to the presumed facility of epimerization.

(43) Sato, M.; Kanuma, N.; Kato, T. *Chem. Pharm. Bull.* **1982**, *30*, 1315.
(44) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738.
(45) Tsumoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 71.
(46) Vedejs, E.; West, F. G. *Chem. Rev. (Washington, D.C.)* **1986**, *86*, 941. Vedejs, E. In *Advances in Cycloaddition Chemistry*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1988; Vol. 1, pp 33−51. Terao, Y.; Imai, N.; Achiwa, K.; Sekiye, M. *Chem. Pharm. Bull.* **1982**, *30*, 3167.
(47) Molander, G. A.; Cameron, K. O. *J. Org. Chem.* **1993**, *58*, 5931.

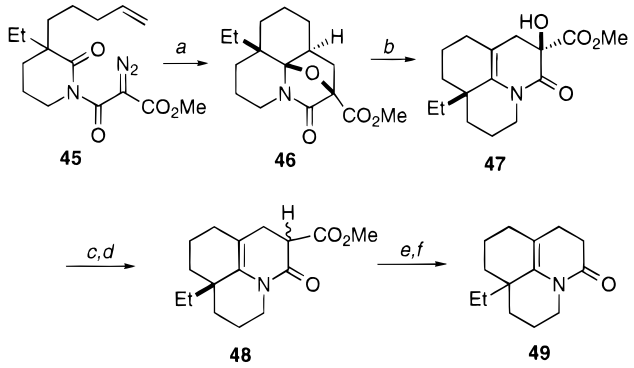
TMSOTf Promoted Cycloaddition as an Approach toward Vallesamidine. Having been encouraged by the preliminary experiments encountered with the alkenyl substituted amides **30** and **32**, we examined the TMSOTf-catalyzed reaction of substrates more closely related to vallesamidine **17** as summarized in Scheme 3. We first examined the [4 + 2]-annulation reaction of 3-ethyl-3-[4-(2-nitrophenyl)-3-butynyl]-2-piperidone (**41**)



with diketene and 0.13 equiv of TMSOTf in benzene at reflux. This reaction afforded piperidone **42** in 77% yield as a 1:1-mixture of atropisomers. Apparently, the steric interaction of the tricyclic pyridone with the nitro and acetyl groups is large enough to allow for atropisomerism. The two diastereomers were easily separated by silica gel chromatography and their structures were established by an X-ray crystallographic study.[37] Interconversion of the two isomeric pyridones occurred upon heating in toluene for 12 h.

Our attention was next directed toward the TMSOTf-catalyzed reaction of the *Z*-alkenyl-substituted amide **43** in order to complete the formal synthesis of vallesamidine **17**. The requisite *cis*-alkene was readily prepared by partial hydrogenation of **41** using the Trost homogeneous palladium protocol.[48] Unfortunately, all attempts to induce the annulation reaction using **43** as the substrate under a variety of conditions failed to produce a cycloadduct. The only product that could be isolated from these attempts was the *N*-acetoacetylated lactam **44** which was obtained as a *cis*/*trans* mixture. One possible explanation to account for why **43** does not undergo the annulation reaction is that the polar nitro group may be coordinated with the TMSOTf, thereby preventing the necessary acid−base chemistry from occurring.

Formal Synthesis of (±)-Vallesamidine Using an Isomünchnone Dipole. The failure of the intramolecular 1,4-dipolar cycloaddition route toward vallesamidine necessitated a new design. Earlier reports from our laboratory have demonstrated that ring-fused polyheterocycles are easily prepared by inter- and intramolecular cycloaddition of isomünchnone dipoles.[49,50] The resultant isomünchnone dipole corresponds to the cyclic equivalent of a carbonyl ylide and readily undergoes 1,3-dipolar cycloaddition with suitable dipolarophiles.[51,52] Our initial goal was to demonstrate that intramolecular dipolar cycloaddition of an isomünchnone across a pendent olefin would proceed in high yield. Furthermore, it was necessary to show that the resulting cycloadduct could be converted to the dihydropyridone ring system. Toward this end, diazoimide **45** was synthesized as a model system. Treatment of **45** with a catalytic amount of rhodium(II) perfluorobutyrate in benzene at 80 °C afforded cycloadduct **46** in 97% yield. Further reaction of **46** with TMSOTf gave the ring-opened lactam **47** in 85% which was obtained as a single diastereomer. The assignment of stereochemistry was based (NMR) on related substrates previously synthesized in these laboratories.[49] Transformation of **47** into **49** was accomplished by a Barton−McCombie deoxygenation reaction[53] followed by base-induced saponification-decarboxylation. Treatment of **47** with NaH and phenyl chlorothionoformate afforded the expected phenyl thiocarbonate derivative. Heating this ester in toluene at 75 °C with slow addition of a solution of AIBN and tributyltin hydride afforded the deoxygenated lactam **48** as a 1:1-mixture of diastereomers in 70% yield. Substrate **48** was hydrolyzed to the corresponding carboxylic acid which was readily decarboxylated upon heating in *p*-xylene at 160 °C to give lactam **49** in 69% yield.



Reaction Conditions: (a) Rh(II) perfluorobutyrate; (b) TMSOTf; (c) C_6H_5OCSCl,NaH; (d) n-Bu_3SnH, AIBN, 75°C; (e) KOH; (f) Δ

Given the success in forming the aza tricyclic system from the intramolecular isomünchnone cycloaddition reaction of **45**, it seemed to us that a related set of transformations with diazoimide **50** would allow for the formal synthesis of vallesamidine via the key Heathcock intermediate **16**. To test this proposition, *N*-malonylacylation of **43** was carried out followed by a standard

(48) Trost, B. M.; Braslau, R. *Tetrahedron Lett.* **1989**, *30*, 4657.

(49) Padwa, A.; Marino, J. P., Jr.; Osterhout, M. H. *J. Org. Chem.* **1995**, *60*, 2704. Padwa, A.; Hertzog, D. L.; Nadler, W. R. *J. Org. Chem.* **1994**, *59*, 7072. Marino, J. P., Jr.; Osterhout, M. H.; Price, A. T.; Semones, M. A.; Padwa, A. *J. Org. Chem.* **1994**, *59*, 5518. Padwa, A.; Hertzog, D. L.; Nadler, W. R.; Osterhout, M. H.; Price, A. T. *J. Org. Chem.* **1994**, *59*, 1418. Hertzog, D. L.; Austin, D. J.; Nadler, W. R.; Padwa, A. *Tetrahedron Lett.* **1992**, *33*, 4731.

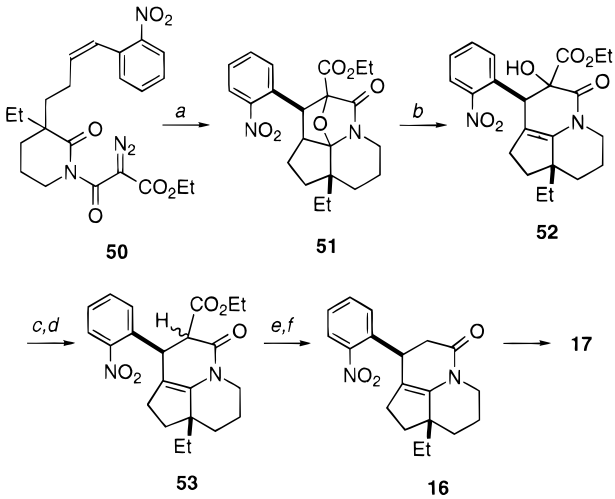
(50) Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis* **1994**, 123.

(51) Hamaguchi, M.; Ibata, T. *Tetrahedron Lett.* **1974**, 4475. Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1975**, 499.

(52) Maier, M. E.; Evertz, K. *Tetrahedron Lett.* **1988**, 1677. Maier, M. E.; Schöffling, B. *Chem. Ber.* **1989**, *122*, 1081.

