Furan-Terminated *N*-Acyliminium Ion Initiated Cyclizations in Alkaloid Synthesis[▽]

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A study of the utility of furan-terminated *N*-acyliminium ion initiated cyclizations for the synthesis of linearly fused alkaloid precursors (Figure 2) is presented. The outcome of the cyclization event depends on the position of furan tether attachment (2 vs 3), tether length, and furan 5-substituent (R = H, CH_3, Ar). 3-Substituted furans cyclized to form 6- and 7-membered ring containing furans **35**−**38**, **50**, and **51** in good to excellent yields. 2-Substituted furans closed to form only 6-membered rings; however, the products obtained were a function of the furan 5-substituent. The 5-H furans **17** and **18** led exclusively to the corresponding furans **21** and **22**, while the 5-CH_3-furans **42** and **43** gave only diketone containing compounds **44** and **45**. 5-Arylfurans **66**−**71** provided mixtures of furan- and diketone-containing products **72**−**83**, with the ratio related to the substitution on the phenyl moiety. A preparation of epilupinine **10** is also discussed.

The exploitation of cationic π-cyclizations in the construction of polycyclic ring systems has been the object of intense study since the early 1950s.[1] Initial forays into this arena demonstrated the syntheses of fused ring terpenoid-type systems, and later efforts demonstrated the construction of spiro and bridged ring carbocyclic systems.[2] These studies have demonstrated that a wide variety of initiating functions (e.g., epoxides, allylic alcohols, enones, olefins, carbinolamides) and terminating moieties (e.g., aromatic rings, acetylenes, allylsilanes, allenes, olefins) can be incorporated into the cyclization substrate to lead to terpenoids and alkaloids.

Our ongoing efforts in the synthesis of biologically relevant alkaloids and terpenoids have been based, in large part, on the use of furan-terminated cationic cyclizations. The furan nucleus imparts regio- and stereochemical control to systems through restricting the freedom of conformationally mobile systems and by the choice of tether attachment point, the furan α- or β-position. Also, a furan terminator is beneficial due to the variety of useful functional groups which can be realized through a one- or two-step procedure from the cyclized product (Figure 1). Through the careful consideration of initiating function, tether length and position of attachment, and initiation conditions we have developed

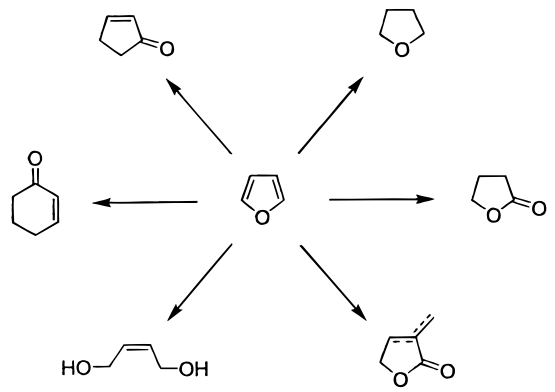

Figure 1. Furan functional equivalencies.

useful furan-terminated cationic cyclization sequences. We have used this method for the construction of linearly-fused, spirocyclic, and bridged-carbocyclic ring systems. Examples of these efforts can be seen in the syntheses of (+)-aphidicolin[3] **1**, (±)- and (−)-fastigilin C[4] **2**, (±)-nakafuran-9[2a] **3**, and perhydrohistrionicotoxin[5] **4**.

Our initial investigations involving the use of furan-terminated cyclizations in the synthesis of carbocycles led us to study the possibility of creating azacycles under the same, or similar, conditions. Alkaloid natural products should be easily and efficiently accessed through a furan-terminated cyclization by employing a nitrogen-containing cationic initiator such as an *N*-acyliminium ion. Much of the chemistry surrounding the synthesis, reactivity, and utility of the acyliminium ion has been very well documented in the pioneering work of Speckamp et al.[6] On the basis of this work and the work of

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(1) See: Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, U.K. 1991; Vol. 3, pp 341−377. See also: Haring, S. R.; Livinghouse, T. *J. Org. Chem.* **1997**, *62*, 6388. Corey, E. J.; Wood, H. B., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 11982. Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765.

(2) See: (a) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1985**, *50*, 3988. (b) Tanis, S. P.; Herrinton, P. M.; Dixon, L. A. *Tetrahedron Lett.* **1985**, *26*, 5347 and references therein.

(3) Tanis, S. P.; Chuang, Y.-H.; Head, D. B. *J. Org. Chem.* **1988**, *53*, 4929.

(4) Tanis, S. P.; Robinson, E. D.; McMills, M. C.; Watt, W. *J. Am. Chem. Soc.* **1992**, *114*, 8349 and references therein.

(5) Tanis, S. P.; Dixon, L. A. *Tetrahedron Lett.* **1987**, *28*, 2495.

(6) For recent work from this laboratory, see: Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3592. Teerhuis, N. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1996**, *38*, 155 and references therein.

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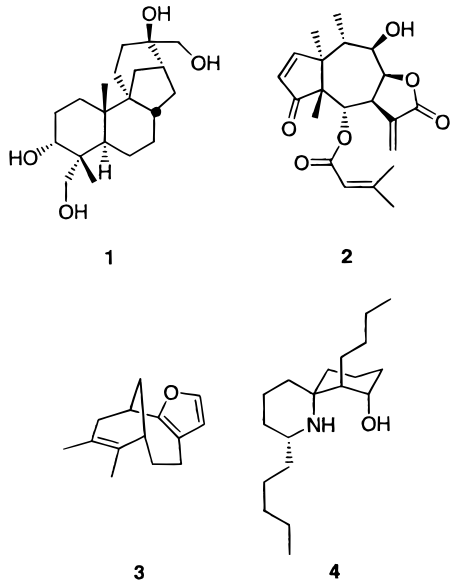


others, such as Chamberlin[7a] and Evans,[7b] we believed that the ease of synthesis and high reactivity of acyliminium ions[7c] were a good match for a furan terminator. A variety of linearly-fused, spirocyclic, and bridged azacycles could be synthesized by simply altering the placement of the furan tether on the *N*-acyliminium ion precursor (Figure 2).

Our first foray into alkaloid synthesis via *N*-acyliminium ion−furan-terminated cyclization[5] was directed toward the preparation of the Kishi precursor to perhydrohistrionicotoxin **5**.[8] This synthesis is outlined in Scheme 1.

The target carbinolamide is readily prepared, as indicated, and this substrate is smoothly cyclized, upon exposure to the two-phase mixture of formic acid in cyclohexane, to give the desired trisubstituted furan **5** in 72% yield. Oxidative cleavage of the furan (MCPBA) and reduction of the resulting ene−dione (H_2, Pd/C) afforded the target dione **6** (70%). Selective thioketalization (TMSOTf, $TMSS(CH_2)_2STMS$) gave **8** (67%), which suffered desulfurization (Raney nickel) to furnish lactam **9** (78%), thus completing the formal total synthesis of perhydrohistrionicotoxin.

With a successful spirocyclic alkaloid synthesis, via a furan terminated-*N*-acyliminium ion cyclization, in hand, we turned our attention to what was assumed to be the much simpler linearly-fused azacycle synthesis. Should we succeed in this venture, we envisioned conducting a synthesis of (±)-epilupinine **10**[9] to demonstrate the utility of the methodology.

Results and Discussion

For our methodological studies into the formation of linearly-fused azacycles, we selected very simple systems to study. The cyclization precursors that were targeted

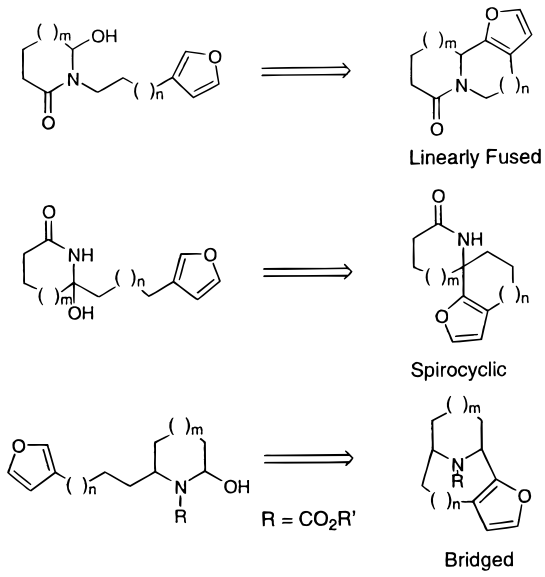


Figure 2. *N*-Acyliminium ion initiators in furan-terminated cyclizations.

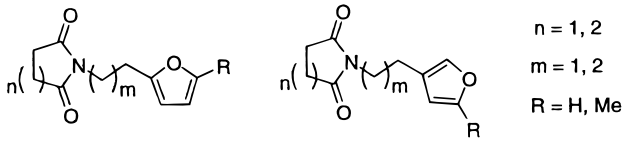


Figure 3. Target cyclization substrates.

for our initial studies are shown in Figure 3. As has been well documented in the literature,[6,7] the imide moiety was chosen as the *N*-acyliminium ion precursor.[7a] In addition, the imide can be efficiently N-substituted with the selected furan alkanol via a Mitsunobu[10] reaction. Hence, we required a source of furyl ethanols ($m = 1$) and furyl propanols ($m = 2$), to couple with succinimide and glutarimide, to initiate this work.

To examine the effects of imide ring size (5- or 6-membered) and tether length (2- or 3-carbon chain) on the furan-terminated cyclization, we targeted a variety of carbinolamides (Scheme 2). Compounds **13**−**16**, representing the furan 2-to-3 cyclization regioisomers, are created starting from either 2-(2-furyl)ethanol **11**[11] or 3-(2-furyl)propanol **12**[12] as shown in Scheme 2. Succinimide and **11** are coupled in the presence of Ph_3P and DEAD (THF) to furnish the indolizidine alkaloid precursor **13** in a disappointing 31% yield. Likewise the combination of **11** and glutarimide afforded a potential quinolizidine alkaloid progenitor **14** (69%). Similarly, the combination of **12** with succinimide and glutarimide gave **15** (51%) and **16** (53%), which could lead to pyrrolo[1,2-*a*]azepine and pyrido[1,2-*a*]azepine systems, respectively. Reduction, according to Chamberlin ($NaBH_4$, MeOH, −4 °C),[7a] gives the carbinolamides **17**−**20** in excellent crude

(7) (a) Chamberlin, A. R.; Nguyen, H. D.; Chung, J. Y. *J. Org. Chem.* **1984**, *49*, 1682. (b) Evans, D. A.; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 3695. (c) For some recent applications, see: Gardette, D.; Gelas-Mialhe, Y.; Gramain, J.-C.; Perrin, B.; Remuson, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1823. Kim, J. H.; Lee, Y. S.; Park, H.; Kim, C. S. *Tetrahedron* **1998**, *54*, 7395. Bardot, V.; Gardette, D.; Gelas-Mailhe, Y.; Gramain, J.-C.; Remuson, R. *Heterocycles* **1998**, *48*, 507.

(8) Fukuyama, T.; Dunkerton, L. V.; Aratani, M.; Kishi, Y. *J. Org. Chem.* **1975**, *40*, 2011.

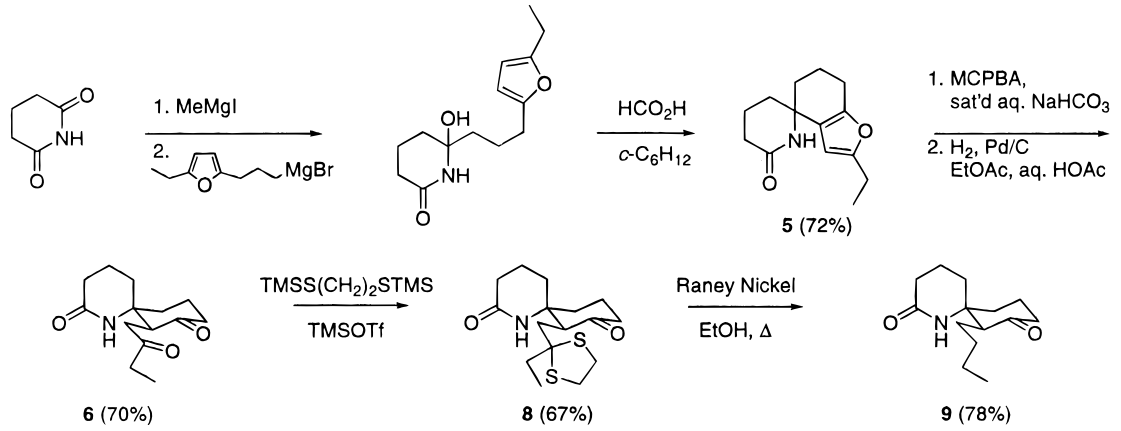
(9) For recent synthetic efforts directed toward epilupinine, see: Naidu, B. N.; West, F. G. *Tetrahedron* **1997**, *53*, 16565. Molander, G. A.; Nichols, P. J. *J. Org. Chem.* **1996**, *61*, 6040 and references therein.

(10) See: Jenkins, I. D. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 8, pp 5379−5390.

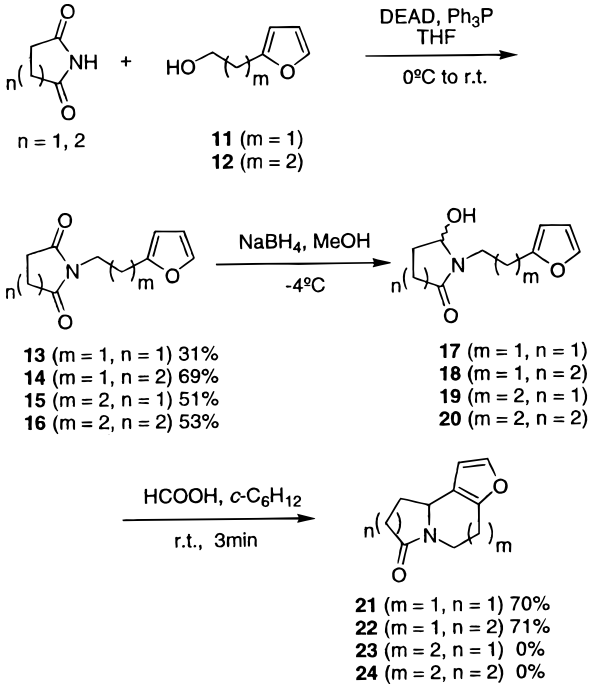
(11) Compound **8** was prepared by reacting ethylene oxide with 2-lithiofuran: Ramanathan, V.; Levine, R. *J. Org. Chem.* **1962**, *27*, 1216. Harmata, M.; Gamlath, C. B.; Barnes, C. L.; Jones, D. E. *J. Org. Chem.* **1995**, *60*, 5077.

(12) Taylor, D. A. H. *J. Chem. Soc.* **1959**, 2767.

