JOC Article

# A New Strategy toward Indole Alkaloids Involving an Intramolecular Cycloaddition/Rearrangement Cascade

Albert Padwa,* Michael A. Brodney, Stephen M. Lynch, Paitoon Rashatasakhon, Qiu Wang, and Hongjun Zhang

*Department of Chemistry, Emory University, Atlanta, Georgia 30322*

*chemap@emory.edu*

*Received February 2, 2004*

The intramolecular Diels−Alder reaction between an amidofuran moiety tethered onto an indole component was examined as a strategy for the synthesis of Aspidosperma alkaloids. Furanyl carbamate **23** was acylated using the mixed anhydride **26** to provide amidofuran **22** in 68% yield. Further N-acylation of this indole furnished **27** in 88% yield. Cyclization precursors were prepared by removing the carbamate moiety followed by N-alkylation with the appropriate alkyl halides. Large substituent groups on the amido nitrogen atom causes the reactive s-trans conformation of the amidofuran to be more highly populated, thereby facilitating the Diels−Alder cycloaddition. The reaction requires the presence of an electron-withdrawing substituent on the indole nitrogen in order for the cycloaddition to proceed. Treatment of *N*-allyl-bromoenamide **48** with *n*-$Bu_3SnH$/AIBN preferentially led to the 6-endo trig cyclization product **50**, with the best yield (91%) being obtained under high dilution conditions. The initially generated cyclohexenyl radical derived from **48** produces the pentacyclic heterocycle **50** by either a direct 6-endo trig cyclization or, alternatively, by a vinyl radical rearrangement pathway.

The indole nucleus is a key structural feature found in numerous natural products, many of which exhibit potent pharmacological activity.[1] As a result, the chemistry of substituted indoles has received an enormous amount of attention.[2] It is well-known that indole behaves as an enamine toward electrophiles and undergoes Michael addition to electron-deficient alkenes.[3] Our interest in the synthesis and reactivity of the indole moiety is ongoing and centers around its [4 + 2]-cycloaddition chemistry.[4] Wenkert's previous observations have already demonstrated the feasibility of Diels−Alder chemistry with five-membered aromatic heterocycles.[5] Compounds such a furans, *N*-benzenesulfonylpyrroles, and benzofurans have been used as dienophiles with both 1,3-butadiene and isoprene at elevated temperatures.[6,7] Since indole derivatives could prove to be appropriate starting materials for alkaloid syntheses if suitable cycloaddition chemistry can be developed, selected attempts have been made to use the 2,3-double bond of indole in Diels−Alder reactions.[5−9] However, the electron-rich indole ring shows only a low tendency to act as a dienophile. In bimolecular Diels−Alder reactions that occur with normal electron demand, indole acts as a dienophile only if electron-withdrawing groups are present in the 1- and 3-position.[5,8] Long reaction times and high temperatures are necessary for the reaction to proceed.[5−9] Use of the indole ring in [4 + 2]-cycloaddition chemistry has mainly been limited to Diels−Alder reactions with inverse electron-demand heterodienes.[10−12] Thus, the Snyder group has nicely demonstrated that indoles can react as dienophiles in formal [4 + 2]-cycloadditions with 1,2,4,5-tetrazines, 1,2,4-triazines, pyridazines, and tetra-

(1) Szantay, C. *Pure Appl. Chem*. **1990**, *62*, 1299. Hibino, S.; Choshi, T. *Nat. Prod. Rep*. **2002**, *19*, 148 and earlier reviews in the series.

(2) For recent reviews, see: Sundberg, R. J. *Indoles*; Academic Press: New York, 1996. Gribble, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. Gribble, G. *Contemp. Org. Synth*. **1994**, *1*, 145. Alvarez, M.; Salas, M.; Joule, J. A. *Heterocycles* **1991**, *32*, 1391. Baudin, J. B.; Comenil, M. G.; Julia, S. A.; Lorne, R.; Mauclaire, L. *Bull. Soc. Chim. Fr*. **1996**, *133*, 329. Black, D. S. C. *Synlett* **1993**, 246. Hughes, D. L. *Org. Prep. Proc. Int*. **1993**, *25*, 607. Gribble, G. W. *Comprehensive Heterocyclic Chemistry*, 2nd ed.; Pergamon Press: New York, 1996; Vol. 2, pp 207−257.