(53) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

diazo transfer reaction[54] to produce the requisite diazoimide **50**. Gratifyingly, the reaction of **50** with rhodium(II) perfluorobutyrate in benzene at 80 °C gave the desired cycloadduct **51** in 85% yield as a single diastereomer. The TMSOTf-catalyzed opening of **51** proceeded uneventfully to furnish enamide **52** in 95% yield. With the ring-opened lactam in hand, we carried out the Barton−McCombie deoxygenation reaction which afforded **53** as a 1:1-mixture of diastereomers in 88% yield. Utilization of the sequential saponification/decarboxylation protocol afforded enamide **16** in 90% overall yield. The above sequence constitutes a formal synthesis of (±)-vallesamidine **17**, based on the successful conversion of **16** into **17** by Heathcock and Dickman.[40]



Reaction Conditions: (a) Rh(II) perfluorobutyrate; (b) TMSOTf; (c) C_6H_5OCSCl,NaH; (d) n-Bu_3SnH, AIBN, 75°C; (e) KOH; (f) Δ

In summary, a new strategy for the synthesis of (±)-vallesamidine has been developed which is based on an intramolecular dipolar cycloaddition reaction of a mesoionic betaine intermediate. This approach is particularly attractive as the starting α-diazoimide can be prepared efficiently on a large scale, and the cycloaddition and subsequent ring opening reactions are highly stereospecific. We are currently investigating the application of the methodology outlined here to other alkaloidal targets.

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 nitrogen. 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.

General Procedure for Lactam Alkylation. To a 0.2 M solution of the appropriate lactam in dry THF at 0 °C was added 2.1 equiv of *n*-butyllithium (10 M in hexane) dropwise via syringe. The resulting solution was stirred for 2 h at 0 °C and cooled to −78 °C, and 1.2 equiv of the appropriate alkylating reagent was added dropwise via syringe. The reaction mixture was stirred overnight, and the mixture was quenched with a saturated NH_4Cl solution. The organic phase was washed with water and brine, the combined aqueous layers were extracted with ethyl acetate, and the organic phase was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography.

3-(2-Indol-1-ylethyl)-3-methyl-pyrrolidine-2-thione (8). Following the general procedure, the reaction of 5.0 g (39 mmol) of 3-ethyl-piperidin-2-one and 21 g (79 mmol) of *N*-(2-iodoethyl)indole gave 8.0 g (76%) of 3-ethyl-3-(2-indol-1-ylethyl)piperidin-2-one as a white solid; mp 164−165 °C; IR (KBr) 3226, 2958, and 1687 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, 3H, J = 7.3 Hz), 1.95 (m, 6H), 3.27 (m, 4H), 4.19 (m, 2H), 6.48 (d, 1H, J = 3.0 Hz), 7.03 (m, 3H), 7.21 (t, 1H, J = 7.7 Hz), 7.37 (d, 1H, J = 8.8 Hz), and 7.62 (d, 1H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.4, 16.8, 22.4, 33.9, 37.4, 38.9, 41.9, 42.4, 101.3, 109.4, 119.3, 121.0, 121.2, 127.5, 128.7, 135.8 and 182.2. Anal. Calcd for $C_{17}H_{22}N_2O$: C, 77.51; H, 8.21; N, 10.37. Found: C, 77.38; H, 8.15; N, 10.39.

The above lactam (3.0 g, 11 mmol) and Lawesson's reagent (1.0 g, 2.8 mmol) gave 2.9 g (94%) of 3-(2-indol-1-ylethyl)-3-methylpyrrolidine-2-thione (**8**) as a white solid; mp 143−144 °C; IR (neat) 3399, 3177, 2884, 1524 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, 3H, J = 7.3 Hz), 1.95 (m, 6H), 3.27 (m, 4H), 4.19 (m, 2H), 6.48 (d, 1H, J = 3.0 Hz), 7.03 (m, 2H), 7.21 (t, 1H, J = 7.7 Hz), 7.37 (d, 1H, J = 8.8 Hz), 7.62 (d, 1H, J = 8.8 Hz), and 8.57 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.4, 16.8, 22.4, 33.9, 37.4, 38.9, 41.9, 42.4, 101.3, 109.4, 119.3, 121.0, 121.2, 127.5, 128.7, 135.8, and 210.9. Anal. Calcd for $C_{17}H_{22}N_2S$: C, 71.29; H, 7.75; N, 9.79. Found: C, 71.08; H, 7.71; N, 9.69.

Cycloadduct 6. Treatment of a 500 mg (1.7 mmol) sample of thiolactam **8** with 2.9 g (10 mmol) of dibromomalonyl dichloride and 2.56 g (40 mmol) of zinc dust afforded 570 mg (95%) of cycloadduct **6** after removal of the solvent and flash silica gel chromatography of the residue; mp 208−209 °C; IR (KBr) 2966, 2863, 1700, 1675, and 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, 3H, J = 7.3 Hz), 1.68−2.03 (m, 7H), 3.23−3.29 (m, 3H), 3.44−3.47 (m, 1H), 4.01−4.08 (m, 2H), 4.13−4.22 (m, 1H), 4.48 (d, 1H, J = 10.4 Hz), 6.33 (d, 1H, J = 7.1 Hz), 6.61 (t, 1H, J = 7.1 Hz), 6.99 (d, 1H, J = 7.1 Hz), and 7.03 (t, 1H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.4, 16.8, 25.5, 27.8, 32.3, 37.6, 38.5, 39.2, 40.7, 41.1, 62.8, 79.9, 105.7, 117.9, 124.8, 125.0, 129.5, 151.9, 168.0, and 194.9. Anal. Calcd for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90; S, 9.05. Found: C, 67.72; H, 6.21; N, 7.84; S, 9.16.

7a-Ethyl-1(*β*),2(*β*),6,7,7a(*β*),8,9,10-octahydro-1*H*-indolo-[3,2,1-*de*]-3*H*,5*H*-benzo[*ij*]quinolizin-3-one (12). A 200 mg (0.6 mmol) sample of cycloadduct **6** was heated neat at 210 °C for 10 min to give the pentacyclic enamide **12** in 98% yield as a yellow solid; mp 258−260 °C; IR (KBr) 2966, 2863, 1700, and 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.51 (m, 1H), 0.73 (t, 3H, J = 7.2 Hz), 1.23−1.44 (m, 4H), 1.66−1.98 (m, 3H), 2.15 (dd, 1H, J = 14.1 and 5.8 Hz), 2.77 (dt, 1H, J = 14.1 and 5.8 Hz), 3.68−3.78 (m, 2H), 4.16−4.28 (m, 2H), 4.81 (dd, 1H, J = 13.1 and 4.1 Hz), 7.19−7.31 (m, 3H), and 7.48 (d, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.8, 16.9, 19.9, 29.8, 30.7, 31.2, 36.5, 39.8, 42.1, 61.4, 103.4, 109.7, 118.5, 120.1, 121.7, 126.7, 129.3, 138.4, and 169.1. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.48; H, 7.46; N, 9.39.

***epi*-16,17-Dihydroeburnamenine (5).** A sample of **5** was prepared by the addition of a 500 mg sample (1.7 mmol) of enamide **12** to a solution containing 10 equiv of TFA/$NaBH_4$ in refluxing dioxane for 8 h. Removal of the solvent followed by flash silica gel chromatography furnished **5** as a white solid; mp 184−185 °C; IR (KBr) 2966, 2863, 1625, and 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (t, 3H, J = 5.9 Hz), 1.17 (td, 1H, J = 13.6 and 4.7 Hz), 1.57−1.59 (m, 2H), 1.69−2.09 (m, 5H), 2.21 (td, 1H, J = 14.1 and 3.0 Hz), 2.68−2.74 (m, 2H), 2.89−2.99 (m, 1H), 2.94 (s, 1H), 3.03−3.11 (m, 2H), 3.78 (dt, 1H, J = 12.2 and 5.3 Hz), 4.11 (dd, 1H, J = 11.7 Hz), 7.06−7.16 (m, 2H), 7.23−7.27 (m, 1H), and 7.479 (d, 1H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.3, 18.5, 21.4, 21.6, 31.4, 31.9, 35.2, 39.3, 53.4, 56.1, 67.9, 105.2, 109.1, 118.1, 119.1, 120.3, 127.9, 134.0, and 137.3. Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.32; H, 8.61; N, 9.90.