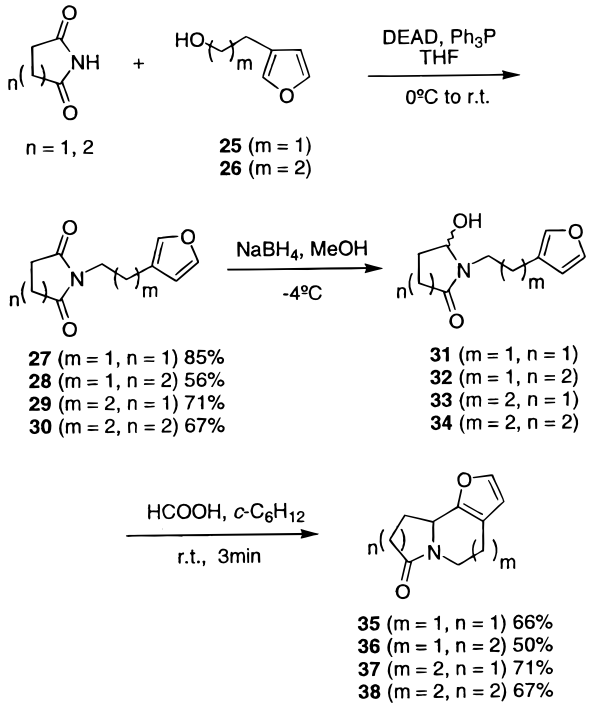
Scheme 1. Formal Total Synthesis of (±)-Perhydrohistrionicotoxin 9



Scheme 2. Furan 2-to-3 Cyclizations



Scheme 3. Furan 3-to-2 Cyclizations



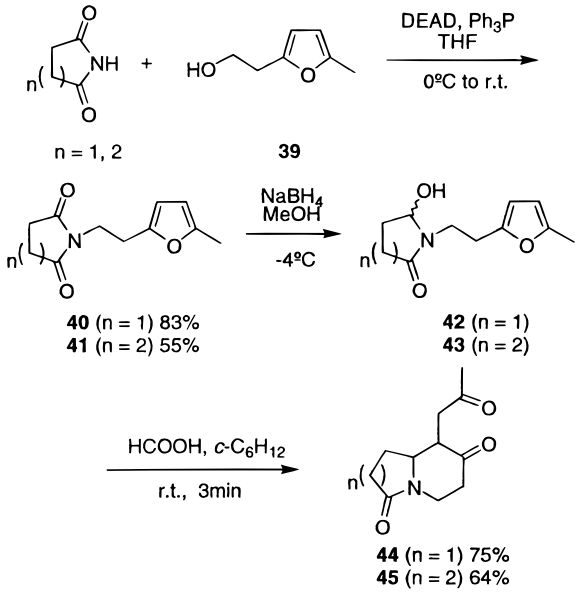
yield. These materials were then exposed to a two-phase mixture of anhydrous formic acid and cyclohexane, for 3 min,[2a,5] to give the indolizidine **21** and the quinolizidine **22** in 70% and 71% yields, respectively, from **13** and **14**. Longer acid exposure results in a time-related diminution in yield and a much dirtier reaction mixture. Conversely, carbinolamides **19** and **20** failed to afford the desired pyrrolo[1,2-*a*]azepine **23** and pyrido[1,2-*a*]azepine **24**, giving instead the related eneamides. This result was not totally unexpected as we have previously observed cyclization difficulties in the electronically less favored furan 2-to-3 closure (vs furan 3-to-2),[2b] and we have reported successful 7-membered ring formations in the furan 3-to-2 manifold.[4]

The syntheses of regioreversed furans (3-to-2 closure), as precursors to indolizidine, quinolizidine, pyrrolo[1,2-*a*]azepine, and pyrido[1,2-*a*]azepine ring systems, are disclosed in Scheme 3. 2-(3-Furyl)ethanol **25**[13] and 3-(3-furyl)propanol **26**[14] were coupled (DEAD, Ph_3P) with succinimide or glutarimide to give imides **27**−**30** in good to excellent yields (56−85%). These compounds were reduced as described in Scheme 2 ($NaBH_4$, MeOH, −4 °C) to furnish the crude carbinolamides **31**−**34**, which were immediately cyclized (anhydrous HCOOH, *c*-C_6H_{12}, 3 min) to yield furans **35**−**38** in 50−71% yields. Of note is the cyclization of **33** and **34** to give the pyrrolo[1,2-*a*]-azepine **37** (71%) and pyrido[1,2-*a*]azepine **38** (67%). These observations support our surmise that 7-membered ring formation in the furan 2-to-3 mode is problematic, while the electronically favored furan 3-to-2 closure readily forms 7-membered rings in an *N*-acyliminium ion initiated process. The chemistry of Schemes 2 and 3 stands in good agreement with prior observations in terpene-type systems. With the target ring systems in hand, and some understanding of the parameters dictating the outcome of furan-terminated, *N*-acyliminium ion initiated cyclizations, we turned our attention to the conversion of **21** and **22** (Scheme 2) to simple target alkaloids.

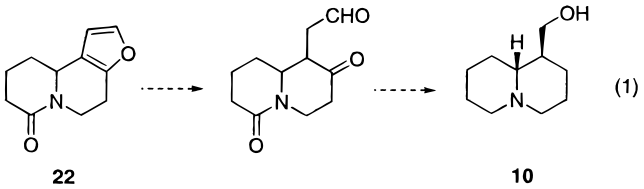
To prepare simple alkaloids such as epilupinine **10**, it is necessary to open the furan moiety of quinolizidine

(13) Sherman, E.; Amstutz, E. D. *J. Am. Chem. Soc.* **1950**, *72*, 2195.
(14) Vig, O. P.; Chugh, O. P.; Handa, U. K.; Vig, A. K. *J. Indian Chem. Soc.* **1975**, *52*, 199.

Scheme 4. 5-Methylfuran 2-to-3 Cyclization



precursor **22** (eq 1), remove one carbon from the side chain, and eliminate the a- and b-ring carbonyl moieties.

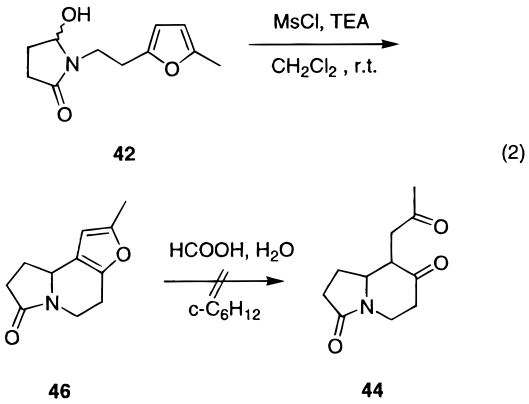


(1)

Toward these ends we began by examining the oxidative cleavage of the 2,3-disubstituted furan of **20** with MCPBA. Compound **22** was treated with MCPBA (buffered[15] or unbuffered[16]), to no avail. Furan **22** was also exposed to Cr^{VI}-based reagents[17] (PCC and variants, such as CNPCC[18]) and Clauson-Kaas oxidation (Br_2, MeOH)[19] to afford either unreacted starting material or, more commonly, a plethora of products and a poor mass balance. Furan **21** was similarly resistant to oxidative opening.

Previously we had reported[3,5,20] that alkyl substitution at the available α′-position of similarly unreactive α,β-disubstituted furyl moieties increased their reactivity toward MCPBA, giving ene−diones in high yield. Because of our inability to oxidize the furans **21** and **22**, we elected to use this strategy in the current study. The furan 5-methyl variants of **21** and **22** were prepared as discussed in Scheme 4. 2-(5-Methyl-2-furyl)ethanol[21] **39** was coupled (DEAD, Ph_3P) with succinimide and glutarimide, as previously described (vide supra) to furnish **40** (83%) and **41** (55%). The imides **40** and **41** were reduced ($NaBH_4$, MeOH, −4 °C) as before to give carbinolamides **42** and **43** in excellent crude yields. These materials were exposed to formic acid in cyclohexane (3 min) to yield *not* the expected furan-containing compounds *but* diketones **44** (75%) and **45** (64%) as the exclusive products. In the course of our formal total synthesis of perhydrohistrionicotoxin,[5] we had encountered similar furan hydrolytic/oxidation problems; these difficulties were overcome (Scheme 1) by the incorporation of an ethyl group at the available furan α-position. However, we did not see an anomalous furan hydrolysis in that *N*-acyliminium ion initiated (HCOOH, cyclohexane)−furan-terminated cyclization.

The chemistry of Scheme 4 suggests a fundamental difference in the reaction outcome results when the planar nitrogen of the product resides within the forming 6-membered ring (Scheme 4) rather than exocyclic (Scheme 1) to the closing cycle. Initially, we surmised that the furan was formed in the reaction and was rapidly hydrolyzed. This was tested as shown in eq 2. Carbinolamide **42** was treated with mesyl chloride and triethylamine (CH_2Cl_2), as described by Chamberlin,[7a] to give the purported furan containing intermediate **46** in 81% yield. This furan was subjected to the original cyclization conditions of formic acid/cyclohexane with ca. 1.5 equiv of water added to simulate carbinolamide dehydration, to give unreacted starting material (**46**). Extended exposure to formic acid/cyclohexane (1.5 equiv of water) led to extensive decomposition. Prior to delving further into the specifics of the production of diketones **44** and **45** from carbinolamides **42** and **43**, we decided to ask if this outcome was specific to cyclization within the 2-substituted furan manifold. Therefore we endeavored to prepare the 5-methyl-3-substituted congeners of **40** and **41**.



(2)

The required furylethanol **47**, prepared as illustrated in Scheme 5,[22] was coupled with succinimide and glutarimide (DEAD, Ph_3P) to give **48** and **49** in 86% and 83% yields, respectively. The imides were smoothly reduced to the desired carbinolamides, and the *standard* cyclization conditions (HCOOH, c-C_6H_{12}, 25 °C, 3 min) led to furoindolizidine **50** (87%) and furoquinolizidine **51** (48%) as the sole identified cyclization products. Clearly the electronically favored furan 3-to-2 closure (vs 2-to-3) behaves very differently to the presence of a planar nitrogen in the forming 6-membered ring than do the compounds of Scheme 4. We must consider alternatives to explain the formation of diketones from the cyclizations of Scheme 4.

(15) Williams, P. D. Ph.D. Dissertation, Michigan State University, 1982.
(16) (a) Williams, P. D.; LeGoff, E. *J. Org. Chem.* **1981**, *46*, 4143. (b) Gingerich, S. B.; Campbell, W. H.; Bricca, C. E.; Jennings, P. W. *J. Org. Chem.* **1981**, *46*, 2589.
(17) Paincatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron* **1980**, *36*, 661 and references therein.
(18) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647.
(19) Clauson-Kaas, N.; Tyle, Z. *Acta Chim. Scand.* **1952**, *6*, 667.
(20) Tanis, S. P.; Chuang, Y.-H.; Head, D. B. *Tetrahedron Lett.* **1985**, *26*, 6147.
(21) Corvers, A.; vanMil, J. H.; Sap, M. M. E.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 18.
(22) Tanis, S. P.; Collins, M. A.; Deaton, M. V. Manuscript in preparation.

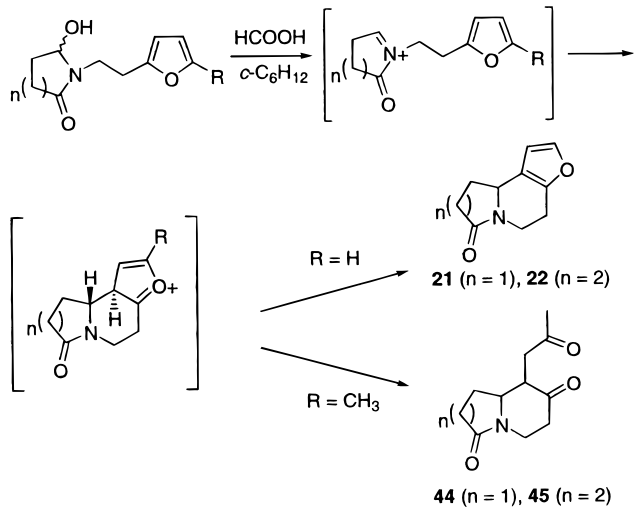
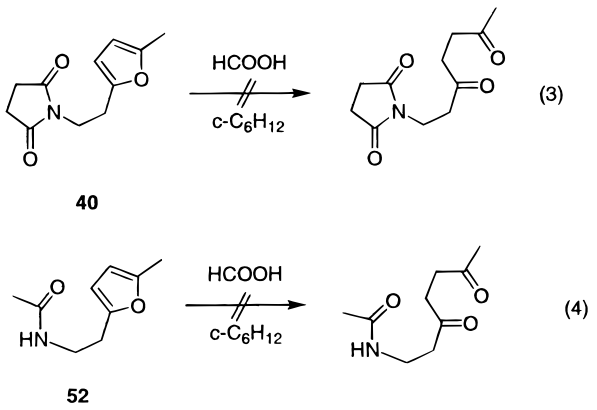


Figure 4. Mechanistic analysis of the furan 2-to-3 cyclization.

We considered several scenarios which might explain the observations of Scheme 4. In the first, the furan might hydrolyze prior to cyclization (via an enol?). Precyclization, direct furan hydrolysis, which we considered unlikely, was examined as shown in eq 3. Imide **40** was treated with formic acid and water (1.5 equiv) in cyclohexane for 3 min and was recovered unchanged. Assisted furan hydrolysis, via the agency of the carbinolamide hydroxyl group, was examined next. Although we could not readily test this theory using carbinolamide **42**, we felt that the secondary amide **52** would be a good substitute. Amides such as a **52** could tautomerize to an imidic form in acidic solutions to afford a stable alternative to the hydroxyl moiety of **42**. Amide **52** was prepared and exposed to formic acid and water (1.5 equiv) in cyclohexane to give unreacted **52** (eq 4).



As the furan apparently resists hydrolysis prior to cyclization, we turned our attention toward the cyclization sequence of Scheme 4. Figure 4 illustrates the assumed cyclization intermediate and the product distribution as a function of furan substitution in the furan 2-to-3 closure mode. A similar crossconjugated oxonium ion would have been an intermediate in the cyclization depicted in Scheme 1; however in that spirocyclic closure there would not be a planar nitrogen within the forming cycle, nor would there be A-ring substituents to provide steric interactions. In the case in hand, the sp^2-hybridization of the amide nitrogen in the forming heterocycle might cause torsional[23] strain, and allylic[24] strain (furan-β-H−C-1) could develop as the onium ion loses a proton and aromatizes. However, these forces would be operative regardless of the nature of the furan 5-substituent, and there is a clear partitioning in this operation to give the observed products, exclusively **21** and **22** when R = H and **44** and **45** when R = CH_3.

Although we believed that strain would play an important role in the reaction outcome, it is clear that any mechanistic rationale would have to explain the all or nothing effect of the substituents on the furan 5-position. If one examines Figure 4, it is clear that charge does not appear on the carbon-bearing R. The effect of this relatively remote substituent would be more readily apparent if the oxonium ion could be rearranged to place charge on the 5 position. Hence, we formulated a new hypothesis that was centered on the possibility of the first formed oxonium ion intermediate undergoing a 1,5-hydrogen shift to form the product-determining intermediate **53** shown in Figure 5. Although prototropic shifts have not been widely observed in reactions involving alkylated furans,[25] there have been several publications discussing this type of event in similarly functionalized pyrroles;[26] 2*H*-pyrroles readily rearrange, under thermolytic or acidic conditions, to give the more stable 3*H*-pyrroles through a [1,5]-sigmatropic shift. The stability of putative intermediate **53** is determined by the stability of the oxonium ion which is, in turn, determined by the nature of the R substituent. The inductive stabilization of the oxonium ion by methyl relative to hydrogen[27] might stabilize this intermediate, facilitating its capture by water or formate, leading to diones **44** and **45**. To test this hypothesis, we elected to prepare 5-aryl-substituted variants of the furans of Figure 5. The electrical effects (inductive and resonance)[28] of an aryl substituent can be readily altered through substitution (4-H vs 4-OMe vs 4-CF_3), perhaps affording us the opportunity to observe behavior, in a predictable fashion, intermediate between the furans of Schemes 2 and 4. The syntheses of these target furans and their behavior under cyclization conditions are discussed in Scheme 6.

Commercially available 2-(tributylstannyl)furan is coupled, under catalysis by tetrakis(triphenylphosphino)-palladium,[29] with 4-CF_3-bromobenzene, bromobenzene, and 4-MeO-bromobenzene to give **54** (Scheme 6), **55**,[30]

(23) For a discussion, see: Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Wiley-Interscience: New York, 1965; pp 5−12. For applications of the concept of torsional angle to conformational descriptions, see: Bucort, R. *Top. Stereochem.* **1974**, *8*, 159.

(24) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

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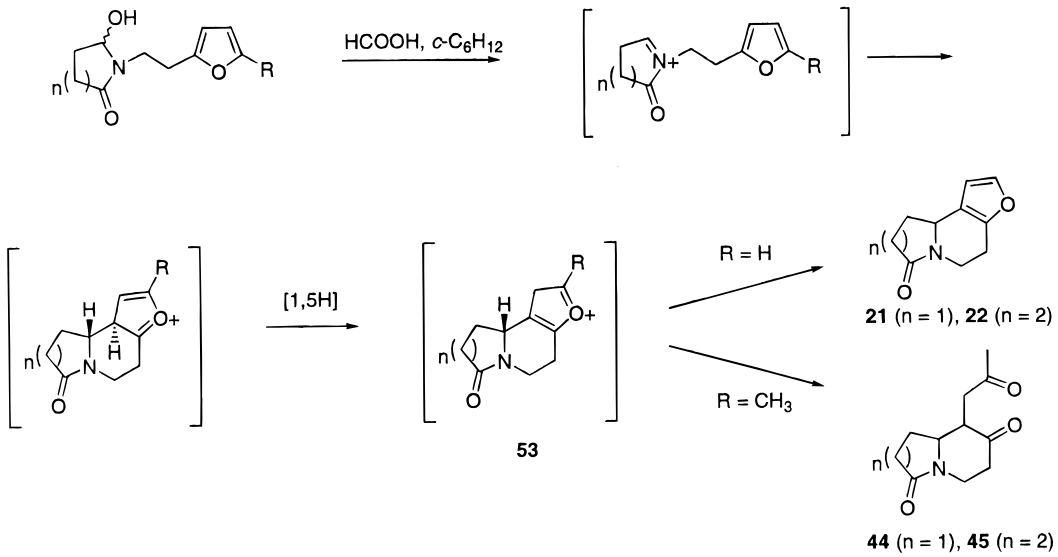
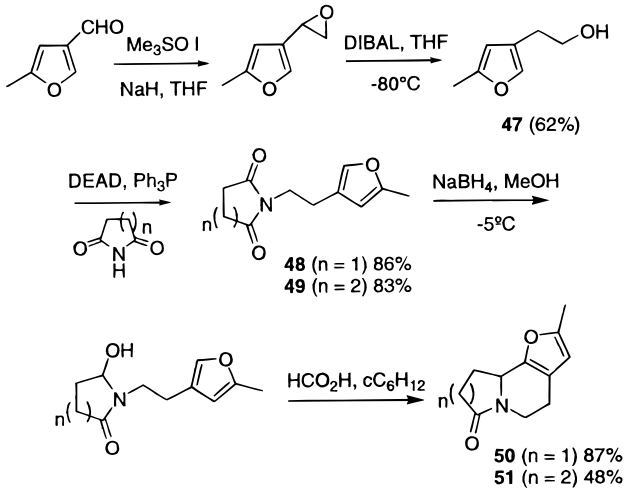


Figure 5. Furan 2-to-3 cyclization, possible [1,5H] shift.