(3) Saxton, J. E. *Indoles*; Wiley-Interscience: New York, 1983; Part 4. Pindur, U.; Adam, R. *J. Heterocycl. Chem*. **1988**, *25*, 1.

(4) Padwa, A.; Price, A. T. *J. Org. Chem*. **1995**, *60*, 6258. Padwa, A.; Price, A. T. *J. Org. Chem*. **1998**, *63*, 556.

(5) Wenkert, E.; Piettre, S. *J. Org. Chem*. **1988**, *53*, 5850. Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc*. **1988**, *110*, 7188.

(6) Lipshutz, B. H. *Chem. Rev*. **1986**, *86*, 795. Woo, S.; Keay, B. A. *Synthesis* **1996**, 669. Dean, F. M. *Adv. Heterocycl. Chem*. **1981**, *30*, 168.

(7) Biolatto, B.; Kneeteman, M.; Paredes, E.; Mancini, M. E. *J. Org. Chem*. **2001**, *66*, 3906.

(8) Kraus, G. A.; Raggon, P. J.; Thomas, P. J.; Bougie, D. *Tetrahedron Lett*. **1988**, *29*, 5605. Kraus, G. A.; Bougie, D.; Jacobsen, R. A.; Su, Y. *J. Org. Chem*. **1989**, *54*, 2425.

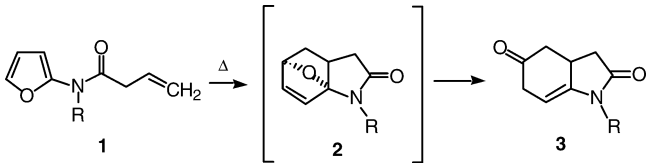
(9) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res*. **1984**, *17*, 35.

(10) Raasch, M. S. *J. Org. Chem*. **1980**, *45*, 856. Padwa, A.; Gareau, Y.; Harrison, B.; Rodriguez, A. *J. Org. Chem*. **1992**, *57*, 3540. Seitz, G.; Kaempchen, T. *Arch. Pharm*. **1976**, *309*, 679. Takahashi, M.; Ishida, H.; Kohmoto, M. *Bull. Chem. Soc. Jpn*. **1976**, *49*, 1725. Seitz, G.; Mohr, R. *Chem.-Ztg*. **1987**, *111*, 81. Gieseler, A.; Steckhan, E.; Wiest, O.; Knoch, F. *J. Org. Chem*. **1991**, *56*, 1405. Markgraff, J. H.; Patterson, D. E. *J. Heterocycl. Chem*. **1996**, *33*, 109. Boger, D. L.; Sakya, S. M. *J. Org. Chem*. **1990**, *55*, 3257.

(11) Dang, Q.; Brown, B. S.; Erion, M. D. *J. Org. Chem*. **1996**, *61*, 5204. Dang, Q.; Liu, Y.; Erion, M. D. *J. Am. Chem. Soc*. **1999**, *121*, 5833. Yu, Z. X.; Dang, Q.; Wu, Y. D. *J. Org. Chem*. **2001**, *66*, 6029. Nesi, R.; Giomi, D.; Turchi, S.; Falai, A. *J. Chem. Soc., Chem. Commun*. **1995**, 2201. Haider, N.; Mereitner, K.; Wanko, R. *Heterocycles* **1995**, *41*, 1445.

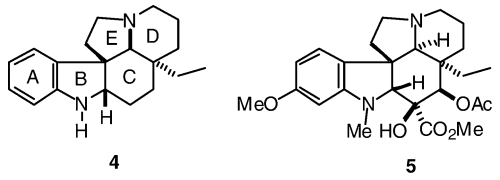
10.1021/jo049808i CCC: $27.50 
Published on Web 04/27/2004