(54) Taber, D. F.; Ruckle, R. E., Jr.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077. Regitz, M.; Hocker, J.; Leidhergener, A. *Organic Syntheses*; John Wiley: New York, 1973; Colloid Vol. 5, pp 179−183.

3-(3-Butenyl)-3-ethyl-2-piperidone (18) was prepared following the general procedure in 63% yield as a colorless oil from 2-piperidone, 4-bromo-1-butene, and iodoethane; IR (neat) 3283, 3202−2866, 1651, and 905 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.71 (t, 3H, J = 7.4 Hz), 1.33 (m, 2H), 1.55 (m, 6H), 1.88 (m, 2H), 3.07 (s, 2H), 4.74 (d, 1H, J = 10.0 Hz), 4.83 (d, 1H, J = 17.4 Hz), 5.61 (m, 1H), and 7.31 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.5, 19.8, 28.6, 30.2, 31.1, 37.4, 42.3, 44.2, 114.1, 138.7, and 177.2. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.80; H, 10.49; N, 7.75.

3-Ethyl-3-(4-pentenyl)-2-piperidone (19) was prepared following the general procedure in 66% yield as a colorless oil from 2-piperidone, 5-bromo-1-pentene and iodoethane; IR (neat) 3283, 3202, 2866, and 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75 (t, 3H, J = 7.4 Hz), 1.23−1.40 (m, 5H), 1.50−1.64 (m, 5H), 1.90 (q, 2H, J = 6.6 Hz), 3.11 (m, 2H), 4.80 (dd, 1H, J = 11.0 and 1.5 Hz), 4.86 (dd, 1H, J = 17.3 and 1.5 Hz), 5.66 (m, 1H), and 6.98 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.4, 19.6, 23.4, 28.8, 30.9, 34.0, 37.7, 42.2, 44.2, 114.1, 138.4, and 177.2. Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.87; H, 10.89; N, 7.15.

3-(3-Butenyl)-1-(1,3-dioxobutyl)-3-ethyl-2-piperidone (20). To a 0.1 M solution of lactam **18** in dry xylene was added 1.2 equiv of 2,2,6-trimethyl-4*H*-1,3-dioxen-4-one dropwise via syringe. The reaction mixture was heated at reflux for 2 h and then cooled to rt. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography to give **20** in 87% yield as a colorless oil; IR (neat) 3075, 2876, 1723, 1688, 1638, and 905 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75 (t, 3H, J = 7.5 Hz), 1.38−1.54 (m, 2H), 1.58−1.77 (m, 6H), 1.81−2.00 (m, 2H), 2.15 (s, 3H), 3.63 (t, 2H, J = 6.2 Hz), 3.84 (d, 2H, J = 1.3 Hz), 4.84 (d, 1H, J = 9.9 Hz), 4.91 (dd, 1H, J = 17.0 and 1.3 Hz), and 5.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.2, 19.5, 28.2, 29.4, 29.8, 31.4, 37.4, 44.8, 47.5, 54.5, 114.6, 137.9, 169.7, 178.3, and 200.9. Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.73; H, 8.65; N, 5.19.

1-(1,3-Dioxobutyl)-3-ethyl-3-(4-pentenyl)-2-piperidone (21) was prepared in 89% yield in a manner similar to that described for **20** starting with lactam **19**; IR (neat) 3075, 2876, 1723, 1681, 1289, 1168, and 905 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75 (t, 3H, J = 7.4 Hz), 1.15−1.49 (m, 5H), 1.53−1.76 (m 5H), 1.94 (q, 2H, J = 6.4 Hz), 2.16 (s, 3H), 3.64 (t, 2H, J = 6.0 Hz), 3.85 (d, 2H, J = 3.6 Hz), 4.86 (d, 1H, J = 10.6 Hz), 4.91 (d, 1H, J = 17.4 Hz), and 5.68 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.3, 19.6, 23.2, 29.6, 29.8, 31.4, 33.8, 37.8, 44.9, 47.7, 54.5, 114.6, 138.1, 169.8, 178.5, and 201.0. Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.77; H, 8.95; N, 5.04.

2-Acetyl-7a-ethyl-5,6,7,7a,8,9-hexahydro-3-oxo-3*H*-cyclopenta[*ij*]quinolizine (22). To a 0.2 M solution of lactam **18** in dry benzene at 25 °C was sequentially added 0.13 equiv of TMSOTf and 1.2 equiv of freshly distilled diketene. The reaction mixture was heated at reflux for 24 h and then cooled to rt. The solution was concentrated under reduced pressure, and the crude product was purified by flash silica gel chromatography to give **22** as a white solid, mp 139−140 °C; IR (KBr) 2960, 2855, 1652, 1640, 1538, and 770 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H, J = 7.4 Hz), 1.34 (m, 1H), 1.44 (q, 2H, J = 7.4 Hz), 1.63−1.78 (m, 1H), 1.95−2.12 (m, 3H), 2.21 (dd, 1H, J = 12.5 and 6.8 Hz), 2.54 (dd, 1H, J = 15.0 and 8.7 Hz), 2.65 (s, 3H), 2.73 (m, 1H), 3.90 (t, 2H, J = 6.8 Hz), and 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.5, 18.8, 26.5, 26.8, 27.7, 30.9, 36.7, 40.7, 46.6, 116.5, 123.1, 140.2, 161.9, 162.1, and 198.1. Calcd for $C_{15}H_{19}NO_2$: C, 73.43; H, 7.81. Found: C, 73.59; H, 7.91 N, 5.39.

2-Acetyl-7a-ethyl-6,7,7a,8,9,10-hexahydro-3-oxo-3*H*,5*H*-benzo[*ij*]quinolizine (23) was obtained as a colorless oil in 26% yield from lactam **19** in a manner similar to **22**; IR (neat) 2960, 2860, 1650, 1640, 1541, and 770 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, 3H, J = 7.2 Hz), 1.30−1.44 (m, 4H), 1.59−1.77 (m, 2H), 1.99−2.10 (m, 3H), 2.17−2.26 (m, 1H), 2.49−2.56 (m, 1H), 2.69 (s, 3H), 2.71 (m, 1H), 3.99 (t, 2H, J = 7.2 Hz), and 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.8, 18.8, 19.1, 26.5, 26.8, 27.7, 31.0, 36.8, 41.0, 46.0, 117.0, 122.4, 141.3, 160.2, 162.4, and 198.5. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.89; H, 8.10; N, 5.49.

General Procedure for the Preparation of Alkynyl-Substituted Lactams. To a 1.0 M solution of the appropriate alkenyl lactam in CCl_4 at 0 °C was added dropwise 1.0 equiv of bromine (2 M solution in CCl_4). The reaction mixture was stirred for 30 min at 0 °C and quenched with a saturated $NaHSO_3$ solution. The organic phase was washed sequentially with water, $NaHCO_3$, and brine. The combined aqueous layers were extracted with CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure to furnish the crude product which was used in the next step without purification.

A flame-dried round-bottomed flask was charged with 5 equiv of $KN(TMS)_2$ (0.5 M in toluene) and an equal volume of anhydrous THF. The resulting solution was cooled to 0 °C, and a solution of the crude dibromide in dry THF (10 mL/1 g of substrate) was added dropwise. The mixture was stirred for 30 min at 0 °C and quenched with a saturated NH_4Cl solution, and the solvent was removed under reduced pressure. The crude product was dissolved in ethyl acetate, washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give the crude product which was purified by flash silica gel chromatography.