Scheme 5. 5-Methylfuran 3-to-2 Cyclization



and **56**.[30] Due to the nonpolar nature of the formed aryl furans, it is very difficult to remove all traces of the tin byproducts. For this reason, the coupling products were usually carried through the next step with some tin impurity present. The reaction of **54** with n-BuLi at room temperature followed by treatment of the resulting α-lithiofuran with ethylene oxide readily provided the desired furyl ethanol **57** (46%). Likewise, furans **55** and **56** led to furylethanols **58** (81%)[31] and **59** (65%). Mitsunobu coupling, as previously described (vide supra), was performed with both succinimide and glutarimide to furnish imides **60**−**65** in 59−91% yields. The imides were then reduced ($NaBH_4$, MeOH, −4 °C) to provide the desired carbinolamides in excellent crude yields. We were now prepared to examine the effect of 5-aryl substitution, electronic modification of the 5-aryl substitutent, and imide ring size upon the *N*-acyliminium ion initiated furan 2-to-3 closure. In the event, the succinimide-derived carbinolamide **66**, substituted at the furan 5 position with a 4-CF_3-Ph moiety, was treated with formic acid in cyclohexane to give a 47:53 mixture of furan **72** and dione **73** in 64% yield. Similarly, the phenyl-substituted carbinolamide **67** gave a 35:65 mixture of furan **74** to dione **75** (79%), while the 4-MeOPh-substituted furan of carbinolamide **68** led to an 82% yield of furan **76** and diketone **77** in a 24:76 ratio. A similar pattern was observed in the glutarimide series; however the product ratios showed a greater preference for the formation of dione over furan in the cyclized products. These results provide some support for the mechanistic paradigm presented in Figure 5. The 5-aryl furan moiety appears to be intermediate between H and methyl in its ability to stabilize the oxonium ion of Figure 5, and within the series 4-CF_3-, 4-H-, and 4-MeOPh the electron poor to electron rich nature of the aryl ring is also reflected in the product ratios.

With a better understanding of the factors governing the outcome of the cyclization process in hand, we embarked upon a synthesis of epilupinine **10**, from diketone **45** (Scheme 7), prepared as described in Scheme 4. A successful synthesis of **10** would support the furan regiochemistry assigned to the cyclization sequences discussed previously (vide supra). To complete a synthesis of epilupinine, we needed to reductively remove the lactam and ring carbonyls of **45** as well as transform the side chain into a methanolic residue. Initial attempts to differentiate the carbonyl groups of **45** via thermodynamic oxo- or thioketalization were unrewarding. These experiments produced gross mixtures and some decomposition. We then turned to kinetic ketalization conditions. On the basis of our experience during our formal total synthesis of perhydrohistrionicotoxin,[5] we had assumed that Noyori kinetic ketalization[32] might favor selective protection of the side chain carbonyl. However, we were surprised and delighted to obtain a 93% yield of a <2:>98 mixture of the bis-ketal **84** and the ring ketal **85** (1.0 equiv of $TMSO(CH_2)_2OTMS$, CH_2Cl_2, 10 mol % TMSOTf, −23 °C to rt). The predominant formation of a ring ketal was suggested by the small shift of the ketone methyl (2.24 to 2.15 ppm) in **85** vs the shift of the methyl signal to 1.53 ppm in **84**. We hoped that this selectivity would also be observed in kinetic thioketalization reac-

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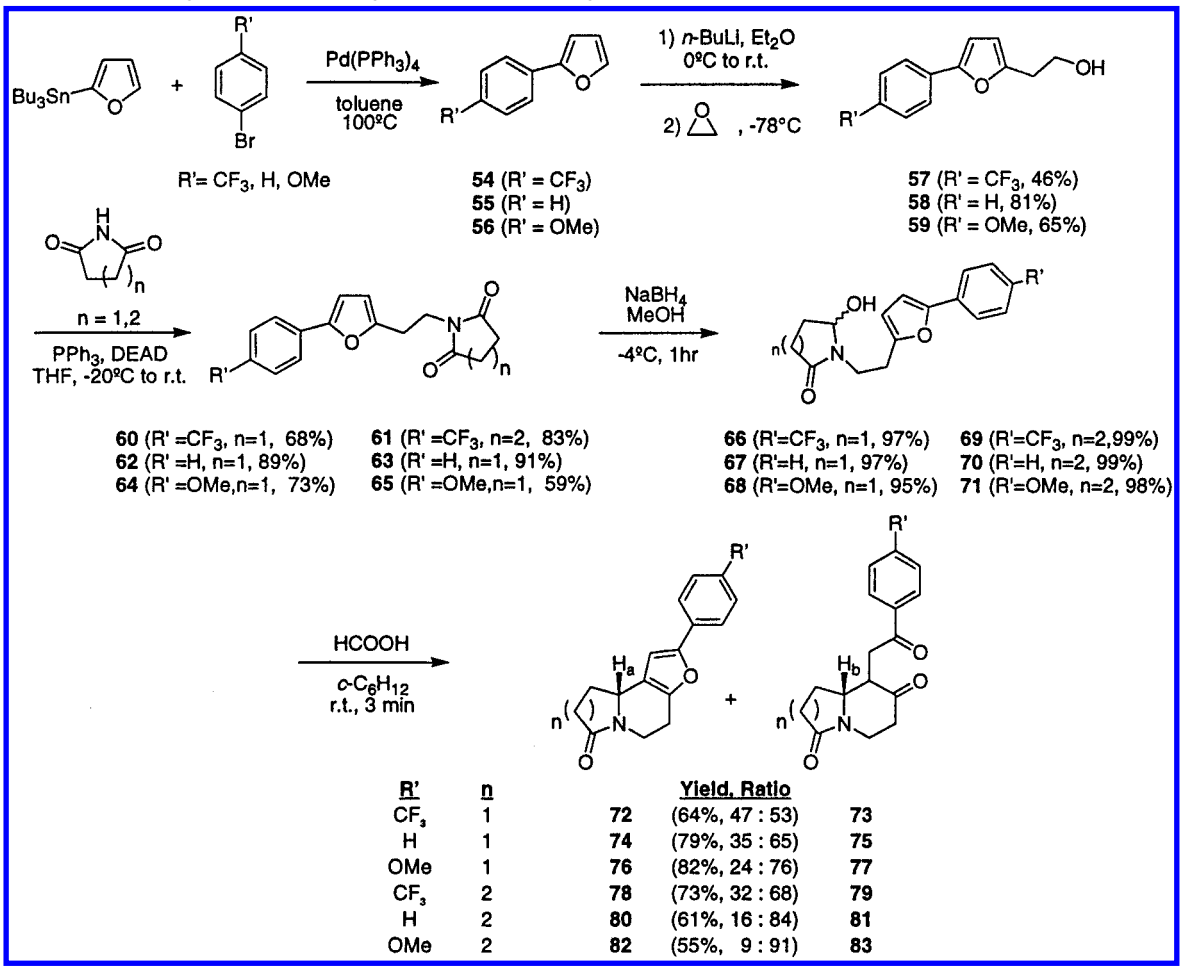
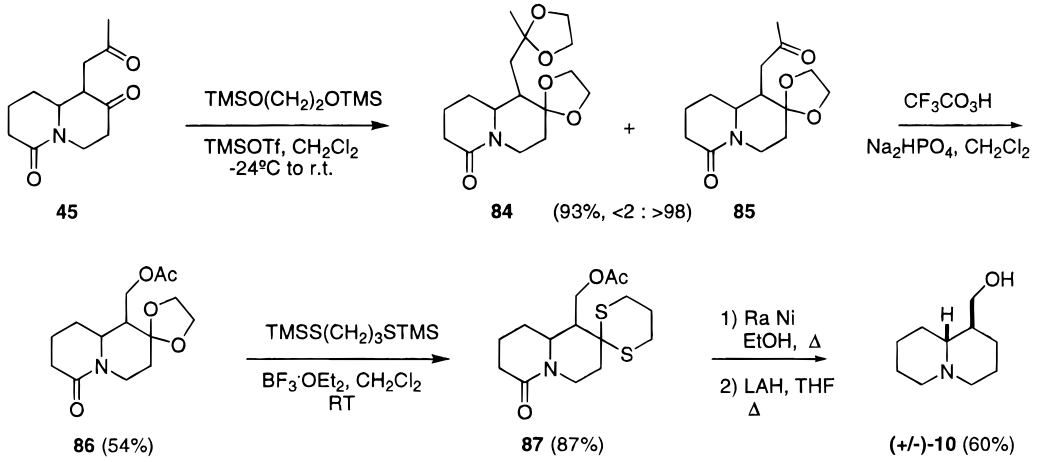
Scheme 6. Synthesis and Cyclization of 5-Aryl-Substituted Furan 2-to-3 Closure Substrates



R'	n		Yield, Ratio	
CF_3	1	**72**	(64%, 47 : 53)	**73**
H	1	**74**	(79%, 35 : 65)	**75**
OMe	1	**76**	(82%, 24 : 76)	**77**
CF_3	2	**78**	(73%, 32 : 68)	**79**
H	2	**80**	(61%, 16 : 84)	**81**
OMe	2	**82**	(55%, 9 : 91)	**83**

Scheme 7. Synthesis of (±)-Epilupinine 10



tion conditions ($TMSS(CH_2)_2STMS$, CH_2Cl_2, TMSOTf); however these attempts afforded inseparable mixtures of products. This failure caused us to reorder the synthesis by performing the side-chain Baeyer−Villiger oxidation, followed by ketal-to-thioketal exchange/removal, rather than ketone removal before side-chain oxidation.

Our next efforts were centered around the transformation of the side chain ketone into the methanolic residue. Toward this end, various oxidative conditions were examined for their utility in our synthesis. Using freshly prepared trifluoroperacetic acid in CH_2Cl_2 buffered with anhydrous Na_2HPO_4,[33] Baeyer−Villiger oxidation of ketal **85** provided the acetate **86** in 54% yield. In an attempt to improve the yield of this step, more mild conditions such as permaleic acid[34] and MCPBA were studied, but led only to recovered starting material. The synthesis was completed as outlined in Scheme 7. The transketalization of oxoketal **86** to thioketal **87** was readily accomplished through the exposure of **86** to the bis-silyl ether of 1,3-propanedithiol and $BF_3{\cdot}OEt_2$ in methylene chloride (87%). Reductive removal of the thioketal with

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Raney nickel occurred without incident to afford the desired acetate which was reduced ($LiAlH_4$) to give epilupinine **10** (60%). The identity of **10** was secured upon a comparison of spectral data of our synthetic material with literature values.[9]

In summary, we have demonstrated the utility of furan-terminated *N*-acyliminium ion initiated cyclizations for the synthesis of linearly-fused alkaloid precursors. The relationship of the furan 5-substituent to the outcome of the cyclization step in the furan 2-to-3 closure was unexpected, as we had never previously observed diones as the product of a furan-terminated cyclization. One can now predictably design cyclization substrates which will afford either a furan or a diketone as the product of the furan−acyliminium ion cyclization. Having demonstrated the utility of a furan terminator in *N*-acyliminium ion initiated closures leading to linearly-fused and spirocyclic systems, we are turning our attention to bridged ring construction, specifically toward syntheses of cocaine and anatoxin-a. These results will be reported in due course.

Experimental Section

General. All reagents were used as received unless otherwise stated. All reactions were performed under a blanket of nitrogen, in oven (150 °C) dried glassware with rigid exclusion of moisture from all reagents and glassware unless otherwise mentioned. Melting points are uncorrected. Proton magnetic resonance spectra (^{1}H NMR) were recorded in deuteriochloroform unless otherwise indicated. Flash column chromatography was performed according to the procedure of Still[35] et al. and eluted with the solvents mentioned.

General Preparation of N-Substituted Imides. *N*-(2-(2-Furyl)ethyl)-2,5-pyrrolidinedione 13. To a solution of 2-furyl ethanol **11** (2.24 g, 20 mmol), triphenylphosphine (5.77 g, 22 mmol), succinimide (1.98 g, 20 mmol), and THF (16.7 mL), chilled in an ice−H_2O bath, was added to a solution of diethyl azodicarboxylate (3.83 g, 22 mmol) in THF (8.9 mL) over 20 min. The mixture was stirred at 25 °C for 48 h and then concentrated in vacuo to a yellow viscous liquid. Ether−petroleum ether (1:1) was added to the residue resulting in the precipitation of a white solid (Ph_3PO) which was removed by filtration. The filtrate was concentrated in vacuo to provide 3.52 g of a viscous pale yellow liquid which was purified by chromatography on a column of silica gel (60−230 mesh, 170 g, 60 mm o.d., ethyl acetate−petroleum ether 35:65, l00 mL fractions) using the flash technique. Fractions 12−25 provided 1.21 g, 31%, of **13** as an off-white crystalline solid, mp = 65−69 °C. ^{1}H NMR (250 MHz): δ = 7.27 (m, 1), 6.22 (m, 1), 6.01 (m, 1), 3.75 (t, J = 8.3 Hz, 2), 2.88 (t, J = 8.3 Hz, 2), 2.63 (s, 4). IR (neat): 1770, 1700, and 815 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 193 (M^+, 0.31), 112 (35.5), 100 (base), 81 (86.3). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.83; H, 5.52; N, 7.12.

***N*-(2-(2-Furyl)ethyl)-2,6-piperidinedione 14.** According to the general procedure for the preparation of N-substituted imides, 2-furylethanol **11** (2.24 g, 20 mmol), triphenylphosphine (5.77 g, 22 mmol), and glutarimide (2.26 g, 20 mmol) in THF (16.7 mL) were allowed to react with diethyl azodicarboxylate (3.83 g, 22 mmol) to provide 5.15 g of crude product. The crude product was purified by chromatography on a column of silica gel (60−230 mesh, 230 g, 20 mm o.d., ethyl acetate−petroleum ether 35:65, 125 mL fractions) using the flash technique. Fractions 13−28 provided 2.84 g, 69%, of **14** as a viscous yellow liquid. ^{1}H NMR (60 MHz): δ = 7.30 (m, 1), 6.27 (m, 1), 6.02 (m, 1), 4.07 (t, J = 8.0 Hz, 2), 2.85 (t, J = 8.0 Hz, 2), 2.59 (t, J = 6.5 Hz, 4), 1.90 (m, 2). IR (neat): 1725, 1670, and 735 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 207 (M^+, 8.07), 126 (0.78), 94 (base), 81 (13.0). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.55; H, 6.21; N, 6.64.

***N*-(3-(2-Furyl)propyl)-2,5-pyrrolidinedione 15.** According to the general procedure for the preparation of N-substituted imides, 3-(2-furyl)propanol **12** (4.0 g, 31.75 mmol), triphenylphosphine (8.32 g, 31.75 mmol), and succinimide (3.52 g, 35.60 mmol) in THF (50 mL) were allowed to react with diethyl azodicarboxylate (5.52 g, 31.75 mmol) in THF (8 mL) for 36 h. The crude product was purified by chromatography on a column of silica gel (60−230 mesh, 200 g, 50 mm o.d., ethyl acetate−petroleum ether 2:3, 60 mL fractions) using the flash technique. Fractions 10−15 provided 3.29 g, 51%, of **15** as a viscous pale yellow liquid. ^{1}H NMR (250 MHz): δ = 7.25 (m, 1), 6.22 (m, 1), 5.98 (m, 1), 3.54 (t, J = 7.3 Hz, 2), 2.63 (m, 4), 2.61 (t, J = 8.0 Hz, 2), 1.91 (m, 2). IR (neat): 3240, 1770, 1700, and 730 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 208 (M^+ + 1, 2.04), 207 (M^+, 11.3), 113 (15.1), 108 (base), 95 (33.9), 81 (73.7). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.39; H, 6.08; N, 6.47.