**SCHEME 1**



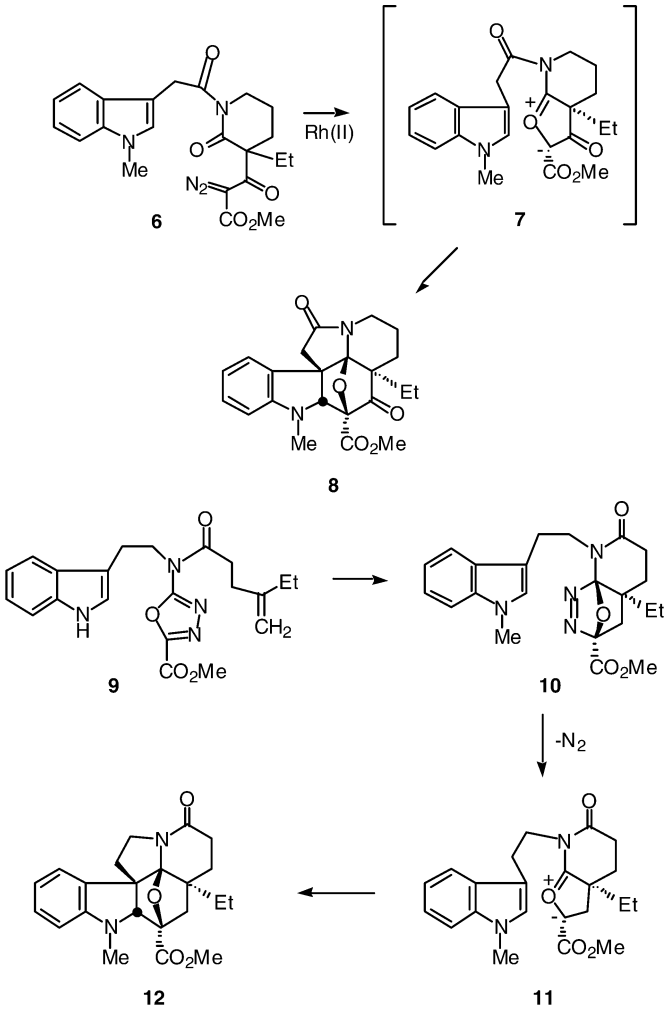
chlorothiophene 1,1-dioxide.[12] Indole magnesium salts were also found to undergo facial [4 + 2]-cycloaddition reactions with 2-phenylsulfonyl 1,3-dienes.[13]

In recent years, we have been investigating the intramolecular *[4 + 2]-cycloaddition/rearrangement cascade* of 2-amidofurans as a strategy for the synthesis of hexahydroindolinone alkaloids (Scheme 1).[14] Intramolecular cycloaddition reactions often benefit from higher reactivity and greater control of stereoselectivity relative to their intermolecular counterparts. Specifically, connecting two $\pi$-substrates via a "tether" generally facilitates the rate of the [4 + 2]-cycloaddition reaction. Our experience with this domino sequence prompted us to examine a Diels−Alder approach to various indole alkaloids, wherein an indole moiety participates as the dienophilic partner. One of the specific problems posed by the indole Aspidosperma skeleton found in aspidospermidine (**4**) and vindoline (**5**) involves the construction of the quaternary C(7) center.[15] Because this center is contained within the six-membered C ring, a reaction that fashions both the C ring and the spirocyclic BE junction represents a very efficient strategy for the construction of this polycyclic array that is also present in many of the *strychnos* alkaloids.[16]



Kuehne's[17] use of a tandem ammonium ion rearrangement/intramolecular Diels−Alder cycloaddition and the more recent amido-diene cycloaddition sequence reported by Rawal[18] are the only approaches that construct the C ring and the BE junction in one synthetic step.[19]

**SCHEME 2**



In earlier work from our laboratory, we reported the efficient participation of the indole C(2)−C(3) double bond as the 2$\pi$ component in 1,3-dipolar cycloadditions with push−pull carbonyl ylides (i.e., **6** → **8**).[4] A later report by Boger outlined a similar approach to the Vinca alkaloids using a tandem intramolecular Diels−Alder/dipolar cycloaddition sequence of 1,3,4-oxadiazoles across the indole double bond (Scheme 2).[20]

More recently, our group published a preliminary account of a concise and efficient synthesis of the ABCE tetracyclic core of the aspidosperma skeleton, in which the key step was a normal electron-demand Diels−Alder reaction of an amidofuran across a tethered indole.[21] The *[4 + 2]-cycloaddition/rearrangement sequence* was found to be remarkably efficient given that two aromatic rings were compromised in the reaction. Herein, we provide a full account of the initial methodology, as well as its general extension to prepare some related pentacyclic analogues.