A flame-dried round-bottomed flask was charged with 1.0 equiv of the appropriate terminal alkyne, 25 mL of freshly distilled triethylamine, 3 equiv of the appropriate iodobenzene, 100 mg of CuI, 100 mg of PPh_3, and 50 mg of $(Ph_3P)_2PdCl_2$. The reaction mixture was stirred at 25 °C for 2 h and filtered through a pad of Celite, and the solid was washed with distilled triethylamine. The combined organic layers were removed under reduced pressure, and the crude product was purified by flash silica gel chromatography.

3-Ethyl-3-(4-phenyl-3-butynyl)-2-piperidone (24) was prepared following the general procedure in 95% yield as a white solid, mp 94−95 °C, from lactam **26** and iodobenzene; IR (KBr) 3285, 3195, 2873, 2222, and 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H, J = 7.4 Hz), 1.54 (m, 1H), 1.69−1.84 (m, 6H), 2.00 (m, 1H), 2.44 (t, 2H, J = 8.1 Hz), 3.34 (s, 2H), 6.68 (brs, 1H), 7.23 (m, 2H), and 7.33 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.3, 14.8, 19.5, 28.9, 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, 79.96; H, 8.29; N, 5.49. Found: C, 79.91; H, 8.35; N, 5.48.

3-Ethyl-3-(5-phenyl-4-pentynyl)-2-piperidone (25) was prepared following the general procedure in 90% yield as a yellow oil from lactam **27** and iodobenzene; IR (neat) 3283, 3202, 2866, 2229, and 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, 3H, J = 7.4 Hz), 1.42−1.74 (m, 10H), 2.34 (t, 2H, J = 5.5 Hz), 3.20 (m, 2H), 6.83 (brs, 1H), 7.23 (m, 3H), and 7.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.7, 19.9, 20.0, 23.9, 29.2, 31.1, 37.7, 42.5, 44.5, 80.1, 90.1, 124.0, 127.5, 128.1, 131.5, and 177.2. Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.30; H, 8.65; N, 5.18.

3-(3-Butynyl)-3-ethyl-2-piperidone (26) was prepared in 73% yield as a white solid, mp 87−88 °C, from lactam **18**; IR (KBr) 3275, 3217, 2866, 2105, and 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H, J = 7.3 Hz), 1.52 (sex, 1H, J = 7.3 Hz), 1.67−1.80 (m, 6H), 1.92 (m, 2H), 2.23 (m, 2H), 3.26, (m, 2H), and 6.12 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.4, 14.0, 19.6, 29.1, 30.5, 36.9, 42.5, 44.4, 68.1, 84.7, and 176.4. Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.71; H, 9.62; N, 7.75.

3-Ethyl-3-(4-pentynyl)-2-piperidone (27) was prepared in 56% yield as a yellow oil from lactam **19**; IR (neat) 3290, 3211, 2866, 2112, and 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (t, 3H, J = 7.4 Hz), 1.15−2.07 (m, 12H), 3.13 (m, 2H), 4.53 (m, 1H), and 6.90 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.3, 28.9, 31.1, 36.3, 41.3, 43.4, 67.2, 85.3, and 178.9. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.51; H, 9.92; N, 7.23.

2-Acetyl-7a-ethyl-5,6,7,7a,8,9-hexahydro-1-phenyl-3*H*-cyclopenta[*ij*]quinolizin-3-one (28) was obtained as a white solid from lactam **24** in 50% yield in a manner similar to that used for the conversion of **20** to **22**; mp 123−124 °C; IR (KBr)

3054, 2855, 1652, and 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H, J = 7.4 Hz), 1.20 (t, 1H, J = 7.0 Hz), 1.35 (ddd, 1H, J = 12.0, 5.7 and 1.4 Hz), 1.51 (q, 2H, J = 7.4 Hz), 1.62 (q, 1H, J = 10.0 Hz), 1.99 (s, 3H), 2.17 (dd, 1H, J = 12.3 and 6.5 Hz), 2.46 (dd, 1H, J = 15.0 and 8.5 Hz), 2.86 (m, 1H), 3.90 (t, 2H, J = 7.0 Hz), 4.06 (q, 1H, J = 7.0 Hz), 6.43 (s, 1H), and 7.23−7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.7, 14.0, 18.7, 26.8, 27.2, 28.4, 36.9, 40.3, 45.9, 60.2, 114.5, 115.1, 127.6, 128.3, 128.4, 138.0, 150.3, 154.6, and 163.6. Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.35. Found: C, 78.39; H, 7.24; N, 4.42.

2-Acetyl-7a-ethyl-6,7,7a,8,9,10-hexahydro-3-oxo-1-phenyl-3*H*,5*H*-benzo[*ij*]quinolizine (29) was prepared as a colorless oil in 65% yield from lactam **25** in a manner similar to that used for the conversion of **20** to **22**; IR (neat) 3055, 2872, 1703, 1625, 1569, and 773 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.81 (t, 3H, J = 7.5 Hz), 1.28−1.44 (m, 3H), 1.49−1.70 (m, 5H), 1.80−1.94 (m, 4H), 2.15 (s, 3H), 3.87 (m, 1H), 4.31 (pent, 1H, J = 7.5 Hz), 7.06 (m, 2H), and 7.29 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.1, 17.1, 17.8, 26.0, 27.9, 28.6, 31.3, 32.4, 36.8, 41.2, 111.5, 127.6, 127.7, 128.0, 128.8, 136.3, 149.8, 150.7, 159.6, and 202.4. Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.81; H, 7.51; N, 4.22.

General Procedure for the Nickel Boride Catalyzed Hydrogenation. The alkynyl-substituted lactams were reduced according the procedure of Brown and Ahuja.[55] To a homogeneous solution of 0.18 equiv of $Ni(OAc)_2 \cdot 4H_20$ in absolute ethanol (1 mL/1 mmol of alkyne) at 25 °C was added 0.18 equiv of $NaBH_4$ (1 M solution in absolute ethanol). The flask was alternatively evacuated (aspirator) and filled with hydrogen, and the catalyst was stirred over 1 atm of hydrogen. Ethylenediamine (0.37 equiv) was added dropwise via syringe followed by a solution of the appropriate alkyne in absolute ethanol (10 mL/1 g alkyne). The mixture was stirred at 25 °C until hydrogenation to the *cis*-alkene was complete. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2. This solution was filtered through a plug of florisil, the solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography.

3-Ethyl-3-[(*Z*)-4-phenyl-3-butenyl]-2-piperidone (32) was obtained as a colorless oil in 96% yield from lactam **24** in a manner similar to that used for the conversion of **20** to **22**; IR (neat) 3283, 3195, 2866, and 1651 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 (brs, 2H), 5.59 (dt, 1H, J = 11.4 and 7.4 Hz), 6.35 (d, 1H, J = 11.4 Hz), 6.95 (brs, 1H), and 7.13−7.31 (m, 5H), ^{13}C NMR ($CDCl_3$, 75 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. Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.13; H, 9.05; N, 5.39.

2-Acetyl-7a-ethyl-1(*β*),2(*β*),5,6,7,7a(*β*),8,9-octahydro-1-phenyl-3*H*-cyclopenta[*ij*]quinolizin-3-one (33) was obtained as a white solid from lactam **32** in 61% yield in a manner similar to that used for the conversion of **20** to **22**, mp 97−98 °C; IR (KBr) 3005, 2862, 1716, 1688, 1645, and 706 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (t, 3H, J = 7.4 Hz), 1.17 (m, 1H), 1.38−1.56 (m, 3H), 1.60−1.79 (m, 3H), 1.86 (dd, 1H, J = 7.0 and 3.5 Hz), 1.90 (dd, 1H, J = 7.0 and 3.5 Hz), 2.04 (m, 1H), 2.04 (s, 3H), 2.95 (m, 1H), 3.82 (d, 1H, J = 13.5 Hz), 3.88 (dt, 1H, J = 13.5 and 3.9 Hz); 4.09 (d, 1H, J = 13.5 Hz), and 7.05−7.23 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.7, 19.1, 27.2, 28.3, 31.7, 32.0, 35.5, 41.0, 41.7, 45.4, 61.3, 116.0, 126.7, 127.9, 128.3, 140.0, 140.2, 167.7, and 204.3. Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 78.11; H, 7.84; N, 4.29.