***N*-(3-(2-Furyl)propyl)-2,6-piperidinedione 16.** According to the general procedure for the preparation of N-substituted imides, 3-(2-furyl)propanol **12** (4.0 g, 31.75 mmol), triphenylphosphine (8.32 g, 31.75 mmol), and glutarimide (4.02 g, 35.60 mmol) were allowed to react with diethyl azodicarboxylate (5.52 g, 31.75 mmol) in THF (8 mL) for 36 h. The crude product was purified by preparative liquid chromatography (300 mL/min) eluting with ethyl acetate−hexane, 30:70, to provide 3.69 g, 53%, of **16** as a viscous pale yellow liquid. ^{1}H NMR (250 MHz): δ = 7.25 (m, 1), 6.23 (m, 1), 5.99 (m, 1), 3.81 (t, J = 7.3 Hz, 2), 2.61 (t, J = 8.3 Hz, 2), 2.59 (t, J = 6.7 Hz, 4), 1.86 (m, 4). IR (neat): 3000, 1730, 1680, and 730 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 221 (M^+, 8.16), 140 (6.42), 126 (11.2), 108 (base), 81 (74.8). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.10; H, 6.71; N, 6.22.

General Procedure for the Reduction of N-Substituted Imides. Preparation of *N*-(2-(2-Furyl)ethyl)-5-hydroxy-2-pyrrolidinone 17. Sodium borohydride (1.52 g, 40 mmol) was added all at once to a solution of the N-substituted imide **13** (769 mg, 3.98 mmol) in methanol (40 mL), chilled to −4 °C in an ice−salt bath. The mixture was stirred at −4 °C for l h and then cast into a rapidly stirred mixture of saturated aqueous $NaHCO_3$ (40 mL) and CH_2C1_2 (40 mL), cooled in an ice−H_2O bath. The aqueous layer was separated and extracted with CH_2C1_2 (3 × 40 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford 684 mg of the crude carbinolamide **17** as a viscous water-white liquid, which was used without further purification. ^{1}H NMR (250 MHz): δ = 7.28 (m, 1), 6.26 (m, 1), 6.05 (m, 1), 4.95 (bs, 1), 3.57 (m, 2), 3.63 (bs, 1), 2.88 (t, J = 7.0 Hz, 2), 2.51 (m, 1), 2.23 (m, 2), 1.85 (m, 1). IR (neat): 3320, 2920, 1690, 1660, and 670 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 196 (M^+ + 1, 1.32), 195 (M^+, 10.0), 177 (4.30), 114 (24.8), 94 (80.9), 46 (base).

***N*-(2-(2-Furyl)ethyl)-6-hydroxy-2-piperidinone 18.** According to the general procedure for the reduction of N-substituted imides, sodium borohydride (1.14 g, 30 mmol) was added to imide **14** (621 mg, 3.0 mmol) in MeOH (30 mL) at −4 °C and stirred for 1 h to provide 620 mg, 98%, of the crude carbinolamide **18** as a viscous pale yellow liquid. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 55 g, 40 mm o.d., ethyl acetate−petroleum ether 4:1, 50 mL fractions) using the flash technique. Fractions 9−18 provided 480 mg, 76%, of **18** as a white crystalline solid, mp = 87−90 °C. ^{1}H NMR (250 MHz): δ = 7.32 (m, 1), 6.29 (m, 1), 6.05 (m, 1), 5.85 (m, 1), 5.06 (m, 1), 3.72 (t, J = 8.0 Hz, 2), 2.90 (t, J = 8.0 Hz, 2), 2.50 (t, J = 8.8 Hz, 2), 2.37 (m, 2), 2.27 (m, 2). IR ($CHCl_3$): 3570, 3320, 1705, 1600, and 835 cm^{-1}. EI-MS (70 eV): 210 (M^+ + 1, 1.87), 209 (M^+, 9.55), 191 (18.2), 128 (8.3), 82 (31.8), 45 (base).

***N*-(3-(2-Furyl)propyl)-5-hydroxy-2-pyrrolidinone 19.** According to the general procedure for the reduction of N-substituted imides, sodium borohydride (1.90 g, 50 mmol) was added to imide **15** (2.03 g, 9.8 mmol) in MeOH (100 mL) at −4 °C and stirred for 45 min to afford 1.93 g, 94%, of the

(35) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

carbinolamide **19** as a viscous pale yellow liquid. ^{1}H NMR (250 MHz): δ = 7.30 (m, 1), 6.27 (m, 1), 6.02 (m, 1), 4.91 (dd, J_1 = 6.0, J_2 = 2.0 Hz, 1), 3.53 (m, 2), 2.65 (t, J = 8.3 Hz, 2), 2.50 (m, 2), 2.29 (m, 2), 2.00 (m, 2). IR ($CHCl_3$): 3900, 3300, 1730, 1680, and 880 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 191 ($M^+ - H_2O$, 43.0), 108 (49.9), 68 (base).

***N*-(3-(2-Furyl)propyl)-6-hydroxy-2-piperidinone 20.** According to the general procedure for the reduction of N-substituted imides, sodium borohydride (1.90 g, 50 mmol) was added to imide **16** (2.21 g, 10 mmol) in MeOH (100 mL) at −4 °C and stirred for 45 min to yield 2.0 g, 90%, of the crude carbinolamide **20** as a viscous pale yellow liquid which crystallized upon cooling (−20 °C) to give an off-white solid, mp = 58−64 °C. ^{1}H NMR (250 MHz): δ = 7.29 (m, 1), 6.27 (m, 1), 6.02 (m, 1), 4.47 (m, 1), 3.68 (m, 2), 2.64 (t, J = 7.8 Hz, 2), 2.58 (m, 4), 1.98 (m, 2), 1.65 (m, 2). IR ($CHCl_3$): 3580, 3330, 1720, 1620, and 930 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 224 (M^+ + 1, 1.78), 223 (M^+, 11.5), 205 (53.9), 108 (base), 81 (42.0).

General Procedure for the Cyclization of Carbinolamides. Preparation of 1-Aza-4,5-(2,3*b*-furyl)bicyclo[4.3.0]-nonan-9-one 21. To a vigorously stirred solution of the carbinolamide **17** (0.207 g, 1.06 mmol) in cyclohexane (17 mL) at 25 °C was rapidly added anhydrous HCOOH (4.25 mL). The two-phase mixture was stirred for 3 min and then immediately cast into CH_2Cl_2 (50 mL) and water (75 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (150 mL), dried (Na_2SO_4), and concentrated in vacuo to yield 220 mg of crude cyclized material **21**. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 40 g, 30 mm o.d., ethyl acetate−petroleum ether 4:1, 30 mL fractions) using the flash technique. Fractions 8−13 yielded 0.131 mg, 70%, of **21** as a viscous water-white liquid. ^{1}H NMR (250 MHz): δ = 7.27 (m, 1), 6.20 (m, 1), 4.98 (m, 2), 4.42 (m, 1), 2.78 (m, 2), 2.33 (m, 2), 1.94−1.62 (m, 2). IR ($CHCl_3$): 3000, 2860, 1675, and 900 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 178 (M^+ + 1, 20.8), 177 (M^+, base), 176 (66.2), 120 (45.5), 91 (27.0). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.56; H, 6.09; N, 7.76.

1-Aza-4,5-(2,3*b*-furyl)bicyclo[4.4.0]decan-10-one 22. According to the general procedure for the cyclization of carbinolamides, a two-phase mixture of HCO_2H (6.0 mL), carbinolamide **18** (326 mg, 1.56 mmol), and cyclohexane (25 mL) was stirred vigorously at 25 °C for 3 min to yield 0.28 g of a viscous pale yellow liquid. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 32 g, 30 mm o.d., ethyl acetate−petroleum ether 4:1, 20 mL fractions) using the flash technique. Fractions 13−22 provided 0.211 g, 71%, of **22** as a viscous water-white liquid. ^{1}H NMR (250 MHz, C_6D_6): δ = 7.02 (bs, 1), 5.84 (m, 1), 5.12 (dd, J_1 = 12.5, J_2 = 5.0 Hz, 1), 3.78 (m, 2), 2.55 (m, 2). IR ($CHCl_3$): 3000, 2945, and 1625 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 192 (M^+ + 1, 14.6), 191 (M^+, base), 121 (54.5), 120 (57.7). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.78; H, 6.57; N, 7.01.

***N*-(2-(3-Furyl)ethyl)-2,5-pyrrolidinedione 27.** According to the general procedure for the preparation of N-substituted imides, 2-(3-furyl)ethanol **25** (1.12 g, 10 mmol), triphenylphosphine (2.88 g, 11 mmol), and succinimide (0.99 g, 10 mmol) in THF (8.3 mL) were allowed to react with diethyl azodicarboxylate (1.91 g, 11 mmol) in THF (4.5 mL) for 24 h to provide 4.20 g of crude product. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 50 mm o.d., ethyl acetate−petroleum ether 30:70, 75 mL fractions) using the flash technique. Fractions 19−27 provided 1.65 g, 85%, of **27** as a viscous pale yellow liquid. ^{1}H NMR (250 MHz): δ = 7.32 (m, 1), 7.23 (m, 1), 6.28 (bs, 1) 3.90 (t, J = 6.7 Hz, 2), 3.51 (t, J = 6.7 Hz, 2), 2.73 (m, 4). IR (neat): 3260, 1750, 1700, and 870 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 193 (M^+, 13.6), 126 (57.0), 112 (7.23), 94 (base), 81 (25.3). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 60.95; H, 5.67; N, 7.22.

***N*-(2-(3-Furyl)ethyl)-2,6-piperidinedione 28.** According to the general procedure for the preparation of N-substituted imides, 2-(3-furyl)ethanol **25** (1.12 g, 10 mmol), triphenylphosphine (2.88 g, 11 mmol), and glutarimide (1.13 g, 10 mmol) in THF (8.3 mL) were allowed to react with diethyl azodicarboxylate (1.92 g, 11 mmol) in THF for 24 h to provide 4.33 g of crude product. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 120 g, 50 mm o.d., ethyl acetate−petroleum ether 1:1, 75 mL fractions) using the flash technique. Fractions 7−12 yielded 1.16 g, 56%, of **28** as a viscous pale yellow liquid. ^{1}H NMR (250 MHz): δ = 7.31 (m, 1), 7.15 (bs, 1), 6.30 (bs, 1), 3.91 (t, J = 7.8 Hz, 2), 3.42 (t, J = 7.8 Hz, 2), 2.61 (m, 4), 1.90 (m, 2). IR ($CHCl_3$): 3420, 1730, 1670, and 870 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 208 (M^+ + 1, 15.0), 207 (M^+, 38.2), 140 (45.5), 126 (4.09), 94 (base), 81 (4.78). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 7.76. Found: C, 63.49; H, 6.09; N, 7.58.

***N*-(3-(3-Furyl)propyl)-2,5-pyrrolidinedione 29.** According to the general procedure for the preparation of N-substituted imides 3-(3-furyl)propanol **26** (2.52 g, 20 mmol), triphenylphosphine (6.03 g, 23 mmol), and succinimide (1.98 g, 20 mmol) in THF (16.7 mL) were allowed to react with diethyl azodicarboxylate (4.01 g, 23 mmol) in THF (8.9 mL) for 24 h. The crude product was purified by chromatography on a column of silica gel (60−230 mesh, 230 g, 60 mm o.d., ethyl acetate−petroleum ether 30:70, 75−100 mL fractions) using the flash technique. Fractions 15−26 provided 2.93 g, 71%, of **29** as a viscous pale yellow liquid. ^{1}H NMR (250 MHz) δ = 7.35 (m, 1), 7.24 (bs, 1), 6.28 (bs, 1), 3.57 (t, J = 8.3 Hz, 2), 2.65 (m, 4), 2.45 (t, J = 8.3 Hz, 2), 1.86 (m, 2). IR ($CHCl_3$): 3400, 2965, 1720, and 1690 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 208 (M^+ + 1, 3.46), 207 (M^+, 15.03), 126 (4.22), 113 (6.64), 108 (base), 81 (20.6). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 7.76. Found: C, 63.38; H, 5.99; N, 7.47.

***N*-(3-(3-Furyl)propyl)-2,6-piperidinedione 30.** According to the general procedure for the preparation of N-substituted imides, 3-(3-furyl)propanol **26** (2.52 g, 20 mmol), triphenylphosphine (6.03 g, 23 mmol), and glutarimide (2.26 g, 20 mmol) in THF (16.7 mL) were allowed to react with diethyl azodicarboxylate (4.01 g, 23 mmol) in THF (8.9 mL) for 48 h. The crude product was purified by chromatography on a column of silica gel (60−230 mesh, 250 g, 60 mm o.d., ethyl acetate−petroleum ether 30:70, 100 mL fractions) using the flash technique. Fractions 18−31 provided 2.96 g, 67%, of **30** as a viscous pale yellow liquid. ^{1}H NMR (250 MHz) δ = 7.34 (m, 1), 7.24 (bs, 1), 6.27 (bs, 1), 3.82 (t, J = 8.3 Hz, 2), 2.62 (t, J = 6.3 Hz, 4), 2.45 (t, J = 8.3 Hz, 2), 1.89 (m, 2), 1.80 (m, 2). IR (neat): 3410, 2995, 1720, and 1660 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 221 (M^+, 7.97), 141 (27.0), 127 (8.04), 108 (base), 81 (26.4). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.21; H, 7.01; N, 6.30.

***N*-(2-(3-Furyl)ethyl)-5-hydroxy-2-pyrrolidinone 31.** According to the general procedure for the reduction of N-substituted imides, sodium borohydride (1.60 g, 42 mmol) was added to imide **27** (0.811 g, 4.20 mmol) in MeOH (41 mL) at −3 °C and stirred for 1 h to yield 0.671 g of the crude carbinolamide **31** as a viscous pale yellow liquid. ^{1}H NMR (250 MHz): δ = 7:32 (m, 1), 7.23 (bs, 1), 6.29 (bs, 1), 5.10 (bs, 1), 3.84−3.29 (m, 3), 2.61 (m, 2), 2.24 (m, 2), 1.86 (m, 2). IR ($CHCl_3$): 3430, 2960, 1770, and 1690 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 178 (M^+ + 1 − H_2O, 31.3), 177 (M^+ − H_2O, 56.6), 176 (base), 82 (2.29).

***N*-(2-(3-Furyl)ethyl)-6-hydroxy-2-piperidinone 32.** According to the general procedure for the reduction of N-substituted imides, sodium borohydride (1.50 g, 39.4 mmol) was added to imide **28** (0.816 g, 3.94 mmol) in MeOH (38 mL) at −4 °C and stirred for 1 h to provide 0.55 g of the crude carbinolamide **32** as a viscous pale yellow liquid. ^{1}H NMR (250 MHz): δ = 7.37 (m, 1), 7.25 (m, 1), 6.33 (bs, 1), 4.37 (m, 1), 3.90 (m, 1), 3.24 (m, 1), 2.73 (m, 2), 2.38 (m, 2), 1.99 (m, 2), 1.63 (m, 2). IR ($CHCl_3$): 3420, 2960, 1730, and 1640 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 210 (M^+ + 1, 0.74), 209 (M^+, 4.49), 191 (5.26), 128 (22.0), 94 (base), 82 (48.3).

***N*-(3-(3-Furyl)propyl)-5-hydroxy-2-pyrrolidinone 33.** According to the general procedure for the reduction of N-substituted imides, sodium borohydride (3.82 g, 100.5 mmol) was added to imide **29** (2.18 g, 10.52 mmol) in MeOH (l00 mL)

at −4 °C and stirred for 1 h to provide 1.85 g, of the crude carbinolamide **33** as a viscous pale yellow liquid. ^{1}H NMR (250 MHz): δ = 7.38 (m, 1), 7.27 (m, 1), 6.30 (bs, 1), 5.22 (m, 0.5), 4.94 (m, 0.5), 3.34 (m, 2), 2.45 (t, J = 8.3 Hz, 2), 2.40 (m, 4), 1.85 (m, 2). IR ($CHCl_3$): 3400, 3290, 2940, 1720, 1675, and 870 cm^{-1}. EI-MS (70 eV) *m*/*z* (rel intensity): 210 (M^+ + 1, 6.23), 209 (M^+, 17.4), 192 (34.3), 191 (65.0), 128 (8.37), 108 (base), 81 (60.9).