## Results and Discussion

We started our studies by carrying out the *N*-alkylation of furan **13** with 3-(2-bromoethyl)indole (**14**), which

(12) Benson, S. C.; Palabrica, C. A.; Snyder, J. K. *J. Org. Chem.* **1987**, *52*, 4610. Benson, S. C.; Gross, J. L.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 3257. Benson, S. C.; Li, J. H.; Snyder, J. K. *J. Org. Chem.* **1992**, *57*, 5285. Lee, L.; Snyder, J. K. *Adv. Cycloaddit.* **1999**, *6*, 119−171. Wan, Z. K.; Woo, G. H. C.; Snyder, J. K. *Tetrahedron* **2001**, *57*, 5497. Li, J. H.; Snyder, J. K. *J. Org. Chem.* **1993**, *58*, 516. Wan, Z.; Snyder, J. K. *Tetrahedron Lett.* **1997**, *38*, 7495. Benson, S. C.; Lee, L.; Yang, L.; Snyder, J. K. *Tetrahedron* **2000**, *56*, 1165.

(13) Backvall, J. E.; Plobeck, N. A. *J. Org. Chem.* **1990**, *55*, 4528.

(14) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088. Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304. Padwa, A.; Brodney, M. A.; Satake, K.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 4617.

(15) *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press: San Diego, 1990; Vol. 37, pp 145−204.

(16) Aimi, N.; Sakai, S.-I. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1989; Vol. 36, pp 1−68.

(17) Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705. Kuehne, M. E.; Bornmann, W. G.; Earley, W. G.; Marko, I. *J. Org. Chem.* **1986**, *51*, 2913.

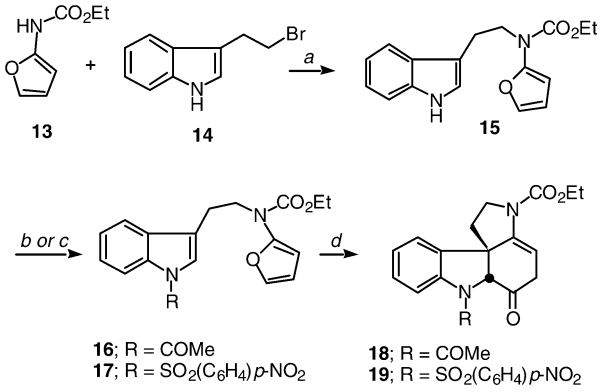
(18) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030. Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685.

(19) For a very recent paper using a related approach, see: Bodwell, G. J.; Li, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3261.

(20) Wilke, G. D.; Elliott, G. I.; Blagg, B. S. J.; Wolkenberg, S. E.; Soenen, D. R.; Miller, M. M.; Pollack, S.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 11292.

(21) Lynch, S. M.; Bur, S. K.; Padwa, A. *Org. Lett.* **2002**, *4*, 4643.

**SCHEME 3**[a]

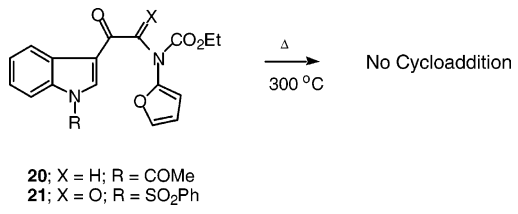



[a] Reagents: (a) $Cs_2CO_3$, DMF/THF (4:1), 80 °C, 80%; (b) $Bu_4NHSO_4$, NaOH, AcCl, $CH_2Cl_2$, rt, 90%; (c) $Bu_4NHSO_4$, NaOH, $ClSO_2(C_6H_4)p$-$NO_2$, $CH_2Cl_2$, rt, 31%; (d) benzene (sealed tube), 240 °C, 18 h.

provided indole **15** in 80% yield (Scheme 3). Not unexpectedly, thermolysis of **15**, which lacks an electron-withdrawing group on the indole, failed to induce cyclization even at temperatures above 200 °C. *N*-Acylation of **15** under phase-transfer conditions provided **16** in 90% yield.

Cyclization to **18** did occur, but only in 30% isolated yield (62% based on recovered starting material), after heating at 240 °C for 18 h. We also examined the thermolysis of the related indole **17**, which contains the strong electron-withdrawing nitrobenzenesulfonyl (nosyl) group on the nitrogen atom. Heating a sample of **17** in toluene at 200 °C for 18 h furnished the rearranged cycloadduct **19** but again in only 36% yield.