7a-Ethyl-2-(1-hydroxyethylidene)-1(*β*),5,6,7,7a(*β*),8,9-heptahydro-1-phenyl-3*H*-cyclopenta[*ij*]quinolizin-3-one (34) was also obtained (31% yield) as a white solid in a manner similar to **33** and was purified by silica gel column chromatography, mp 138−139 °C; IR (KBr) 3025, 2855, 1702, 1614, 1588, 969, and 706 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.66 (t, 3H, J = 7.4 Hz), 1.07−1.24 (m, 3H), 1.41 (m, 2H), 1.68 (s, 3H), 1.71−1.97 (m, 6H), 3.28 (m, 1H), 3.78 (dt, 1H, J = 15.0 and 3.0 Hz), 4.23 (s, 1H), and 7.06−7.27 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.4, 19.4, 19.9, 25.9, 28.7, 30.0, 34.8, 39.9, 43.6, 45.4, 99.3, 113.7, 125.9, 127.1, 128.2, 136.7, 145.3, 170.9, and 176.4. Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 78.19; H, 7.80; N, 4.25.

3-Ethyl-3-[(*E*)-4-phenyl-3-butenyl]-2-piperidone (30) was prepared by a modification of the procedure of Schwarz.[56] A mixture of 1.0 g (3.9 mmol) of lactam **32**, 218 mg (2.0 mmol) of thiophenol, and 840 mg (5.1 mmol) of AIBN in 50 mL of benzene was heated for 8 h in a sealed tube at 80 °C. Removal of the solvent followed by chromatography on silica gel gave lactam **30** in 92% as a colorless oil; IR (neat) 3281, 3205, 2899, and 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, 3H, J = 7.5 Hz), 1.51−1.71 (m, 8H), 1.89−2.25 (m, 2H), 3.25 (s, 2H), 6.13−6.25 (m, 1H,), 6.34 (s, 1H), 6.38−6.48 (s, 1H), and 7.13−7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.6, 19.8, 28.0, 29.1, 31.1, 37.7, 42.5, 44.6, 125.8, 126.7, 128.4, 129.7, 130.7, 137.7, and 176.9. Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.10; H, 9.10; N, 5.41.

2-Acetyl-7a-ethyl-1(*β*),2(*β*),5,6,7,7a(α),8,9-octahydro-1-phenyl-3*H*-cyclopenta[*ij*]quinolizin-3-one (31) was obtained as a colorless oil from lactam **30** in 63% yield in a manner similar to that used for the conversion of **20** to **22**; IR (neat) 3010, 2877, 1712, 1680, 1645, and 706 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, 3H, J = 7.4 Hz), 1.21−1.60 (m, 4H), 1.69−1.80 (m, 4H), 1.95−2.14 (m, 3H), 2.21−2.40 (m, 1H), 2.25 (s, 1H,) 2.88−3.01 (m, 1H), 3.51 (s, 1H), 3.96 (s, 1H), 4.01−4.04 (m, 1H), and 7.21−7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.7, 19.5, 26.2, 27.7, 28.7, 32.5, 36.1, 39.6, 41.9, 45.4, 65.7, 117.7, 127.0, 127.1, 128.9, 140.4, 140.6, 166.7, and 201.5. Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 78.03; H, 7.74; N, 4.29.

The 2,4-DNPH derivative of **31** was prepared in the following fashion. To a solution of 30 mg of 2,4-dinitrophenylhydrazine in 0.50 mL of methanol and 50 μL of H_2SO_4 was added 20 mg of **31** in 200 μL of methanol. After stirring for 10 min, a few drops of concentrated H_2SO_4 was added to the mixture and an orange precipitate appeared. Filtration gave the 2,4-DNPH of **31** in 63% yield as an orange solid, mp 187−188 °C; IR (KBr) 3317, 3100, 2900, 1663, 1615, 1503, and 1334 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.65 (t, 3H, J = 7.4 Hz), 1.21−1.36 (m, 3H), 1.54−1.62 (m, 1H), 1.77−1.79 (m, 2H), 1.96−2.05 (m, 3H), 2.18 (s, 3H), 2.26−2.38 (m, 1H), 3.02−3.09 (m, 1H), 3.57 (s, 1H), 3.95 (s, 1H), 4.00−4.05 (m, 1H), 7.01−7.32 (m, 5H), 7.91 (d, 1H, J = 10.0 Hz), 8.31 (dd, 1H, J = 10.0 and 2.0 Hz), 9.12 (d, 1H, J = 2.0 Hz), and 11.09 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.9, 15.0, 19.8, 26.7, 29.3, 32.8, 36.5, 41.2, 42.1, 45.7, 60.0, 116.3, 116.6, 123.7, 123.7, 127.3, 127.4, 129.3, 130.2, 138.4, 140.7, 140.9, 145.2, 153.0, and 167.5; HRMS Calcd for $C_{27}H_{29}N_5O_5$: 503.2168. Found: 503.2166.

3-Ethyl-3-[4-(2′-nitrophenyl)-3-butynyl]-2-piperidone (41) was prepared in 73% yield as a yellow solid from lactam **26** and 2-nitro-1-bromobenzene, mp 93−94 °C, IR (KBr) 3553, 3289, 2863, 2211, 1646, and 1522 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H, J = 7.3 Hz), 1.53 (m, 1H), 1.68−1.88 (m, 6H), 2.02 (m, 1H), 2.51 (t, 2H, J = 7.0 Hz), 3.26 (m, 2H), 6.45 (brs, 1H), 7.25−7.54 (m, 3H), and 7.92 (d, 1H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.4, 15.4, 19.6, 29.1, 30.3, 30.6, 36.5, 42.4, 44.4, 75.8, 99.2, 119.1, 124.2, 127.9, 132.6, 134.7, and 176.5. Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.81; H, 6.77; N, 9.27.

2-Acetyl-7a-ethyl-5,6,7,7a,8,9-hexahydro-1-(2-nitrophenyl)-3*H*-cyclopenta[*ij*]quinolizin-3-one (42) was obtained from lactam **41** in 77% yield in a manner similar to that used for the conversion of **20** to **22** as 1:1-mixture of diastereomers which could be separated by silica gel chromatography. One of the diastereomers showed the following properties: mp 156−157 °C; IR (neat) 2963, 2864, 1639, 1526, and 1343 cm^{-1};

(55) Brown, C. A.; Ahuja, V. K. *J. Chem. Soc., Chem. Commun.* **1973**, 553.

(56) Schwarz, M.; Graminski, G. F.; Waters, R. M. *J. Org. Chem.* **1986**, *51*, 260.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, J = 7.3 Hz), 1.46−1.60 (m, 3H), 1.72−1.75 (m, 1H), 2.03−2.17 (m, 5H), 2.34−2.43 (m, 1H), 2.50 (s, 3H), 3.98 (t, 2H, J = 7.3 Hz), 7.11 (dd, 1H, J = 7.5 and 1.1 Hz), 7.50 (dt, 1H, J = 7.5 and 1.1 Hz), 7.61 (dt, 1H, J = 7.5 and 1.1 Hz), and 8.16 (dd, 1H, J = 7.5 and 1.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.6, 18.9, 26.1, 27.4, 28.4, 31.3, 36.2, 40.6, 46.9, 116.2, 123.7, 124.5, 128.6, 129.4, 133.3, 133.9, 146.9, 149.1, 157.6, 161.7, and 200.2. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.82; H, 6.06; N, 7.65. Found: C, 68.77; H, 6.09; N, 7.68.