***N*-(3-(3-Furyl)propyl)-6-hydroxy-2-piperidinone 34.** According to the general procedure for the reduction of N-substituted imides, sodium borohydride (35.17 g, 136 mmol) was added to imide **30** (3.0 g, 13.57 mmol) in MeOH (l36 mL) at −4 °C and stirred for 1.25 h to provide 3.02 g of the crude carbinolamide **34** as a viscous pale yellow liquid. ^{1}H NMR (250 MHz): δ = 7.34 (m, 1), 7.24 (m, 1), 6.28 (m, 1), 6.00 (m, 1), 5.14 (m, 1), 3.50 (t, J = 8.3 Hz, 2), 2.46 (m, 4), 2.28 (m, 2), 1.84 (m, 4). IR (neat): 3310, 2960, 1720, 1670, and 780 cm^{-1}. EI-MS (70 eV) *m*/*z* (rel intensity): 206 ($M^+ + 1 - H_2O$, 19.4), 205 ($M^+ - H_2O$, base), 177 (5.76), 149 (5.58), 82 (48.9).

1-Aza-4,5-(2,3a-furyl)bicyclo[4.3.0]nonan-9-one 35. According to the general procedure for the cyclization of carbinolamides, a two-phase mixture of HCO_2H (1.0 mL), carbinolamide **31** (50 mg, 0.256 mmol), and cyclohexane (4.0 mL) was stirred vigorously at 25 °C for 3 min to yield a viscous pale yellow liquid. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 15 g, 20 mm o.d., ethyl acetate−petroleum ether 4:1, 10 mL fractions) using the flash technique. Fractions 10−22 provided 30 mg, 66%, of **35** as a white crystalline solid, mp = 84−87 °C; ^{1}H NMR (250 MHz): δ = 7.28 (m, 1), 6.21 (m, 1), 4.69 (m, 1), 4.35 (dd, J = 19.5, 5.8 Hz, 2), 2.87 (m, 2), 2.70−2.35 (m, 2), 1.89 (m, 2). IR ($CHCl_3$): 3000, 1680, and 900 cm^{-1}. EI-MS (70 eV) *m*/*z* (rel intensity): 178 (M^+ + 1, 64.8), 177 (M^+, base). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.69; H, 6.13; N, 7.71.

1-Aza-4,5-(2,3a-furyl)bicyclo[4.4.0]decan-10-one 36. According to the general procedure for the cyclization of carbinolamides, a two-phase mixture of HCO_2H (2.4 mL), carbinol amide **32** (128 mg, 0.612 mmol), and cyclohexane (9.5 mL) was stirred vigorously at 25 °C for 2 min to afford a viscous white-water liquid. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 39 g, 30 mm o.d., ethyl acetate−petroleum ether 4:1, 30 mL fractions) using the flash technique. Fractions 9−15 provided 58 mg, 50%, of **36** as a white crystalline solid, mp = 82−84 °C. ^{1}H NMR (250 MHz): δ = 7.25 (m, 1), 6.21 (m, 1), 4.98 (m, 2), 4.50 (m, 1), 2.65 (m, 2), 2.39 (m, 2), 1.92−1.55 (m, 4). IR ($CHCl_3$): 2965, 2860, and 1630 cm^{-1}; EIMS (70 eV): 192 (M^+ + 1, 13.7), 191 (M^+, base), 190 (M^+ − 1, 85.1), 121 (45.0), 120 (54.0). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.14; H, 6.60; N, 7.41.

1-Aza-5,6-(2,3a-furyl)bicyclo[5.3.0]decan-11-one 37. According to the general procedure for the cyclization of carbinolamides, a two-phase mixture of HCO_2H (3.1 mL), carbinol amide **33** (1.66 g, 7.94 mmol), and cyclohexane (124 mL) was stirred vigorously at 25 °C for 3 min to yield a tan solid. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 50 g, 40 mm o.d., ethyl acetate−petroleum ether 4:1, 50 mL fractions) using the flash technique. Fractions 7−14 provided 1.07 g, 71%, of **37** as a pale yellow liquid. ^{1}H NMR (250 MHz): δ = 7.20 (m, 1), 6.14 (m, 1), 4.75 (m, 1), 4.30 (m, 2), 2.88 (m, 2), 2.56 (m, 2), 2.00−1.71 (m, 4). IR (neat): 2940, 2860, 1660, and 920 cm^{-1}. EI-MS (70 eV) *m*/*z* (rel intensity): 192 (M^+ + 1, 23.4), 191 (M^+, base), l90 (M^+ − 1, 98.3), 135 (33.5), 134 (46.4), 120 (28.5). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.71; H, 6.52; N, 6.94.

1-Aza-5,6-(2,3a-furyl)bicyclo[5.4.0]undecan-11-one 38. According to the general procedure for the cyclization of carbinolamides, a two-phase mixture of HCO_2H (3.6 mL), carbinol amide **34** (2.09 g, 9.0 mmol), and cyclohexane (144 mL) was stirred vigorously for 3 min to yield 2.08 g of a viscous yellow liquid. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 60 g, 40 mm o.d., ethyl acetate−petroleum ether 4:1, 50 mL fractions) using the flash technique. Fractions 6−17 provided 1.23 g, 67%, of **38** as a white solid, mp = 72−74 °C. ^{1}H NMR (250 MHz): δ = 7.23 (m, 1), 6.19 (m, 1), 4.62 (t, J = 5.0 Hz, 2), 4.56 (t, J = 4.2 Hz, 1), 2.72 (m, 2), 2.43 (m, 2), 2.09 (m, 2), 1.91 (m, 2), 1.78 (m, 2). IR ($CHCl_3$): 3380, 2940, 2870, 1620, and 880 cm^{-1}. EI-MS (70 eV) *m*/*z* (rel intensity): 206 (M^+ + 1, 14.6), 205 (M^+, 92.3), 204 (M^+ − 1, 18.7), 135 (base), 134 (31.6), 120 (22.5). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.92. Found: C, 69.99; H, 7.42; N, 6.89.

***N*-(2-(5-Methyl-2-furyl)ethyl)-2,5-pyrrolidinedione 40.** According to the general procedure for the preparation of N-substituted imides, 2-(5-methyl-2-furyl)ethanol **39** (1.62 g, 12.86 mmol), triphenylphosphine (3.88 g, 14.79 mmol), and succinimide (1.27 g, 12.86 mmol) in THF (10.8 mL) were allowed to react with diethyl azodicarboxylate (2.58 g, 14.79 mmol) to provide 4.38 g of crude product. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 130 g, 50 mm o.d., ethyl acetate−petroleum ether 30:70, 125 mL fractions) using the flash technique. Fractions 15−22 provided 4.28 g, 83%, of **40** as a viscous yellow liquid. ^{1}H NMR (250 MHz): δ = 5.80 (m, 1), 5.75 (m, 1), 3.49 (t, J = 7.00 Hz, 2), 2.83 (t, J = 7.50 Hz, 2), 2.64 (s, 4), 2.20 (s, 3). IR (CCl_4): 3300, 2940, 2860, 1770, 1700, and 820 cm^{-1}. EI-MS (70 eV) *m*/*z* (rel intensity): 208 (M^+ + 1, 0.53), 207 (M^+, 5.17), 108 (base), 95 (53.7). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.57; H, 6.42; N, 6.69.

***N*-(2-(5-Methyl-2-furyl)ethyl)-2,6-piperidinedione 41.** According to the general procedure for the preparation of N-substituted imides, 2-(5-methyl-2-furyl)ethanol **39** (5.03 g, 40 mmol), triphenylphosphine (12.06 g, 46 mmol), and glutarimide (4.52 g, 40 mmol) in THF (50 mL) were allowed to react with diethyl azodicarboxylate (8.01 g, 46 mmol) to provide 7.18 g of crude product. The crude product was purified by chromatography on a column of silica gel (60−230 mesh, 250 g, 60 mm o.d., ethyl acetate−petroleum ether 30:70, 125 mL fractions) using the flash technique. Fractions 12−22 provided 4.85 g, 55%, of **41** as a white solid, mp 64−67 °C. ^{1}H NMR (60 MHz): δ = 5.92 (m, 2), 4.12 (t, J = 8.0 Hz, 2), 2.87 (t, J = 8.0 Hz, 2), 2.70 (t, J = 6.0 Hz, 4), 2.38 (s, 3), 2.02 (m, 2). IR (CCl_4): 3280, 2980, 1730, and 1680 cm^{-1}. EI-MS (70 eV) *m*/*z* (rel intensity): 221 (M^+, 2.14), 108 (base), 95 (75.8). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.22; H, 6.72; N, 6.30.

***N*-(2-(5-Methyl-2-furyl)ethyl)-5-hydroxy-2-pyrrolidinone 42.** According to the general procedure for the reduction of N-substituted imides, sodium borohydride (2.07 g, 54.6 mmol) was added to imide **40** (1.13 g, 5.46 mmol) in MeOH (55 mL) at −4 °C and stirred for 1 h to provide 1.13 g, 99%, of the crude carbinolamide **42** as a viscous pale yellow liquid. ^{1}H NMR (250 MHz): δ = 5.89 (m, 1), 5.81 (m, 1), 4.98 (m, 1), 3.55 (m, 2), 3.63 (bs, 1), 2.82 (t, J = 7.0 Hz, 2), 2.50 (m, 1), 2.25 (n, 2), 1.85 (m, 1). IR (CCl_4): 3340, 2920, 1680, 1570, and 980 cm^{-1}. EI-MS (70 eV) *m*/*z* (rel intensity): 209 (M^+, 10.2), 191 ($M^+ - H_2O$, 12.6), 108 (base), 95 (21.1).

***N*-(2-(5-Methyl-2-furyl)ethyl)-6-hydroxy-2-piperidinone 43.** According to the general procedure for the reduction of N-substituted imides, sodium borohydride (3.44 g, 90.5 mmol) was added to imide **41** (2.0 g, 9.05 mmol) in MeOH (90 mL) at −4 °C and stirred for 1 h to provide 1.98 g, 98%, of the crude carbinolamide **43** as a viscous pale yellow liquid. ^{1}H NMR (250 MHz): δ = 5.92 (m, 1), 5.85 (m, 1), 4.73 (bs, 1), 3.66 (m, 2), 3.37 (bs, 1), 2.89 (t, J = 7.0 Hz, 2), 2.36 (m, 2), 2.26 (s, 3), 1.60−2.13 (4). IR(neat): 3280, 2940, 1720, and 850 cm^{-1}. EI-MS (70 eV) *m*/*z* (rel intensity): 223 (M^+, 4.56), 205 ($M^+ - H_2O$, 1.58), 108 (base), 95 (12.1).

1-Aza-5-(2-oxopropyl)bicyclo[4.3.0]nonane-4,9-dione 44. According to the general procedure for the cyclization of carbinolamides, a two-phase mixture of HCO_2H (22 mL), carbinol amide **42** (1.17 g, 5.6 mmol), and cyclohexane (90 mL) was stirred vigorously for 3 min to yield 1.10 g of a viscous yellow liquid. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 60 g, 40 mm o.d., ethyl acetate−methanol−triethylamine 93:4.6:2.4, 50 mL fractions) using the flash technique. Fractions 8−15 provided 0.87 g, 75%, of **44** as a viscous, pale yellow liquid. ^{1}H NMR

(250 MHz): δ = 4.37 (m, 1), 3.50 (m, 2), 2.85 (m, 3), 2.44 (m, 2), 2.26 (m, 2), 2.19 (s, 3), 1.72 (m, 2). IR ($CHCl_3$): 3000, 2910, 1720, and 1690 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 210 ($M^+ + 1$, 1.59), 152 (base), 96 (71.9). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.72; H, 7.53; N, 7.01.

1-Aza-5-(2-oxopropyl)bicyclo[4.4.0]decane-4,10-dione 45. According to the general procedure for the cyclization of carbinolamides, a two-phase mixture of HCO_2H (27.5 mL), carbinol amide **43** (1.44 g, 6.46 mmol), and cyclohexane (110 mL) was stirred vigorously for 3 min to yield 1.34 g of a viscous yellow liquid. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 70 g, 40 mm o.d., ethyl acetate−methanol−triethylamine 93:4.6:2.4, 50 mL fractions) using the flash technique. Fractions 9−14 provided 0.922 g, 64%, of **45** as a viscous, pale yellow liquid. ^{1}H NMR (250 MHz): δ = 4.98 (m, 1), 3.58 (m, 2), 2.89 (m, 3), 2.54 (m, 4), 2.24 (s, 3), 1.54−2.00 (m, 4). IR ($CC1_4$): 2960, 2880, 1770, and 1700 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 224 ($M^+ + 1$, 2.32), 166 (base), 110 (48.2). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.67; H, 8.03; N, 6.49.

1-Aza-4,5-(2,3b-(5-methylfuryl))bicyclo[4.3.0]nonan-9-one 46. To a stirring solution of carbinolamide **42** (0.130 g, 0.622 mmol) in CH_2Cl_2 (10 mL), cooled in a −20 °C bath, were added in order triethylamine (0.203 mL, 1.86 mmol) and methanesulfonyl chloride (0.089 g, 0.933 mmol). The reaction mixture was allowed to warm to room temperature over 3 h and was quenched with saturated aqueous $NaHCO_3$ (20 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 20 mL), the combined organic phases were washed with brine (60 mL), dried ($MgSO_4$), and concentrated in vacuo to give crude **46** as a clear, colorless oil. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 10 g, 20 mm o.d.; EtOAc−hexanes, 2:1) using the flash technique. Fractions 12−27 gave 96 mg (81%) of **46** as a clear, colorless oil. ^{1}H NMR (250 MHz): δ = 5.84 (s, 1), 4.59 (m, 1), 4.43 (dd, J = 9.36, 6.21 Hz, 1), 3.55 (m, 1), 2.33−3.05 (4), 2.26 (s, 3), 1.73 (m, 2). IR (neat): 2950, 2922, 1702, and 825 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 192 ($M^+ + 1$, 13.78), 191 (M^+, base), 135 (27.61), 134 (44.59), 91 (17.71). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.19; H, 7.17; N, 7.56.

***N*-(2-(5-Methyl-3-furyl)ethyl)-2,5-pyrrolidinedione 48.** According to the general procedure for the preparation of N-substituted imides, 2-(5-methyl-3-furyl)ethanol **47** (3.5 g, 27.7 mmol), triphenylphosphine (8.01 g, 30.47 mmol), and succinimide (3.03 g, 30.47 mmol) in THF (100 mL) were allowed to react with diethyl azodicarboxylate (5.29 g, 30.47 mmol) provide 6.24 g of crude product. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 250 g, 70 mm o.d., ethyl acetate−petroleum ether 30:70, 75 mL fractions) using the flash technique. Fractions 15−25 provided 5.31 g, 86%, of **48** as a viscous pale yellow liquid. ^{1}H NMR (300 MHz): δ = 7.09 (s, 1), 5.90 (s, 1), 3.67 (t, J = 7.75 Hz, 2), 2.68 (s, 4), 2.67 (m, 2), 2.24 (s, 3). IR (neat): 2954, 2925, 1770, 1697, and cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 207 (M^+, 21.8), 108 (base), 95 (15.7). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.84; H, 6.37; N, 6.69.

***N*-(2-(5-Methyl-3-furyl)ethyl)-2,6-piperidinedione 49.** According to the general procedure for the preparation of N-substituted imides, 2-(5-methyl-3-furyl)ethanol **47** (3.5 g, 27.7 mmol), triphenylphosphine (8.01 g, 30.47 mmol), and glutarimide (3.46 g, 30.47 mmol) in THF (100 mL) were allowed to react with diethyl azodicarboxylate (5.29 g, 30.47 mmol) to provide 6.07 g of crude product. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 250 g, 70 mm o.d., ethyl acetate−petroleum ether 30:70, 75 mL fractions) using the flash technique. Fractions 12−27 provided 5.44 g, 83%, of **49** as a viscous pale yellow liquid. ^{1}H NMR (300 MHz): δ = 7.09 (s, 1), 5.92 (s, 1), 3.91 (m, 2), 2.63 (t, J = 6.53 Hz, 4), 2.58 (m, 2), 2.24 (s, 3), 1.91 (m, 2). IR (neat): 2964, 2923, 1724, and 1674 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 221 (M^+, 23.5), 108 (base), 94 (27.7). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.97; H, 6.76; N, 6.20.