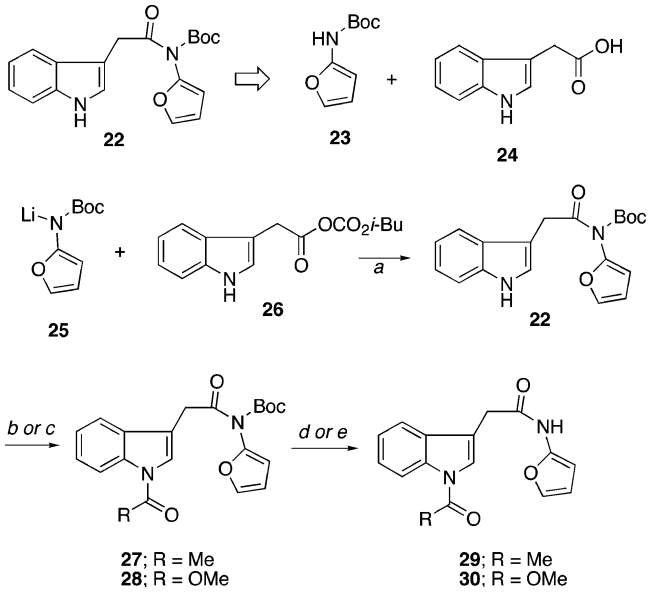
Somewhat encouraged by the above results, we searched for a way to increase the efficiency of the cycloaddition reaction. In previous studies, structural features that facilitated the intramolecular Diels−Alder reaction of amidofurans were discovered.[22,23] We reasoned that the incorporation of a carbonyl group in the tether adjacent to the indole ring should facilitate the reaction by providing a favorable FMO electronic effect. We found, however, that the independently synthesized furanyl indoles **20** and **21** resisted cycloaddition even at temperatures up to 300 °C. Dramatic effects on the rate of the Diels−Alder reaction were previously noted to occur when an amido group was used to anchor the diene and dienophile.[24] In one example involving an intramolecular dipolar cycloaddition, a severe steric interaction was found in the transition state, while no such interaction was identifiable in either the starting material or product ground states.[25]




(22) Padwa, A.; Gin, J. D.; Bur, S. K.; Eidell, C. K.; Lynch, S. M. *J. Org. Chem.* **2002**, *64*, 3412.

(23) Bur, S. K.; Lynch, S. M.; Padwa, A. *Org. Lett.* **2002**, *4*, 473.

**SCHEME 4**[a]




[a] Reagents: (a) **24**, *i*-$BuO_2CCl$, *N*-methylmorpholine, filter, then **25**, 0 °C, 68%; (b) $Bu_4NHSO_4$, NaOH, AcCl, $CH_2Cl_2$ rt, 88%; (c) $O(CO_2Me)_2$, DMAP THF, rt, 70%; (d) benzene, sealed tube, 200 °C; (e) $MgClO_4$, $CH_3CN$, 50 °C, 77%.

Introduction of a carbonyl group on the tethered dipolarophile relieved the source of the strain. Similarly, the effects of amide and ester-linked tethers on the diastereoselectivity of intramolecular Diels−Alder reactions have been attributed to relative transition state stabilities.[26] Jung and Gervay, however, reported data for intramolecular Diels−Alder reactions of furans that suggest that substitution on the tether results in an increase in the population of reactive rotomers.[27] Thus, the rate enhancement encountered could also originate from a restricted rotation that enforces a more reactive conformer in the lowest energy ground state.

With this possibility in mind, we decided to synthesize an indolyl-tethered amidofuran such as **22** in order to evaluate its cycloaddition behavior. Initially, we had envisioned **22** arising from simple acylation of **23** with the acid chloride derived from indole acetic acid (**24**). However, under a variety of conditions (DMAP, 4 Å molecular sieves, etc.), furanyl carbamate **23** proved to be remarkably resistant toward acylation. After some experimentation, we found that the addition of **25**, formed by the action of *n*-BuLi on **23**, to a solution of the mixed anhydride **26** provided **22** in 68% yield (Scheme 4). Subsequent *N*-acylation under phase-transfer conditions smoothly produced **27** in 88% yield. Similarly, treatment of **22** with dimethyl pyrocarbonate in the presence of DMAP afforded the closely related *N*-carbomethoxy-

(24) Oppolzer, W.; Fröstl, W. *Helv. Chim. Acta* **1975**, *58*, 590. Oppolzer, W.; Fröstl, W.; Weber, H. P. *Helv. Chim. Acta* **1975**, *58*, 593.