The second diastereomer exhibited the following spectral characteristics: mp 142−143 °C; IR (neat) 2962, 2869, 1642, 1520, and 1341 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, 3H, J = 7.6 Hz), 1.40−1.67 (m, 3H), 1.69−1.71 (m, 1H), 2.01−2.20 (m, 5H), 2.32−2.43 (m, 1H), 2.48 (s, 3H), 3.96 (t, 2H, J = 7.2 Hz), 7.19 (dd, 1H, J = 8.4 and 1.2 Hz), 7.50 (dt, 1H, J = 8.4 and 1.2 Hz), 7.62 (dt, 1H, J = 8.4 and 1.2 Hz), and 8.16 (dd, 1H, J = 8.4 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.6, 19.0, 26.3, 27.5, 28.4, 31.4, 36.3, 40.7, 46.9, 116.3, 123.7, 124.6, 128.7, 129.6, 133.3, 134.1, 147.1, 149.9, 157.8, 161.9, and 200.6. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.82; H, 6.06; N, 7.65. Found: C, 68.87; H, 6.04; N, 7.64.

3-Ethyl-3-[(*Z*)-4-(2′-nitrophenyl)-3-butynyl]-2-piperidone (43) was prepared by a modification of the procedure of Trost.[48] A mixture of 870 mg (2.9 mmol) of alkyne **41** in 10 mL of anhydrous benzene was added to a 50 mL solution of benzene containing 77 mg (0.075 mmol) of the Trost palladium catalyst,[45] 87 mg of tri-*o*-tolylphosphine, 175 mg (2.9 mmol) of acetic acid, and 388 mg (2.9 mmol) of tetramethyldihydrodisiloxane. The reaction was stirred for 40 min at rt. Removal of the solvent followed by chromatography on silica gel gave lactam **43** in 88% as a yellow solid, mp 85−86 °C; IR (KBr) 3553, 3289, 2863, 2211, 1646, and 1522 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H, J = 7.3 Hz), 1.41−1.81 (m, 9H), 2.02 (m, 1H), 3.26 (m, 2H), 5.61 (dt, 1H, J = 11.5 and 7.3 Hz), 6.45 (brs, 1H), 6.61(d, 1H, J = 11.5 Hz), 7.25−7.54 (m, 3H), and 7.92 (d, 1H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.5, 19.6, 23.6, 28.9, 30.9, 37.7, 42.4, 44.4, 99.2, 124.3, 125.2, 127.6, 131.8, 132.7, 134.4, 148.2, and 176.5. Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.51; H, 7.30; N, 9.27.

1-(1,3-Dioxobutyl)-3-ethyl-3-[4-(2′-nitrophenyl)-3-butenyl]-2-piperidone (44) was obtained as a 1:1 inseparable *Z*/*E*-mixture in 88% yield; IR (neat) 3085, 2976, 1723, 1688, 1638, and 905 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87−0.93 (m, 6H), 1.31−1.91 (m, 18H), 2.10−2.18 (m, 2H), 2.14 (s, 3H), 2.19 (s, 3H), 3.26−3.36 (m, 4H), 3.84−3.99 (m, 4H), 5.61 (dt, 1H, J = 11.5 and 7.4 Hz), 6.13−6.25 (m, 1H), 6.34 (s, 1H), 6.61 (d, 1H, J = 11.5 Hz), 7.25−7.54 (m, 6H), and 7.92−7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.2, 8.4, 19.1, 19.5, 22.9, 23.6, 28.9, 29.2, 30.9, 31.2, 36.7, 37.1, 42.4, 42.9, 44.4, 44.6, 47.2, 48.5, 54.5, 55.1, 99.2, 100.0, 123.9, 124.3, 125.2, 126.3, 127.6, 127.8, 131.8, 132.4, 132.7, 132.9, 133.6, 134.4, 148.2, 149.4, 169.7, 170.1, 177.9, 178.3, 200.6, and 200.9. Anal. Calcd for $C_{21}H_{26}N_2O_5$: C, 65.27; H, 6.78; N, 7.25. Found: C, 65.31; H, 6.82; N, 7.27.

General Procedure for the Synthesis of Diazo Imides. To a 0.1 M solution of the appropriate lactam in anhydrous benzene was added 3.0 equiv of the appropriate malonyl chloride. The reaction mixture was heated at reflux for 1 h then cooled to rt. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography. A variation of the procedure described by Taber and co-workers[54] was used to prepare the diazo imide system. To a solution containing 2 mmol of azide in 5 mL of acetonitrile was added 4.0 mmol of NEt_3 under argon at rt. After the solution was stirred for 4 h, the solvent was removed under reduced pressure and was purified by flash silica gel chromatography.

3-Ethyl-1-(2-(diazomethyl)-1-oxo-3-propanoyl)-3-(4-pentenyl)-2-piperidone (45) was prepared following the general procedure in 75% yield as a yellow oil from methyl malonyl chloride, lactam **27**, and mesyl azide; IR (neat) 2134, 1716, 1655, 1322, and 905 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75 (t, 3H, J = 7.4 Hz), 1.23−1.40 (m, 5H), 1.50−1.64 (m, 5H), 1.90 (q, 2H, J = 6.6 Hz), 3.60−3.69 (m, 2H), 3.81 (s, 3H), 4.80 (dd, 1H, J = 11.0 and 1.5 Hz), 4.86 (dd, 1H, J = 17.3 and 1.5 Hz), and 5.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.4, 19.9, 23.4, 29.7, 31.6, 34.1, 37.1, 45.3, 46.6, 48.1, 98.1, 115.8, 137.2, 165.9, 168.3, and 176.8.

1(*β*),2(*β*),6,7,7a(*β*),8,9,10,10a(α),10b(*β*)-Decahydro-2,10b-epoxy-7a-ethyl-3*H*,5*H*-benzo[*ij*]quinolizin-2-carboxylic Acid Methyl Ester (46). To 1.5 g (5.6 mmol) of diazoimide **45** in 100 mL of anhydrous benzene at 25 °C was added 2 mg of rhodium(II) perfluorobutyrate. The reaction mixture was heated at reflux for 25 min and then cooled to rt. The solution was concentrated under reduced pressure, and the crude product was purified by flash silica gel chromatography to give 1.61 g (97%) of **46** as a white solid, mp 147−148 °C; IR (KBr) 3075, 2876, 1723, 1688, and 905 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.66 (t, 3H, J = 7.5 Hz), 1.19−2.03 (m, 2H),1.41−1.99 (m, 11H), 2.05−2.10 (m, 2H), 2.55−2.65 (m, 1H), 3.80 (m, 1H), and 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.4, 18.5, 19.8, 25.6, 26.7, 32.1, 32.7, 35.7, 37.2, 38.2, 38.9, 52.8, 85.2, 97.6, 166.5, and 170.6. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.45; H, 7.89; N, 4.71.