1-Aza-4,5-(2,3a-(5-methyl)furyl)bicyclo[4.3.0]nonan-9-one 50. According to the general procedure for the reduction of N-substituted imides, sodium borohydride (0.54 g, 14 mmol) was added to imide **48** (0.296 g, 1.4 mmol) in MeOH (30 mL) at −4 °C and stirred for 1 h to provide the crude carbinolamide as a viscous pale yellow liquid. According to the general procedure for the cyclization of carbinolamides, a two-phase mixture of HCO_2H (6 mL), the carbinolamide prepared above, and cyclohexane (30 mL) was stirred vigorously at 25 °C for 3 min to yield a viscous pale yellow liquid. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 50 g, 40 mm o.d., ethyl acetate−petroleum ether 4:1, 50 mL fractions) using the flash technique. Fractions 15−30 provided 0.235 g, 87%, of **50** as a clear colorless, viscous oil. ^{1}H NMR (300 MHz): δ = 5.83 (s, 1), 4.70 (m, 1), 4.35 (dd, J = 13.08, 5.90 Hz, 1), 2.89 (m, 1), 2.30−2.70 (5), 2.27 (s, 3), 1.90 (m, 1). IR (neat): 2977, 2932, 1708, and 1445 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 191 (M^+, 39.6), 190 (base), 176 (32.3). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.22; H, 6.81; N, 7.14.

1-Aza-4,5-(2,3a-(5-methyl)furyl)bicyclo[4.4.0]decan-10-one 51. According to the general procedure for the reduction of N-substituted imides, sodium borohydride (0.6 g, 15.8 mmol) was added to imide **49** (0.349 g, 1.58 mmol) in MeOH (30 mL) at −4 °C and stirred for 1 h to provide the crude carbinolamide as a viscous pale yellow liquid. According to the general procedure for the cyclization of carbinolamides, a two-phase mixture of HCO_2H (6 mL), the carbinolamide prepared above, and cyclohexane (30 mL) was stirred vigorously at 25 °C for 3 min to yield a viscous pale yellow liquid. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 50 g, 40 mm o.d., ethyl acetate−petroleum ether 4:1, 50 mL fractions) using the flash technique. Fractions 17−27 provided 0.154 g, 48%, of **51** as a clear colorless, viscous oil. ^{1}H NMR (300 MHz): δ = 5.64 (s, 1), 5.26 (dd, J = 13.48, 4.82 Hz, 1), 4.12 (m, 1), 1.90−2.70 (6), 2.08 (s, 3), 1.10−1.45 (3). IR (neat): 2978, 2863, 1657, and 846 cm^{-1}. EI-MS (70 eV) *m/z* (rel intensity): 205 (M^+, base), 204 (98.8), 190 (57.7), 135 (56.5), 134 (57.6). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.98; H, 7.12; N, 6.69.

General Procedure for the Preparation of Aryl Furans. 2-(4-Trifluoromethyl)phenylfuran 54. To a solution of 2-tri-*n*-butylstannylfuran (36.85 g, 0.103mol) and 4-bromobenzotrifluoride (24.426 g, 0.108mol) in toluene (350 mL) was added a catalytic amount (50 mg) of tetrakis(triphenylphosphine)palladium(0). The mixture was refluxed for 5 h, and additional 50 mg quantities were added at 1 h intervals during this reflux period. Upon completion, the mixture was cooled to room temperature followed by filtration over a pad of Celite and silica gel, and the filter cake was rinsed with toluene (150 mL). The toluene was removed in vacuo to give the crude product as a yellow semisolid. The crude product was purified by chromatography on a column of silica gel (60−230 mesh, 500 g, 70 mm o.d., ethyl acetate−hexanes 5:95, 250 mL fractions) using the flash technique. Fractions 12−21 afforded 25.20 g of the target compound **54** contaminated with tri-*n*-butylstannyl bromide as a clear colorless oil. This material was carried into the next step without further purification. ^{1}H NMR (300 MHz): δ = 7.76 (d, J = 8.1 Hz, 2), 7.62 (d, J = 8.3 Hz, 2), 7.52 (d, J = 1.3 Hz, 1), 6.76 (d, J = 3.4 Hz, 1), 6.51 (dd, J = 3.4, 1.8 Hz, 1).

2-Phenylfuran 55. According to the general procedure for the preparation of aryl furans, 2-tri-*n*-butylstannylfuran (5.270 g, 14.76 mmol), 4-bromobenzene (2.386 g, 15.195 mmol), and a catalytic amount of palladium catalyst (50 mg) were refluxed, in toluene (40 mL), for 24 h to provide the crude product **55** as yellow oil. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 200 g, 20 mm o.d., petroleum ether, 20 mL fractions) using the flash technique. Fractions 4−12 provided 2.145 g, 100%, of **55**[30] as a yellow oil. ^{1}H NMR (300 MHz): δ = 7.71 (br d, J = 8.0 Hz, 2), 7.49 (d, J = 0.84 Hz, 1), 7.44−7.39 (m, 2), 7.31−7.26 (m, 1), 6.67 (d, J = 3.4 Hz, 1), 6.50 (dd, J = 3.2 Hz, 1.0 Hz, 1). IR

(neat): 1609, 1507, 1479, and 885 cm^{-1}. MS (EI) *m/z* (rel intensity): 145 (10), 144 (M^+, base). HRMS (EI): calcd for $C_{10}H_8O$ 144.0575, found 144.0572.

2-(4-Methoxy)phenylfuran 56. According to the general procedure for the preparation of arylfurans, 2-tri-*n*-butylstannylfuran (4.876 g, 13.66 mmol), 4-bromoanisole (2.689 g, 14.38 mmol), and a catalytic amount of palladium catalyst (50 mg) were refluxed, in toluene (40 mL), for 18 h to provide the crude product **56** as yellow oil. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 400 g, 50 mm o.d., hexanes, 50 mL fractions) using the flash technique. Purification provided 2.044 g, 86%, of **56** as a white crystalline solid, mp = 37−38 °C (lit.[30d] mp 53−54 °C). ^1H NMR (300 MHz): δ = 7.60 (d, J = 8.9 Hz, 2), 7.42 (m, 1), 6.92 (d, J = 8.9 Hz, 2), 6.51 (d, J = 3.5 Hz, 1), 6.44 (dd, J = 3.3, J = 1.8 Hz, 1), 3.83 (s, 3). IR (mull): 1515, 1484, 1301, 1254, and 834 cm^{-1}. MS (EI); *m/z* (rel intensity) 175 (12), 174 (M^+, base), 159 (64). HRMS (EI): calcd for $C_{11}H_{10}O_2$ 174.0681, found 174.0676.

General Procedure for the Synthesis of 5-Arylfuran 2-Ethanols. 2-(5-[4-Trifluoromethyl]phenyl-2-furyl)ethanol 57. To a solution of 2-(4-trifluoromethyl)phenylfuran **54** (21.248 g, 0.102 mol) in THF (300 mL), chilled in an ice−H_2O bath, was added *n*-butyllithium (n-BuLi, 90 mL, 0.144 mmol). The mixture was stirred at 0 °C for 1 h before warming to room temperature and stirring for 3 h. After cooling in a dry ice−^{i}PrOH bath, the mixture was treated with ethylene oxide (7.974 g, 0.181mol). The solution was then allowed to warm to room temperature overnight. The reaction was quenched by pouring into ice (300 g)−saturated aqueous NH_4Cl (200 mL). The mixture was extracted with ethyl acetate (2 × 250 mL), and the organic extracts were combined, washed with brine (2 × 200 mL), and concentrated in vacuo to afford the crude product **57** as a brown oil (21.25 g). The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 1000 g, 70 mm o.d., ethyl acetate−hexanes 2:98, 200 mL) using the flash technique. Purification provided 11.74 g, 46%, of **57** as a white solid, mp = 88−89 °C. ^1H NMR (300 MHz): δ = 7.71 (d, J = 8.2 Hz, 2), 7.60 (d, J = 8.3 Hz, 2), 6.69 (d, J = 3.3 Hz, 1), 6.25 (d, J = 3.2 Hz, 1), 3.96 (t, J = 6.3 Hz, 2), 2.99 (t, J = 6.3 Hz, 2). IR (mull): 3276, 1617, and 844 cm^{-1}. MS (EI); *m/z* (rel intensity) 256 (M^+, 21), 225 (base). Anal. Calcd for $C_{13}H_{11}F_3NO_2$: C, 60.94; H, 4.33; F, 22.24. Found: C, 60.71; H, 4.17; F 21.97.

2-(5-Phenyl-2-furyl)ethanol 58. According to the general procedure for the preparation of furyl alcohols, 2-phenylfuran **55** (12.504 g, 86.83 mmol) in THF (300 mL) was sequentially treated with n-BuLi (76 mL, 0.122 mmol) and ethylene oxide (5.759 g, 0.131 mmol) to afford the crude product **58** as a brown oil (17.98 g). The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 600 g, 50 mm o.d., $CHCl_2$, 100 mL fractions) using the flash technique. Purification provided 13.268 g, 81%, of **58**[31] as a yellow oil. ^1H NMR (300 MHz): δ = 7.64 (m, 2), 7.37 (m, 2), 7.23 (m, 1), 6.57 (d, J = 3.2 Hz, 1), 6.20 (d, J = 3.2 Hz, 1), 3.93 (t, J = 6.3 Hz, 2), 2.96 (t, J = 6.3 Hz, 2). IR (neat): 3357, 2954, and 1595 cm^{-1}. MS (EI); *m/z* (rel intensity) 188 (M^+, 29), 157 (base). HRMS (EI): calcd for $C_{12}H_{12}O_2$ 188.0837, found 188.0841.

2-(5-[4-Methoxy]phenyl-2-furyl)ethanol 59. According to the general procedure for the preparation of furyl alcohols, 2-(4-methoxy)phenylfuran **56** (19.3 g, 0.111 mmol) in THF (400 mL) was sequentially treated with n-BuLi (83 mL, 0.133 mmol) and ethylene oxide (6.379 g, 0.145 mmol) to afford the crude product **59** as a brown oil (5.85 g). The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 600 g, 50 mm o.d., $CHCl_2$, 100 mL fractions) using the flash technique. Purification provided 18.15 g, 75%, of **59**[31] as a white solid, mp = 49−50 °C (lit.[31] mp 61−62 °C). ^1H NMR (300 MHz): δ = 7.56 (d, J = 8.9 Hz, 2), 6.90 (d, J = 8.9 Hz, 2), 6.42 (d, J = 3.2 Hz, 1), 6.16 (d, J = 3.3 Hz, 1), 3.92 (t, J = 6.3 Hz, 2), 3.83 (s, 3), 2.95 (t, J = 6.2 Hz, 2), 0.89 (t, J = 7.2 Hz, 1). IR (mull): 3246, 1501, and 834 cm^{-1}. MS (EI): *m/z* (rel intensity) 219 (5), 218 (M^+, 32), 188 (13), 187 (base). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.77; H, 6.53.

***N*-(2-(5-[4-Trifluoromethyl]phenyl-2-furyl)ethyl)-2,5-pyrrolidinedione 60.** According to the general procedure for the preparation of N-substituted imides, alcohol **57** (6.17 g, 24.13 mmol), triphenylphosphine (7.01 g, 26.73 mmol), and succinimide (2.82 g, 28.47 mmol) in THF (100 mL) were allowed to react with diethyl azodicarboxylate (4.64 g, 26.66 mmol) to provide the crude product **60**. The crude product was purified by chromatography on a column of sllica gel (60−230 mesh, 500 g, 50 mm o.d., CH_2Cl_2, 100 mL fractions) using the flash technique. Purification provided 5.40 g, 68%, of **60** as a pale yellow crystalline solid, mp = 161−163 °C. ^1H NMR (300 MHz): δ = 7.71 (d, J = 8.3 Hz, 2), 7.59 (d, J = 8.3 Hz, 2), 6.64 (d, J = 3.3 Hz, 1), 6.20 (d, J = 3.3 Hz, 1), 3.89 (t, J = 7.1 Hz, 2), 3.03 (t, J = 7.1 Hz, 2), 2.68 (s, 4). IR (mull): 1703, 1616, and 839 cm^{-1}. MS (EI): *m/z* (rel intensity) 337 (M^+, 10), 239 (15), 238 (base). HRMS (EI): calcd for $C_{17}H_{14}F_3NO_3$ 337.0926, found 337.0932. Anal. Calcd for $C_{17}H_{14}F_3NO_3$: C, 60.54; H, 4.18; N, 4.15. Found: C, 60.20; H, 4.23; N, 4.22.

***N*-(2-(5-[4-Trifluoromethyl]phenyl-2-furyl)ethyl)-2,6-piperidinedione 61.** According to the general procedure for the preparation of N-substituted imides, alcohol **57** (5.56 g, 21.72 mmol), triphenylphosphine (6.28 g, 23.94 mmol), and glutarimide (2.85 g, 25.26 mmol) in THF (100 mL) were allowed to react with diethyl azodicarboxylate (4.20 g, 24.12 mmol) to provide the crude product **61**. The crude product was purified by chromatography on a column of sllica gel (60−230 mesh, 400 g, 50 mm o.d., CH_2Cl_2, 100 mL fractions) using the flash technique. Purification provided 6.33 g, 83%, of **61** as a pale yellow crystalline solid, mp = 129−130 °C. ^1H NMR (300 MHz): δ = 7.71 (d, J = 8.2 Hz, 2), 7.60 (d, J = 8.3 Hz, 2), 6.65 (d, J = 3.3 Hz, 1), 6.16 (d, J = 3.3 Hz, 1), 4.12 (t, J = 7.2 Hz, 2), 2.96 (t, J = 7.2 Hz, 2), 2.62 (t, J = 6.5 Hz, 2), 1.90 (m, 2). IR (mull): 1670, 1618, and 838 cm^{-1}. MS (EI): *m/z* (rel intensity) 351 (M^+, 7), 239 (17), 238 (base). Anal. Calcd for $C_{18}H_{16}F_3NO_3$: C, 61.54; H, 4.59; N, 3.99. Found: C, 61.77; H, 4.68; N, 4.02.

***N*-(2-(5-Phenyl-2-furyl)ethyl)-2,5-pyrrolidinedione 62.** According to the general procedure for the preparation of N-substituted imides, alcohol **58** (6.67 g, 35.49 mmol), triphenylphosphine (10.04 g, 38.31 mmol), and succinimide (4.07 g, 41.10 mmol) in THF (150 mL) were allowed to react with diethyl azodicarboxylate (6.74 g, 38.73 mmol) to provide the crude product **62**. The crude product was purified by chromatography on a column of sllica gel (60−230 mesh, 500 g, 50 mm o.d., CH_2Cl_2, 100 mL fractions) using the flash technique. Purification provided 8.5 g, 89%, of **62** as a white crystalline solid, mp = 108−109 °C. ^1H NMR (300 MHz): δ = 7.62 (m, 2), 7.36 (m, 2), 7.22 (m, 1), 6.52 (d, J = 3.3 Hz, 1), 6.15 (d, J = 3.3 Hz, 1), 3.85 (t, J = 7.2 Hz, 2), 3.01 (t, J = 7.2 Hz, 2), 2.67 (s, 4). IR (mull): 1776, 1701, 1437, and 945 cm^{-1}. MS (EI): *m/z* (rel intensity) 269 (M^+, 16), 171 (14), 170 (base). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.05; H, 5.78; N, 5.23.

***N*-(2-(5-Phenyl-2-furyl)ethyl)-2,6-piperidinedione 63.** According to the general procedure for the preparation of N-substituted imides, alcohol **58** (6.59 g, 35.08 mmol), triphenylphosphine (10.18 g, 38.84 mmol), and glutarimide (4.65 g, 41.16 mmol) in THF (150 mL) were allowed to react with diethyl azodicarboxylate (6.74 g, 38.73 mmol) to provide the crude product **63**. The crude product was purified by chromatography on a column of sllica gel (60−230 mesh, 500 g, 50 mm o.d., CH_2Cl_2, 100 mL fractions) using the flash technique. Purification provided 9.08 g, 91%, of **63** as a pale yellow crystalline solid, mp = 77−78 °C. ^1H NMR (300 MHz): δ = 7.64 (m, 2), 7.35 (m, 2), 7.22 (m, 1), 6.52 (d, J = 3.3 Hz, 1), 6.13 (d, J = 3.3 Hz, 1), 4.11 (t, J = 7.2 Hz, 2), 2.94 (t, J = 7.3 Hz, 2), 2.61 (t, J = 6.5 Hz, 2), 1.89 (m, 2H). IR (mull): 1725, 1715, 1666, 1441, and 766 cm^{-1}. MS (EI): *m/z* (rel intensity) 283 (M^+, 29), 171 (41), 170 (base), 158 (7), 157 (55). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.99; H, 6.01; N, 4.76.