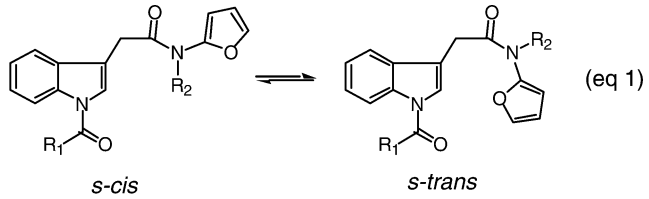
(25) Weingarten, M. D.; Prein, M.; Price, A. T.; Snyder, J. P.; Padwa, A. *J. Org. Chem.* **1997**, *62*, 2001.

(26) White, J. D.; Demnitz, F. W. J.; Oda, H.; Hassler, C.; Snyder, J. P. *Org. Lett.* **2000**, *2*, 3313. Turner, C. I.; Williamson, R. M.; Padon-Row, M. N. *J. Org. Chem.* **2001**, *66*, 3963. Tantillo, D. J.; Houk, K. N.; Jung, M. E. *J. Org. Chem.* **2001**, *66*, 1938.

(27) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224. Sternbach, D. D.; Rossana, D. M.; Onan, D. D. *Tetrahedron Lett.* **1985**, *26*, 591. Giessner-Prettre, C.; Hükel, S.; Maddaluno, J.; Jung, M. E. *J. Org. Chem.* **1997**, *62*, 1439.

protected indole **28** in 60% yield. Unfortunately, all of our attempts to effect the [4 + 2]-cycloaddition of **27** (or **28**) resulted only in the removal of the thermally labile *tert*-butyloxy carbonyl group to give **29** (or **30**). While **29** should still be a viable cyclization precursor, the use of temperatures exceeding 300 °C failed to promote the desired cycloaddition; only starting indole was recovered.

Upon further consideration, this result is not so surprising: conformational preferences about an amide bond have been implicated in the efficiency of other cyclization reactions.[28] The strong preference of secondary amides to adopt an *s*-cis conformation is well established.[29] More than likely, **29** resides predominantly in the s-cis conformation where the furan ring is far removed from the indole $\pi$-bond (eq 1). We reasoned that replacing the hydrogen with a larger group would cause the reactive *s*-trans conformation to be more highly populated, and therefore the cycloaddition will be more prone to occur.

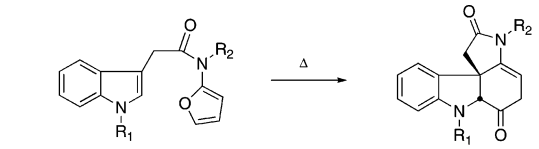



(eq 1)

To test this hypothesis, several tertiary amides derived from **29** were prepared. This necessitated a more experimentally benign protocol for removing the carbamate moiety from **27**, and we found that $MgClO_4$ in $CH_3CN$ efficiently provided **29**.[30] Alkylating the sodium salt of **29** with methyl iodide, benzyl bromide, or allyl iodide provided the desired indoles **31**−**33** in high yield (Scheme 5). Indole **31**, which contains the relatively small methyl group on the amido nitrogen, resisted cycloaddition even at temperatures up to 300 °C. In stark contrast, thermolysis of related indoles that contain a larger substituent group on the amide nitrogen did result in products derived from a Diels−Alder reaction. Thus, heating a sample of the *N*-benzyl indole **32** gave the novel azatricycle **39** in 56% yield. Similarly, the thermolysis of the *N*-allyl-substituted indole **33** cleanly afforded **40** in 77% yield after only 2 h.

We also examined the cyclization of indoles **34** and **35**, which bear an iodo functionality on the side chain that may allow for eventual functionalization of the D-ring of the aspidosperma skeleton. We were pleased to note that heating both indoles **34** and **35** at 200 °C for 2 h furnished the rearranged cycloadducts **41** and **42** in 74 and 84% yields, respectively. Furans **36** and **37**, which contain the *N*-methoxycarbonyl group on the indole nitrogen, also produced the rearranged cycloadducts **43** and **44** on heating at 200 °C in 91 and 50% yields, respectively.