1(*β*),2(*β*),6,7,7a(*β*),8,9,10,10a(α),10b(*β*)-Decahydro-7a-ethyl-2-hydroxy-3*H*,5*H*-benzo[*ij*]quinolizin-2-carboxylic Acid Methyl Ester (47). To a solution of 3.0 g (10 mmol) of cycloadduct **46** in 100 mL of CH_2Cl_2 at 0 °C was added 11.1 g (50 mmol) of TMSOTf. This solution was allowed to warm to rt and was stirred at this temperature for 3 h. The reaction was quenched with aqueous NH_4Cl, and the solution was extracted with CH_2Cl_2. The extracts were washed with brine, dried over $MgSO_4$, and filtered. The solution was concentrated under reduced pressure, and the crude residue was purified by flash silica gel chromatography to give 2.55 g (85%) of **47** as a white solid, mp 126−127 °C; IR (KBr) 3420, 3075, 2876, 1723, 1688, and 905 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, 3H, J = 7.5 Hz), 1.19−2.03 (m, 2H), 1.42−1.90 (m, 8H), 2.05−2.10 (m, 3H), 2.85−2.90 (m, 1H), 3.40−3.50 (m, 1H), 3.90 (s, 3H), 3.92−3.99 (m, 1H), and 4.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.6, 17.4, 18.7, 27.2, 29.2, 29.9, 32.9, 35.0, 35.7, 40.1, 53.1, 74.5, 110.4, 136.6, 167.0, and 172.2. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.41; H, 7.90; N, 4.74.

7a-Ethyl-1,2,6,7,7a,8,9,10-octahydro-5*H*-pyrido[3,2,1-*ij*]quinolin-3-one (49). To a solution of 200 mg (0.68 mmol) of enamide **47** in 5 mL of THF was added 75 mg (2.0 mmol) of NaH (60% dispersion in mineral oil), and the solution was stirred a rt for 1 h. To this mixture was added 130 mg (0.75 mmol) of phenyl chlorothionocarbonate dropwise, and the mixture was stirred for 3 h at rt. The reaction mixture was quenched with an aqueous NH_4Cl solution and was extracted with ether. The extracts were washed with brine, dried over Na_2SO_4, and filtered. The solution was concentrated under reduced pressure, and the crude residue was purified by flash silica gel chromatography to give 218 mg (75%) of 1(*β*),2(*β*),6,7,7a(*β*),8,9,10,10a(α),10b(*β*)-decahydro-7a-ethyl-2-((phenoxythiocarbonyl)oxy)-3*H*,5*H*-benzo[*ij*]quinolizin-2-carboxylic acid methyl ester as a yellow oil; IR (neat) 1743, 1688, 1646, and 1488 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (t, 3H, J = 7.5 Hz), 1.20−2.03 (m, 2H),1.45−1.94 (m, 8H), 2.05−2.10 (m, 3H), 2.85−2.90 (m, 1H), 3.40−3.50 (m, 1H), 3.93 (s, 3H), 3.94−3.99 (m, 1H), and 7.09−7.87 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.6, 16.4, 19.7, 28.2, 29.2, 29.9, 32.9, 35.0, 41.1, 54.1, 76.5, 111.4, 121.7, 126.2, 129.6, 135.4, 136.9, 155.3, 167.9, 172.2, and 190.6.

To a solution of 150 mg (0.35 mmol) of the above phenyl thiocarbonate in 10 mL of toluene was added 58 mg (0.35 mmol) of AIBN and 510 mg (1.75 mmol) of tributyltin hydride. The reaction was heated at 75 °C for 8 h. The reaction was cooled to rt, the mixture was concentrated under reduced pressure, and the crude residue was purified by flash silica gel chromatography to give 67 mg (70%) of 1(*β*),2(*β*),6,7,7a(*β*),8,9,10,10a(α),10b(*β*)-decahydro-7a-ethyl-3-oxo-3*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic acid methyl ester (**48**) as a 1:1-inseparable mixture of diastereomers which was used in the next step without purification; IR (neat) 2907, 1723, and 1688 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, 3H, J = 7.5

Hz), 1.19−2.03 (m, 2H), 1.42−1.90 (m, 8H), 2.05−2.10 (m, 3H), 2.85−2.90 (m, 1H), 3.40−3.50 (m, 1H), 3.80 (s, 3H), 3.92−3.99 (m, 1H), and 4.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.8, 8.0, 17.5, 17.9, 18.9, 19.1, 27.5, 27.8, 29.9, 30.1, 31.8, 32.9, 34.1, 34.8, 35.0, 35.7, 39.5, 40.1, 53.1, 53.7, 110.4, 111.1, 136.6, 138.2, 166.9, 167.0, 170.2, and 172.2.

To a solution of 100 mg (0.36 mmol) of the above mixture in 2 mL of THF was added 2.1 mL of a 1 M KOH solution. The mixture was heated at 65 °C for 6 h and then cooled to rt and washed with EtOAc. The aqueous layer was acidified with 3 M H_2SO_4 to pH 2 and was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and filtered. The solution was concentrated under reduced pressure, and the crude acid was used in the next step without purification. A solution containing 80 mg (0.34 mmol) of the above acid in 2 mL of xylene was heated at reflux for 3 h and then cooled to rt. The mixture was concentrated under reduced pressure, and the crude residue was purified by flash silica gel chromatography to give 55 mg (69%) of **49** as a clear oil; IR (neat) 3100, 3010, 1688, and 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81 (t, 3H, J = 7.5 Hz), 1.09−2.03 (m, 2H), 1.39−1.80 (m, 9H), 1.91−2.40 (m, 3H), and 3.21−3.90 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.5, 17.5, 18.8, 27.4, 29.4, 20.4, 33.0, 35.0, 35.1, 35.7, 40.3, 111.0, 135.9, and 171.4. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.66; N, 6.39. Found: C, 76.60; H, 9.63; N, 6.41.

3-Ethyl-3-[(2-(diazethyl)-1-oxo-3-propanoyl)(*Z*)-4-(2′-nitrophenyl)-3-butynyl]-2-piperidone (50) was prepared in 86% yield as a yellow oil from ethyl malonyl chloride, lactam **43**, and 4-acetamidobenzenesulfonyl azide; IR (neat) 2211, 1716, 1655, and 1522 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, 3H, J = 7.3 Hz), 1.10 (t, 3H, J = 7.3 Hz), 1.40−1.79 (m, 8H), 2.02 (m, 2H), 3.51−3.81 (m, 2H), 4.01 (q, 2H, J = 7.3 Hz), 5.61 (dt, 1H, J = 11.4 and 7.3 Hz), 6.61 (d, 1H, J = 11.4 Hz), 7.25−7.54 (m, 3H), and 7.92 (d, 1H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.2, 14.3, 19.7, 23.5, 29.5, 31.4, 37.8, 45.2, 46.8, 47.9, 109.2, 124.4, 125.7, 127.9, 131.6, 132.4, 132.7, 133.4, 148.2, 164.1, 165.3, and 177.2.

***cis*-1(*β*),2(*β*),6,7,7a(*β*),8,9,10,10a(α),10b(*β*)-decahydro-2,10b-epoxy-7a-ethyl-1-(2-nitrophenyl)-3-oxocyclopenta[*ij*]quinolizine-2-carboxylic Acid Ethyl Ester (51).** To a 262 mg (0.59 mmol) sample of diazoimide **50** in 15 mL of anhydrous benzene at 25 °C was added 2 mg of rhodium(II) perfluorobutyrate. The reaction mixture was heated at reflux for 1 h and then cooled to rt. The solution was concentrated under reduced pressure and the crude product was purified by flash silica gel chromatography to give 210 mg (85%) of **51** as a white solid, mp 219−220 °C; IR (KBr) 3289, 2863, 2211, 1646, and 1522 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (m, 6H), 1.01−1.21 (m, 1H), 1.22−1.30 (m, 2H), 1.51−1.99 (m, 7H), 2.89−3.00 (m, 1H), 3.31 (dd, 1H, J = 9.3 and 9.2 Hz), 3.70−3.81 (m, 1H), 3.91 (d, 1H, J = 8.7 Hz), 4.01−4.21 (m, 2H), 7.31 (t, 1H, J = 8.3 Hz), and 7.50 (t, 1H, J = 8.3 Hz), 7.59 (d, 1H, J = 8.3 Hz), and 7.81 (d, 1H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.4, 13.6, 18.9, 22.0, 23.4, 29.8, 37.1, 39.7, 40.4, 46.1, 51.5, 61.7, 91.7, 104.8, 124.5, 127.7, 129.2, 132.4, 132.7, 150.3, 164.9, and 170.3. Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.74; H, 6.33; N, 6.76. Found: C, 63.77; H, 6.29; N, 6.78.