***N*-(2-(5-[4-Methoxy]phenyl-2-furyl)ethyl)-2,5-pyrrolidinedione 64.** According to the general procedure for the preparation of N-substituted imides, alcohol **59** (7.66 g, 35.14 mmol), triphenylphosphine (10.39 g, 39.63 mmol), and succin-

imide (4.24 g, 42.77 mmol) in THF (150 mL) were allowed to react with diethyl azodicarboxylate (6.63 g, 38.09 mmol) to provide the crude product **64**. The crude product was purified by chromatography on a column of sllica gel (60−230 mesh, 500 g, 50 mm o.d., CH_2Cl_2, 100 mL fractions) using the flash technique. Purification provided 7.70 g, 73%, of **64** as a pale yellow crystalline solid, mp = 141−142 °C. ^{1}H NMR (300 MHz): δ = 7.54 (d, J = 8.8 Hz, 2), 6.90 (d, J = 8.8 Hz, 2), 6.38 (d, J = 3.2 Hz, 1), 6.12 (d, J = 3.1 Hz, 1), 3.84 (t, J = 7.2 Hz, 2), 3.82 (s, 3), 3.00 (t, J = 7.2 Hz, 2), 2.66 (s, 4). IR (mull): 1766, 1698, 1499, 1444, and 835 cm^{-1}. MS (EI): *m*/*z* (rel intensity) 300 (8), 299 (M$^+$, 42), 201 (14), 200 (base), 188 (13), 187 (97). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.22; H, 5.80; N, 4.67.

***N*-(2-(5-[4-Methoxy]phenyl-2-furyl)ethyl)-2,6-piperidinedione 65.** According to the general procedure for the preparation of N-substituted imides, alcohol **59** (7.53 g, 34.55 mmol), triphenylphosphine (9.93 g, 37.89 mmol), and glutarimide (4.86 g, 43.07 mmol) in THF (150 mL) were allowed to react with diethyl azodicarboxylate (6.63 g, 38.09 mmol) to provide the crude product **65**. The crude product was purified by chromatography on a column of sllica gel (60−230 mesh, 500 g, 50 mm o.d., CH_2Cl_2, 100 mL fractions) using the flash technique. Purification provided 6.41 g, 59%, of **65** as a pale yellow crystalline solid, mp = 138−139 °C. ^{1}H NMR (300 MHz): δ = 7.55 (d, J = 8.8 Hz, 2), 6.89 (d, J = 8.8 Hz, 2), 6.38 (d, J = 3.2 Hz, 1), 6.09 (d, J = 3.2 Hz, 1), 4.10 (t, J = 7.2 Hz, 2), 3.82 (s, 3), 2.92 (t, J = 7.3 Hz, 2), 2.61 (t, J = 6.5 Hz, 4), 1.88 (m, 2). IR (mull): 1725, 1670, 1666, 1500, and 827 cm^{-1}. MS (EI): *m*/*z* (rel intensity) 314 (4), 313 (M$^+$, 22), 201 (14), 200 (base), 188 (5), 187 (36). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found: C, 68.93; H, 6.10; N, 4.48.

***N*-(2-(5-[4-Trifluoromethyl]phenyl-2-furyl)ethyl)-5-hydroxy-2-pyrrolidinone 66.** According to the general procedure for the reduction of N-substituted imides, sodium borohydride (0.87 g, 22.91 mmol) was added to imide **60** (0.778 g, 2.31 mmol) in MeOH (12 mL) at −4 °C. THF (10 mL) was also added to aid in the solubility of the imide. The mixture was stirred for 1 h to provide 0.762 g, 97%, of the crude carbinolamide **66** as a white semisolid. ^{1}H NMR (300 MHz): δ = 7.71 (d, J = 8.3 Hz, 2), 7.61 (d, J = 8.3 Hz, 2), 6.67 (d, J = 3.3 Hz, 1), 6.21 (d, J = 3.3 Hz, 1), 5.08 (brs, 1), 3.78 (m, 1), 3.61 (m, 1), 3.02 (m, 2), 2.59 (m, 1), 2.30 (m, 2), 1.88 (m, 1). IR (mull): 3200, 1644, 1619, and 841 cm^{-1}. MS (EI): *m*/*z* (rel intensity) 339 (M$^+$, 5), 239 (16), 238 (base). HRMS (FAB): calcd for $C_{17}H_{16}F_3NO_3$ + H^1 340.1160, found 340.1154.

***N*-(2-(5-Phenyl-2-furyl)ethyl)-5-hydroxy-2-pyrrolidinone 67.** According to the general procedure for the reduction of N-substituted imides, sodium borohydride (0.31 g, 8.17 mmol) was added to imide **62** (0.219 g, 0.816 mmol) in MeOH (6 mL) at −4 °C. THF (3 mL) was also added to aid in the solubility of the imide. The mixture was stirred for 1 h to provide 0.215 g, 97%, of the crude carbinolamide **67** as a white semisolid. ^{1}H NMR (300 MHz): δ = 7.61 (m, 2), 7.36 (m, 2), 7.23 (m, 1), 6.55 (d, J = 3.2 Hz, 1), 6.16 (d, J = 3.2 Hz, 1), 5.03 (brs, 1), 3.79 (m, J = 6.8 Hz, 1), 3.56 (m, J = 6.8 Hz, 1), 3.00 (td, J = 7.0, 2.1 Hz, 2), 2.54 (m, 1), 2.34−2.19 (m, 2), 1.83 (m, 1). IR (mull): 3207, 3127, 1649, 1546, 1487, and 800 cm^{-1}. MS (EI): *m*/*z* (rel intensity) 271 (M$^+$, 7), 171 (15), 170 (base). HRMS (EI): calcd for $C_{16}H_{17}NO_3$ 271.1208, found 271.1213.

***N*-(2-(5-[4-Methoxy]phenyl-2-furyl)ethyl)-5-hydroxy-2-pyrrolidinone 68.** According to the general procedure for the reduction of N-substituted imides, sodium borohydride (0.294 g, 7.73 mmol) was added to imide **64** (0.226 g, 0.756 mmol) in MeOH (3 mL) at −4 °C. THF (3 mL) was also added to aid in the solubility of the imide. The mixture was stirred for 1.5 h to provide 0.215 g, 95%, of the crude carbinolamide **68** as a white semisolid. ^{1}H NMR (300 MHz): δ = 7.55 (d, J = 8.9 Hz, 2), 6.90 (d, J = 8.9 Hz, 2), 6.40 (d, J = 3.2 Hz, 1), 6.13 (d, J = 3.2 Hz, 1), 5.02 (m, 1), 3.82 (s, 3), 3.82−3.70 (m, 3), 3.57 (m, 1), 2.98 (t, J = 6.9 Hz, 2), 2.62−2.10 (2), 1.85 (m, 1). IR (mull): 3157, 1643, 1619, 1503, 1445, and 826 cm^{-1}. MS (EI): *m*/*z* (rel intensity) 301 (M$^+$, 13), 212 (4), 201 (16), 200 (base), 188 (7), 187 (47). HRMS (EI): calcd for $C_{17}H_{19}NO_4$ 301.1314, found 301.1314.

***N*-(2-(5-[4-Trifluoromethyl]phenyl-2-furyl)ethyl)-6-hydroxy-2-piperidinone 69.** According to the general procedure for the reduction of N-substituted imides, sodium borohydride (1.07 g, 28.13 mmol) was added to imide **61** (0.98 g, 2.81 mmol) in MeOH (14 mL) at −4 °C. THF (6 mL) was also added to aid in the solubility of the imide. The mixture was stirred for 1 h to provide 1.01 g, 99%, of the crude carbinolamide **69** as a white solid, mp = 104−106 °C. ^{1}H NMR (300 MHz): δ = 7.69 (d, J = 8.4 Hz, 2), 7.58 (d, J = 8.4 Hz, 2), 6.64 (d, J = 3.3 Hz, 1), 6.17 (d, J = 3.3 Hz, 1), 4.78 (dt, J = 7.2, 3.6 Hz, 1), 3.90 (m, 1), 3.59 (m, 1), 3.10−2.85 (2), 2.50−1.50 (6). IR (mull): 3303, 1644, 1619, 1551, and 839 cm^{-1}. MS (EI): *m*/*z* (rel intensity) 353 (M$^+$, 3), 239 (16), 238 (base). HRMS (EI): calcd for $C_{18}H_{18}F_3NO_3$ 353.1239, found 353.1246.

***N*-(2-(5-Phenyl-2-furyl)ethyl)-6-hydroxy-2-piperidinone 70.** According to the general procedure for the reduction of N-substituted imides, sodium borohydride (0.325 g, 8.57 mmol) was added to imide **63** (0.233 g, 0.824 mmol) in MeOH (4 mL) at −4 °C. THF (2 mL) was also added to aid in the solubility of the imide. The mixture was stirred for 1.5 h to provide 0.244 g, 99%, of the crude carbinolamide **70** as a viscous, colorless oil. ^{1}H NMR (300 MHz): δ = 7.62 (d, J = 7.3 Hz, 2), 7.36 (t, J = 7.3 Hz, 2), 7.22 (t, J = 7.3 Hz, 1), 6.54 (d, J = 3.3 Hz, 1), 6.13 (d, J = 3.3 Hz, 1), 5.88 (brd, J = 7.7 Hz, 1), 5.02 (dt, J = 7.7, 4.4 Hz, 1), 3.80−3.70 (2), 2.96 (t, J = 7.0 Hz, 2), 2.50 (m, 2), 2.27 (m, 2), 1.85 (m, 2). IR (neat): 3335, 2954, 1621, 1548, 1485, and 760 cm^{-1}. MS (EI): *m*/*z* (rel intensity) 285 (M$^+$, 4), 17 (15), 170 (base). HRMS (EI): calcd for $C_{17}H_{19}NO_3$ 285.1365, found 285.1366.

***N*-(2-(5-[4-Methoxy]phenyl-2-furyl)ethyl)-6-hydroxy-2-piperidinone 71.** According to the general procedure for the reduction of N-substituted imides, sodium borohydride (1.25 g, 32.90 mmol) was added to imide **65** (1.08 g, 3.44 mmol) in MeOH (14 mL) at −4 °C. THF (10 mL) was also added to aid in the solubility of the imide. The mixture was stirred for 1 h to provide 1.067 g, 98%, of the crude carbinolamide **71** as a white semisolid. ^{1}H NMR (300 MHz): δ = 7.55 (d, J = 8.9 Hz, 2), 6.90 (d, J = 8.9 Hz, 2), 6.39 (d, J = 3.3 Hz, 1), 6.10 (d, J = 3.3 Hz, 1), 5.87 (dt, J = 7.7, 1.6 Hz, 1), 5.02 (dt, J = 7.7, 4.4 Hz, 1), 3.82 (s, 3), 3.76 (m, 3), 2.94 (t, J = 7.0 Hz, 2), 2.50 (t, J = 7.6 Hz, 2), 2.27 (m, 2). IR (mull): 3251, 1618, 1498, and 836 cm^{-1}. MS (EI): *m*/*z* (rel intensity) 315 (M$^+$, 7), 313 (3), 201 (15), 200 (base). HRMS (EI): calcd for $C_{18}H_{21}NO_4$ 315.1470, found 315.1468.

1-Aza-4,5-(2,3b-(5-[4-trifluoromethylphenyl]furyl))-bicyclo[4.3.0]nonan-9-one 72 and 1-Aza-5-(2-oxo-2-[4-trifluoromethylphenyl]ethyl)bicyclo[4.3.0]nonane-4,9-dione 73. According to the general procedure for the cyclization of carbinolamides, a two-phase mixture of HCO_2H (1.0 mL), carbinolamide **66** (91 mg, 0.267 mmol), and cyclohexane (4 mL) was stirred vigorously at 25 °C for 3 min to yield 0.096 g of a viscous, colorless oil. The crude mixture was purified by chromatography on a Chromatotron (CH_2Cl_2, 50 mL fractions). Fractions 5−8 provided 0.0256 g, 30%, of furanoid compound **72** as a viscous, colorless oil. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.46 (s, 4), 6.09 (s, 1), 4.47 (m, 1), 3.97 (m, 1), 2.46 (m, 2), 2.19 (m, 3), 1.82 (m, 1), 1.28 (m, 1). IR (neat): 1692, 1615, 1419, and 844 cm^{-1}. MS (FAB): *m*/*z* (rel intensity) 323 (M$^+$ + 1, 19), 322 (M$^+$, base), 321 (32), 320 (53). HRMS (FAB): calcd for $C_{17}H_{14}F_3NO_2$ + H^1 322.1055, found 322.1065.

Fractions 11−14 provided 0.0305 g, 34%, of dicarbonyl compound **73** as a white solid, mp = 127−129 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.72 (d, J = 8.1 Hz, 2), 7.36 (d, J = 8.1 Hz, 2), 4.30 (m, 1), 3.10 (dd, J = 17.5, 8.0 Hz, 1), 2.90−2.62 (2), 2.44 (m, 1), 2.25−1.90 (5), 1.43 (m, 1), 1.06 (m, 1). IR (mull): 1715, 1694, 1685, 1426, and 998 cm^{-1}. MS (FAB): *m*/*z* (rel intensity) 341 (M$^+$ + 1, 15), 340 (M$^+$, base). HRMS (FAB): calcd for $C_{17}H_{16}F_3NO_3$ + H^1 340.1160, found 340.1166. Anal. Calcd for $C_{17}H_{16}F_3NO_3$: C, 60.18; H, 4.75; N, 4.13. Found: C, 59.84; H, 4.98; N, 4.13.

1-Aza-4,5-(2,3b-(5-[phenyl]furyl))bicyclo[4.3.0]nonan-9-one 74 and 1-Aza-5-(2-oxo-2-[phenyl]ethyl)bicyclo[4.3.0]-nonane-4,9-dione 75. According to the general procedure for the cyclization of carbinolamides, a two-phase mixture of HCO_2H (3.0 mL), carbinolamide **67** (272 mg, 1.0 mmol), and

cyclohexane (12 mL) was stirred vigorously at 25 °C for 3 min to yield 0.294 g of a colorless oil. The crude mixture was purified by chromatography on a column of silica gel (230−400 mesh, 20 g, 10 mm o.d., ethyl acetate−hexanes 30:70, 10 mL fractions) using the flash technique. Fractions 20−43 provided 0.070 g, 28%, of furanoid compound **74** as a yellow semisolid. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.70 (d, J = 8.1 Hz, 2), 7.27 (m, 2), 7.12 (m, 1), 6.16 (s, 3), 4.47 (m, 1), 4.00 (m, 1), 2.62−2.40 (2), 2.19 (m, 3), 1.80 (m, 1), 1.31 (m, 1). IR (neat): 1734, 1687, 1603, 1553, and 762 cm^{-1}. MS (FAB): *m*/*z* (rel intensity) 255 (18), 254 (M^+ + 1, base), 253 (M^+, 55), 252 (30). HRMS (EI): calcd for $C_{16}H_{15}NO_2$ 253.1103, found 253.1092.

Fractions 50−78 provided 0.139 g, 51%, of dicarbonyl compound **75** as a white solid, mp = 107−109 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.96 (m, 2), 7.22−7.13 (3), 4.29 (m, 1), 3.30 (dd, J = 17.6, 7.4 Hz, 1), 2.86−2.75 (2), 2.48 (m, 1), 2.26 (dd, J = 17.6, 3.3 Hz, 1), 2.20−1.95 (4), 1.41 (m, 1), 1.07 (m, 1). IR (mull): 1698, 1684, 1597, and 1439 cm^{-1}. MS (FAB): *m*/*z* (rel intensity) 273 (19), 272 (M^+, base), 270 (12), 186 (54). HRMS (FAB): calcd for $C_{16}H_{17}NO_3$ + H^1 272.1286, found 272.1294. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.67; H, 6.36; N, 4.98.