**SCHEME 5**

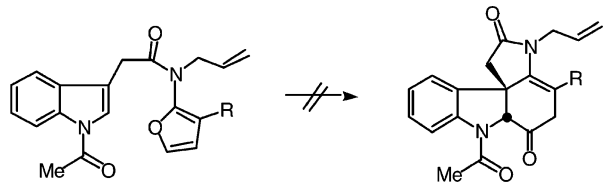


**29**; $R_1$ = COMe; $R_2$ = H
**31**; $R_1$ = COMe; $R_2$ = Me
**32**; $R_1$ = COMe; $R_2$ = $CH_2Ph$
**33**; $R_1$ = COMe; $R_2$ = allyl
**34**; $R_1$ = COMe; $R_2$ = $CH_2CH_2CH_2I$
**35**; $R_1$ = COMe; $R_2$ = $CH_2CH$=CHI
**36**; $R_1$ = $CO_2Me$; $R_2$ = allyl
**37**; $R_1$ = $CO_2Me$; $R_2$ = $CH_2C(Br)$=$CH_2$
**38**; $R_1$ = Me; $R_2$ = allyl

**39**; $R_1$ = COMe; $R_2$ = $CH_2Ph$ (56%)
**40**; $R_1$ = COMe; $R_2$ = allyl (77%)
**41**; $R_1$ = COMe; $R_2$ = $CH_2CH_2CH_2I$ (74%)
**42**; $R_1$ = COMe; $R_2$ = $CH_2CH$=CHI (84%)
**43**; $R_1$ = $CO_2Me$; $R_2$ = allyl (91%)
**44**; $R_1$ = $CO_2Me$; $R_2$ = $CH_2C(Br)$=$CH_2$ (50%)

These cycloadditions do require the presence of an electron-withdrawing substituent on the indole nitrogen in order for the reaction to proceed. For example, indole **38**, which contains a methyl substituent on the indole nitrogen, failed to undergo the cycloaddition even at 300 °C. The failure of **38** to undergo the Diels−Alder reaction is consistent with FMO theory.[31] Placement of an alkyl substituent on the nitrogen atom raises the LUMO energy of the indole $C_2$−$C_3$ $\pi$-bond, thereby diminishing the rate of the normal electron-demand Diels−Alder reaction.

At this stage of our investigations we decided to study the effect of substitution on the furan ring and how it would influence the Diels−Alder reaction. In particular, we were interested in knowing whether the incorporation of functionality at the 3-position of the furan would effect its reactivity toward cycloaddition. Our hope was to use the furan ring to install the requisite ethyl group that is common to many members of the aspidosperma alkaloid family (i.e., **5**). With this in mind, we prepared the desired 3-ethyl-substituted furan **45**. We were quite disappointed to find that **45** did not undergo cycloaddition analogous to that observed with the unsubstituted furan **33**. In seeking a possible explanation for its lack of reactivity, we carried out some molecular mechanics calculations. Low-energy conformers of indole **45** were obtained using Monte Carlo conformation searching (MCMM) as implicated by MacroModel 7.0[32] with either MM2* or MMFF parameters.



**45**; R = $C_2H_5$
**46**; R = Br

No Cycloaddition

The calculations show that a restricted rotation exists about the amide bond as a consequence of a steric interaction between the furanyl ethyl group and the *N*-allyl substituent. This interaction prevents the furan ring from adopting the proper conformation necessary for

(28) For recent examples, see: Jones, K.; Wilkinson, J.; Ewin, R. *Tetrahedron Lett.* **1994**, *35*, 7673. Tamura, O.; Matsukida, H.; Toyao, A.; Takeda, Y.; Ishibashi, H. *J. Org. Chem.* **2002**, *67*, 5537.