***cis*-7a-Ethyl-2-hydroxy-2,3,5,6,7,7a,8,9-octahydro-1-(2-nitrophenyl)-3-oxocyclopenta[*ij*]quinolizine-2-carboxylic Acid Ethyl Ester (52).** To a solution containing 200 mg (0.48 mmol) of cycloadduct **51** in 10 mL of CH_2Cl_2 at 0 °C was added 533 mg (2.4 mmol) of TMSOTf. This solution was allowed to warm to rt and was stirred at 25 °C for 1 h. The reaction was quenched with aqueous NH_4Cl, and the solution was extracted with CH_2Cl_2. The extracts were washed with brine, dried over $MgSO_4$, and filtered. The solution was concentrated under reduced pressure, and the crude residue was purified by flash silica gel chromatography to give 188 mg (95%) of **52** as a white solid, mp 199−200 °C; IR (KBr) 3420, 2211, 1646, and 1522 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, J = 7.5 Hz), 1.21−1.28 (t, 3H, J = 7.5 Hz), 1.29−1.39 (m, 1H), 1.61−1.70 (m, 3H), 1.79−2.14 (m, 6H), 2.22−2.32 (m, 1H), 3.15−3.25 (m, 1H), 3.83−3.91 (m, 1H), 3.99−4.09 (m, 1H), 4.21−4.31 (m, 1H), 5.10 (s, 1H), 7.31 (dt, 1H, J = 7.8 and 1.3 Hz), and 7.50 (dt, 1H, J = 7.8 and 1.3 Hz), and 7.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.8, 13.6, 19.3, 27.5, 28.8, 31.7, 36.2, 39.9, 40.8, 45.8, 63.5, 78.1, 112.8, 123.9, 128.3, 128.4, 131.4, 133.3, 140.7, 151.0, 166.4, and 171.3. Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.74; H, 6.33; N, 6.76. Found: C, 63.79; H, 6.26; N, 6.80.

***cis*-7a-Ethyl-2,3,5,6,7,7a,8,9-octahydro-1-(2-nitrophenyl)-3-oxocyclopenta[*ij*]quinolizine-2-carboxylic Acid Ethyl Ester (53).** To a solution containing 100 mg (0.24 mmol) of enamide **52** in 5 mL of THF was added 12 mg (0.29 mmol) of NaH (60% dispersion in mineral oil), and the solution was stirred at rt for 1 h. To this mixture was added dropwise 46 mg (0.28 mmol) of phenyl chlorothionocarbonate, the reaction mixture was stirred for 30 min at rt. The reaction was quenched with aqueous NH_4Cl, and the solution was extracted with ether. The extracts were washed with brine, dried over Na_2SO_4, and filtered. The solution was concentrated under reduced pressure, and the crude residue was purified by flash silica gel chromatography to give 110 mg (83%) of *cis*-7a-ethyl-2,3,5,6,7,7a,8,9-octahydro-2-((phenoxythiocarbonyl)oxy)-1-(2-nitrophenyl)-3-oxocyclopenta[*ij*]quinolizine-2-carboxylic acid ethyl ester as a yellow solid, mp 198−200 °C; IR (KBr) 1743, 1688, 1646, and 1488 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, 3H, J = 7.5 Hz), 1.21−1.28 (t, 3H, J = 7.5 Hz), 1.22−1.39 (m, 1H), 1.59−1.70 (m, 3H), 1.79−2.14 (m, 6H), 2.22−2.30 (m, 1H), 3.15−3.25 (m, 1H), 3.83−3.91 (m, 1H), 3.99−4.09 (m, 1H), 4.21−4.31 (m, 1H), 7.01 (m, 3H), 7.21−7.44 (m, 3H), 7.57 (dt, 1H, J = 8.1 and 1.3 Hz), and 7.75 (d, 1H, J = 8.1 Hz), 7.80 (d, 1H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.8, 13.7, 19.5, 27.0, 29.2, 32.3, 35.9, 42.0, 42.1, 45.8, 63.1, 86.5, 114.0, 121.5, 124.3, 126.8, 128.3, 128.8, 129.5, 132.4, 133.5, 141.6, 151.2, 153.2, 162.9, 164.9, and 190.4.

To a solution containing 69 mg (0.12 mmol) of the above phenylthiocarbonate in 2 mL of toluene was added 20 mg (0.12 mmol) of AIBN and 173 mg (0.59 mmol) of tributyltin hydride. The reaction was heated at 75 °C for 12 h and cooled to rt, and the mixture was concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 52 mg (88%) of **53** as an inseparable 1:1-mixture of diastereomers which was used in the next step without any purification; IR (neat) 1744, 1686, 1645, and 1489 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, J = 7.5 Hz), 1.21−1.28 (t, 3H, J = 7.5 Hz), 1.29−1.39 (m, 1H), 1.61−1.70 (m, 3H), 1.79−2.14 (m, 6H), 2.22−2.32 (m, 1H), 3.15−3.25 (m, 1H), 3.83−3.91 (m, 1H), 3.99−4.09 (m, 1H), 4.21−4.31 (m, 2H), 7.31 (dt, 1H, J = 7.8 and 1.3 Hz), 7.50 (dt, 1H, J = 7.8 and 1.3 Hz), and 7.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.7, 8.9, 12.6, 12.9, 19.3, 19.5, 27.5, 27.8, 28.8, 28.9, 31.7, 32.3, 36.2, 36.5, 39.9, 40.0, 40.8, 41.3, 45.8, 46.9, 63.5, 63.2, 112.8, 113.0, 123.9, 124.4, 128.3, 128.4, 128.9, 129.9, 131.4, 132.8, 133.3, 133.6, 140.7, 141.1, 151.0, 152.2, 166.4, 167.1, 171.2, and 171.3.

***cis*-7a-Ethyl-5,6,7,7a,8,9-hexahydro-1-(2-nitrophenyl)cyclopenta-[*ij*]quinolizin-3(2*H*)-one (16).** To a solution containing 31 mg (0.077 mmol) of **53** in 2 mL of THF was added 0.42 mL of 1 M KOH. The reaction mixture was heated at 65 °C for 4 h, cooled, and washed with EtOAc. The aqueous layer was acidified with 3 M H_2SO_4 to pH 2 and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and filtered. The solution was concentrated under reduced pressure, and the crude acid was used in the next step without purification. A solution containing 25 mg (0.067 mmol) of the above acid in 2 mL of xylene was heated at reflux for 3 h and then cooled to rt. The mixture was concentrated under reduced pressure, and the resulting residue was purified by flash silica gel chromatography to give 21 mg (90%) of **16** as a white solid, mp 135−136 °C; IR (neat) 3189, 2863, 1669, and 1522 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, J = 7.4 Hz), 1.21−1.28 (m, 1H), 1.46−1.64 (m, 3H), 1.71−1.90 (m, 5H), 2.08−2.14 (m, 1H), 2.62 (dd, 1H, J = 15.3 and 13.9 Hz), 2.98 (dd, 1H, J = 15.3 and 5.9 Hz), 3.03−3.11 (m, 1H), 4.01−4.41 (m, 2H), 7.31 (dt, 1H, J = 7.8 and 1.3 Hz), 7.50 (dt, 1H, J = 6.4 and 1.1 Hz), and 7.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.9, 19.6, 27.4, 28.1, 31.8, 34.7, 40.7, 40.9, 45.6, 114.4, 124.1, 127.4, 129.8, 132.5, 132.7, 143.3, 150.0,

and 170.0. Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.98; H, 6.87; N, 8.61.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for new compounds lacking analyses together with an ORTEP drawing for structures **5**, **31**, **33**, **34**, **42a**, and **42b** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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