1-Aza-4,5-(2,3b-(5-[4-methoxyphenyl]furyl))bicyclo[4.3.0]-nonan-9-one 76 and 1-Aza-5-(2-oxo-2-[4-methoxyphenyl]-ethyl)bicyclo[4.3.0]nonane-4,9-dione 77. According to the general procedure for the cyclization of carbinolamides, a two-phase mixture of HCO_2H (2 mL), carbinolamide **68** (0.201 g, 0.667 mmol), and cyclohexane (8 mL) was stirred vigorously at 25 °C for 3 min to yield 207 mg of a colorless oil. The crude product was purified by chromatography on a column of silica gel (230−400 mesh, 20 g, 10 mm o.d., ethyl acetate−hexanes 1:5, 10 mL fractions) using the flash technique. Fractions 15−26 yielded 0.038 g, 20%, of furanoid compound **76** as a pale, yellow solid, mp = 141−143 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.67 (d, J = 8.8 Hz, 2), 6.90 (d, J = 8.8 Hz, 2), 6.10 (s, 1), 4.51 (m, 1), 4.04 (t, J = 7.8 Hz, 1), 3.37 (s, 3), 2.54 (m, 2), 2.20 (m, 3), 1.83 (m, 1), 1.37 (m, 1). IR (mull): 1698, 1684, 1673, 1500, 1444, and 838 cm^{-1}. MS (EI): *m*/*z* (rel intensity) 284 (M^+ + 1, 20), 283 (M^+, base), 282 (26). Anal. Calcd for $C_{17}H_{17}$-NO_3: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.75; H, 6.17; N, 4.73.

Fractions 38−50 yielded 0.124 g, 62%, of dicarbonyl compound **77** as a yellow solid, mp = 135−137 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 8.00 (d, J = 8.9 Hz, 2), 6.75 (d, J = 8.9 Hz, 2), 4.29 (m, 1), 3.36 (dd, J = 17.4, 7.0 Hz, 1), 3.28 (s, 3), 2.84 (m, 2), 2.49 (m, 1), 2.30 (dd, J = 17.4, 3.5 Hz, 1), 2.22−1.90 (4), 1.43 (m, 1), 1.14 (m, 1). IR (mull): 1711, 1702, 1676, 1605, 1578, and 1440 cm^{-1}. MS (FAB): *m*/*z* (rel intensity) 303 (M^+ + 1, 20), 302 (M^+, base). HRMS (FAB): calcd for $C_{17}H_{19}NO_4$ + H^1 302.1392, found 302.1399. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.58; H, 6.34; N, 4.63.

1-Aza-4,5-(2,3b-(5-[4-trifluoromethylphenyl]furyl))-bicyclo[4.4.0]decan-10-one 78 and 1-Aza-5-(2-oxo-2-[4-trifluoromethylphenyl]ethyl)bicyclo[4.4.0]decane-4,10-dione 79. According to the general procedure for the cyclization of carbinolamides, a two-phase mixture of HCO_2H (5.0 mL), carbinolamide **69** (504 mg, 1.43 mmol), and cyclohexane (20 mL) was stirred vigorously at 25 °C for 3 min to yield 0.523 g of a yellow oil. The crude mixture was purified by chromatography on a column of silica gel (230−400 mesh, 20 g, 10 mm o.d., ethyl acetate−hexanes 15:85, 10 mL fractions) using the flash technique. Fractions 20−38 provided 0.110 g, 23%, of furanoid compound **78** as a pale, yellow semisolid. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.48−7.08 (5), 6.15 (s, 1), 5.24 (dd, J = 12.8, 5.8 Hz, 1), 3.97 (m, 1), 2.65−2.10 (6), 1.40−1.05 (2). IR (neat): 1718, 1683, 1639, 1617, 1447, and 846 cm^{-1}. MS (EI): *m*/*z* (rel intensity) 336 (M^+ + 1, 22), 335 (M^+, 99), 334 (25), 265 (28), 264 (26). HRMS (EI): calcd for $C_{18}H_{16}F_3NO_2$ 335.1133, found 335.1136.

Fractions 55−90 provided 0.2522 g, 50%, of diketone **79** as a viscous, pale yellow oil. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.76 (d, J = 8.1 Hz, 2), 7.40 (d, J = 8.1 Hz, 2), 5.02 (m, 1), 3.10 (dd, J = 17.9, 6.3 Hz, 1), 3.05 (m, 1), 2.77 (m, 1), 2.52 (m, 1), 2.42 (dd, J = 17.9, 4.1 Hz, 1), 2.23 (m, 4), 1.38 (m, 2), 1.17−0.96 (2). IR (neat): 1716, 1692, 1645, 1468, 1444, 1412, 1325, 1259, 1241, 1197, 1167, 1128, 1111, 1067, and 1001 cm^{-1}. MS (EI): *m*/*z* (rel intensity) 354 (M^+ + 1, 46), 180 (28), 173 (20), 166 (base), 165 (35). Anal. Calcd for $C_{18}H_{18}F_3NO_3$: C, 61.19; H, 5.13; N, 3.96. Found: C, 61.52; H, 5.04; N, 3.69.

1-Aza-4,5-(2,3b-(5-[phenyl]furyl))bicyclo[4.4.0]decan-10-one 80 and 1-Aza-5-(2-oxo-2-[phenyl]ethyl)bicyclo-[4.4.0]decane-4,10-dione 81. According to the general procedure for the cyclization of carbinolamides, a two-phase mixture of HCO_2H (2.5 mL), carbinolamide **70** (244 mg, 0.856 mmol), and cyclohexane (11 mL) was stirred vigorously at 25 °C for 3 min to yield 0.206 g of a viscous, colorless oil. The crude mixture was purified by chromatography on a column of silica gel (230−400 mesh, 20 g, 10 mm o.d., ethyl acetate−hexanes 30:70, 10 mL fractions) using the flash technique. Fractions 14−30 provided 0.022 g, 10%, of furanoid compound **80** as a viscous, colorless oil. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.72 (brd, J = 7.2 Hz, 2), 7.27 (m, 2), 7.13 (t, J = 7.3 Hz, 1), 6.22 (s, 1), 5.26 (dd, J = 12.7, 5.5 Hz, 1), 3.89 (m, 1), 2.71 (m, 1), 2.50−2.10 (4), 1.72 (m, 1), 1.40−1.10 (3). IR (neat): 2933, 1639, 1466, and 762 cm^{-1}. MS (FAB): *m*/*z* (rel intensity) 268 (M^+ + 1, base), 267 (M^+, 53), 266 (27). HRMS (EI): calcd for $C_{17}H_{17}NO_2$ 267.1259, found 267.1266.

Fractions 50−80 provided 0.125 g, 51%, of dicarbonyl compound **81** as a pale yellow solid, mp = 128−129 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.95 (d, J = 6.9 Hz, 2), 7.24−7.14 (3), 5.00 (m, 1), 3.30 (dd, J = 17.9, 5.6 Hz, 1), 3.06 (m, 1), 2.76 (m, 1), 2.58 (m, 2), 2.22 (m, 4), 1.35 (m, 2), 1.04 (m, 2). IR (mull): 1714, 1687, 1650, 1596, and 1440 cm^{-1}. MS (FAB): *m*/*z* (rel intensity) 287 (M^+ + 1, 20), 286 (M^+, base). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.47; H, 6.68; N, 4.76.

1-Aza-4,5-(2,3b-(5-[4-methoxyphenyl]furyl))bicyclo[4.4.0]-decan-10-one 82 and 1-Aza-5-(2-oxo-2-[4-methoxyphenyl]-ethyl)bicyclo[4.4.0]decane-4,10-dione 83. According to the general procedure for the cyclization of carbinolamides, a two-phase mixture of HCO_2H (2 mL), carbinolamide **71** (0.213 g, 0.677 mmol), and cyclohexane (9 mL) was stirred vigorously at 25 °C for 3 min to yield 0.224 g of a viscous, colorless oil. The crude mixture was purified by chromatography on a column of silica gel (230−400 mesh, 20 g, 10 mm o.d., ethyl acetate−hexanes 30:70, 10 mL fractions) using the flash technique. Fractions 12−20 provided 0.0085 g, 4%, of furanoid compound **82** as a viscous, colorless oil. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.68 (d, J = 8.7 Hz, 2), 6.90 (d, J = 8.7 Hz, 2), 6.16 (s, 1), 5.29 (m, 1), 3.95 (brs, 1), 3.66 (m, 1), 3.39 (s, 3), 2.74 (m, 1), 2.50−2.15 (3), 1.70−1.20 (4). IR (neat): 2932, 1640, 1613, 1500, 1463, and 834 cm^{-1}. MS (FAB): *m*/*z* (rel intensity) 299 (M^+ + 1, 20), 298 (M^+, base), 297 (85), 296 (24). HRMS (EI): calcd for $C_{18}H_{19}NO_3$ 297.1365, found 297.1370.

Fractions 32−42 yielded 0.1088 g, 51%, of dicarbonyl compound **83** as a yellow solid. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.99 (d, J = 8.9 Hz, 2), 6.75 (d, J = 8.9 Hz, 2), 5.00 (m, 1), 3.33 (dd, J = 17.5, 5.0 Hz, 1), 3.29 (s, 3), 3.10 (m, 1), 2.79 (m, 1), 2.68−2.54 (3), 2.25 (m, 3), 1.36 (m, 2), 1.06 (m, 2). IR (neat): 1715, 1675, 1642, 1601, 1576, and 1172 cm^{-1}. MS (EI): *m*/*z* (rel intensity) 315 (M^+, 1), 200 (11), 167 (10), 166 (base). Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.36; H, 6.43; N, 4.19.

Preparation of Monoketal 85. To a solution of **45** (188.8 mg, 0.84 mmol) in CH_2CI_2 (3 mL) cooled to −24 °C in a dry ice−CCl_4 bath was added $TMSOCH_2CH_2OTMS$ (174.4 mg, 0.845 mmol) followed by TMSOTf (31 drops). The cooling bath was maintained at −24 °C for 3 h; then stirring was continued overnight while allowing the yellowish solution to warm to room temperature. Pyridine (15 drops) was added, the solution was cast into saturated aqueous $NaHCO_3$ (5 mL) and the aqueous layer was extracted with CH_2CI_2 (4 × 5 mL). The combined organic layers were washed with 1 N aqueous HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to provide 85.3 mg of a yellow oil. The crude product was purified on a column of silica (230−400 mesh, 20 g, 20 mm o.d., ethyl acetate−methylene chloride−methanol, 8:1:1, 4.5 mL fractions) using the flash technique. Fractions 13−23 provided 210.8 mg, 93%,

of **85** as a colorless, amorphous solid. ^{1}H NMR (250 MHz): δ = 4.77 (ddd, J = 14.4, 6.4, 3.4 Hz, 1), 3.98 (m, 4), 3.3 (m, 1), 2.70−2.16 (5) 2.15 (s, 3), 1.90−1.75 (4), 1.60−1.40 (3). ^{13}C NMR (75.4 MHz): δ = 207, 169, 108, 64.6, 65.0, 58.7, 44.2, 40.3, 39.7, 33.7, 32.9, 29.6, 27.5, 18.5. IR (CCl_4): 2945, 2780, 1715, 1640, and 1440 cm^{-1}. EI-MS (70 eV): 268 (M^+ + 1, 3.4), 224 (10.2), 209 (53.2), 179 (19.4), 150 (15.4), 137 (31.0), 99 (base). Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 70.02; H, 7.85; N, 4.97.

Preparation of Acetate 86. To a solution of **85** (34.9 mg, 0.013 mmol) in dry CH_2Cl_2 (2 mL) were added anhydrous Na_2HPO_4 (720 mg, 5 mmol) and then freshly prepared trifluouroperacetic acid (0.6 mL). The mixture was warmed to reflux for 4 h. After cooling to room temperature, saturated aqueous $Na_2S_2O_4$ was added until the reaction mixture tested negative to peroxides by the starch iodide test. The aqueous layer was concentrated *in vacuo* and taken up in CH_2Cl_2 (10 mL), and the organic layer was dried (Na_2SO_4) and concentrated in vacuo to give 38.8 mg of an amorphous solid which was purified on a column of silica gel (230−400 mesh, 4 g, 20 mm o.d., ethyl acetate−methanol−methylene chloride 8:1:1, 1.5 mL fractions) using the flash technique. Fractions 5−8 provided 18.8 mg, 54%, of **86** as a clear, colorless oil. ^{1}H NMR (250 MHz): δ = 4.70 (ddd, J = 14.4, 6.4, 3.4 Hz, 1), 4.25−4.09 (2), 4.00 (m, 4) 3.58 (m, 1), 2.70 (dt J = 13.1, 3.4 Hz, 1), 2.45 (m, 2), 2.06 (s, 3), 2.00−1.65 (6), 1.56 (dt, J = 14.4, 4.7 Hz, 1). IR ($CHCl_3$): 2980, 1735, and 1625 cm^{-1}. El-MS (70 eV): 284 (M^+ + 1, 6.8), 293 (M^+, 2.8), 224 (10.7), 210 (20.7), 99 (base). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.04; H, 7.28; N, 4.68.

Preparation of Thioketal 87. To a solution of **86** (26.4 mg, 0.093 mmol) in dry CH_2Cl_2 (2 mL) was added 1,3-propanedithiol (20.2 mg, 0.186 mmol) followed by $BF_3{-}OEt_2$ (13.2 mg, 0.093 mmol). After stirring overnight, 10% aqueous NaOH was added (8 mL), and the aqueous layer was extracted with CH_2Cl_2 (4 × 8 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo to give 30 mg of an oil which was purified on a column of silica gel (230400 mesh, 3 g, 20 mm o.d., EtOAc−MeOH−CH_2Cl_2, 40:1:1, 2 mL fractions) using the flash technique. Fractions 8−13 provided 26.7 mg, 87%, of **87** as a colorless oil. ^{1}H NMR (250 MHz): δ = 4.68 (m, 2), 4.20 (dd, J = 11.9, 5.5 Hz, 1), 3.62 (m, 1), 3.19−2.8 (4), 2.70−2.20 (6), 2.03 (s, 3), 1.90−1.50 (6). IR ($CHCl_3$): 3010, 2960, 1730, 1620, and 1440 cm^{-1}. El-MS (70 eV): 330 (M^+ + 1, 10.3), 329 (M^+, 81.0), 222 (60.3), 55 (65.5), 54 (base). Anal. Calcd for $C_{15}H_{23}NO_3S_2$: C, 54.68; H, 7.04; N, 4.25. Found: C, 54.45; H, 6.89; N, 4.14.

(±)-*epi*-Lupinine 10. To a solution of **87** in absolute EtOH (1 mL) was added Raney nickel (0.25 mL) as a slurry in EtOH (commercial Raney Nickel was rinsed with 8 × 5 mL EtOH). After 1 h at room temperature followed by 6 h at reflux, the catalyst was quenched by adding 1 N aqueous HCl (50 mL) and then a few drops of 6 N aqueous HCl. The green solution was extracted with CH_2Cl_2 (4 × 50 mL), and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give 9.1 mg of a brownish-green oil which was purified on a column of silica gel (230−400 mesh, 10 g, 10 mm o.d., EtOAc−CH_2Cl_2−MeOH 40:1:1, 0.5 mL fractions) using the flash technique. Fractions 7−15 provided 5.4 mg, 60%, of the target reduction product as a water-white oil. ^{1}H NMR (250 Mz): δ = 4.81 (m, 1), 4.06 (dd, J = 11.01, 4.2 Hz, 1), 4.00 (dd, J = 11.01, 4.2 Hz, 1), 3.15 (m, 1), 2.50−2.10 (4), 2.04 (s, 3), 1.90−1.30 (8). IR ($CHCl_3$): 3040, 3005, 2960, 1730, 1620, and 1440 cm^{-1}. El-MS (70 eV): 227 (M^+ + 2, 4.4), 226 (M^+ + 1, 34.9), 251 (M^+, 43.9), 197 (17.5), 182 (25.5), 166 (64.8), 151 (56.3), 138 (62.1), 124 (20.8), 112 (84.1), 96 (46.8), 84 (38.1), 69 (89 7), 55 (base).

To a suspension of lithium aluminum hydride (3.5 mg, 0.091 mmol) in THF (1 mL) was added a solution of the above prepared lactam (4.1 mg, 0.0182 mmol) in THF (2 mL). The mixture was heated to reflux overnight, then cooled to room temperature, and carefully quenched with 15% aqueous NaOH (5 drops) and H_2O (5 drops). The mixture was dried over Na_2SO_4 and concentrated *in vacuo to* give 1.9 mg (60%) of **10** as a white semisolid. Recrystallization from petroleum ether gave a white crystalline solid, mp 79−80 °C. ^{1}H NMR (250 MHz): δ = 3.80 (m, 2), 3.00 (m, 2), 2.20−1.60 (10), 1.50−1.00 (5). IR ($CHCl_3$): 3360, 2940, 1400, 1240, 1060, 1000, and 750 cm^{-1}. El-MS (70 eV): 169 (M^+, 40.9), 168 (52.5), 152 (59.2), 138 (60.7), 111 (48.7), 97 (34.9), 83 (base). HRMS (EI): calcd for $C_{10}H_{19}NO$ 169.1467, found 169.1462.

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