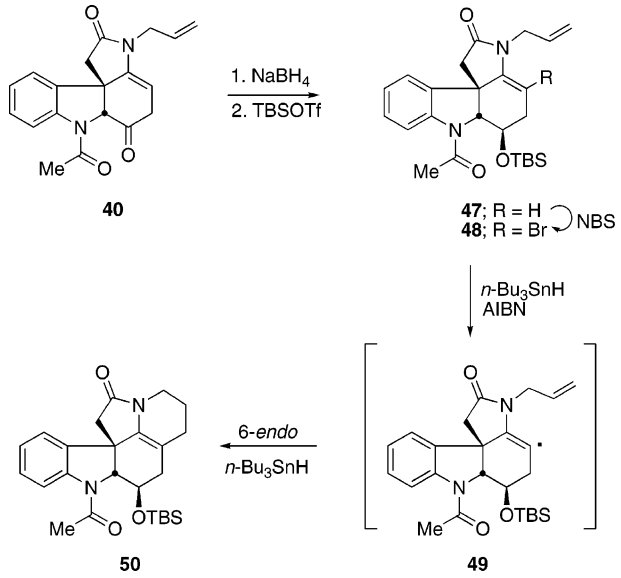
(29) Stewart, W. E.; Siddall, T. H. *Chem. Rev.* **1970**, *70*, 517. See also: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; p 620.

(30) Stafford, J. A.; Brackeen, M. F.; Karanewsky, D. S.; Valvano, N. L. *Tetrahedron Lett.* **1993**, *34*, 7873.

(31) Fleming, I.; *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Interscience: New York, 1976.

(32) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

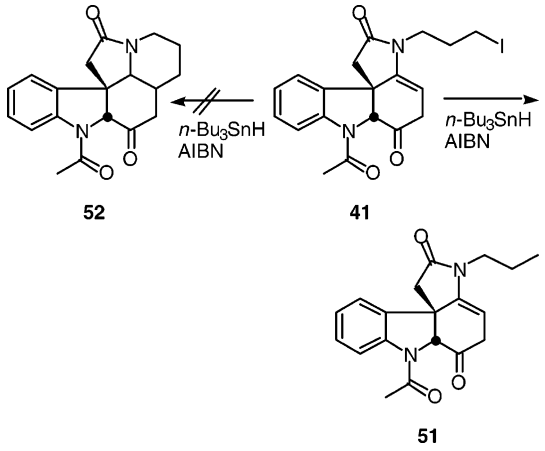
**SCHEME 6**




the cycloaddition to proceed. We thought that by using a furanyl substrate that possessed a smaller substituent in the 3-position we would be able to overcome the conformation issue. There is some evidence in the literature indicating that a bromo group in the 3-position of furans accelerates the Diels−Alder reaction.[33] If the cycloaddition were to proceed, the resulting vinyl bromide present in the rearranged cycloadduct could then be used as a handle to install the desired ethyl group by a variety of methods. To evaluate this possibility, bromofuran **46** (R = Br) was prepared. Unfortunately, this furan was rather unstable and afforded intractable material when subjected to thermolysis.

To use the *cycloaddition/rearrangement strategy* for assembly of the aspidosperma skeleton, we needed to address the problem of assembling the final D-ring of the pentacyclic skeleton. With this in mind, we subjected cycloadduct **40** to sodium borohydride reduction. The resulting alcohol was obtained as a single diastereomer in 90% yield and subsequently protected as the corresponding *tert*-butyldimethylsilyl derivative **47**. Treatment of **47** with NBS in $CH_2Cl_2$ gave the corresponding bromoenamide **48**. Exposure of **48** to several radical cyclization conditions preferentially led to the 6-endo trig cyclization product **50**, with the best yields (91%) being obtained using *n*-$Bu_3SnH$/AIBN in refluxing benzene under slow addition conditions (Scheme 6). By analogy with related results obtained in our laboratory,[34] we assume that the initially generated cyclohexenyl radical **49** derived from **48** would produce the pentacyclic heterocycle **50** either by a direct 6-endo trig cyclization or alternatively by a vinyl radical rearrangement pathway.[35] Early studies by Beckwith[36] and Stork[37] have shown that vinyl radical cyclization generally leads to a mixture of both 5-exo and 6-endo products. The kinetic work of

**SCHEME 7**




Beckwith[36] revealed that the formation of the six-membered ring is not solely due to a 6-endo trig cyclization but is the result of a rapid rearrangement of the methylene cyclopentyl radical, via a reversible 3-exo trig cyclization.[38] More than likely, this pathway is also involved in the formation of **50**, especially since the reaction was carried out at low concentrations of *n*-$Bu_3SnH$ (0.01 M), which facilitates the radical rearrangement and minimizes the formation of the 5-exo trig product. Interestingly, our attempts to cyclize the *N*-(3-iodopropyl)-substituted azatetracycle **41** failed and instead afforded the reduction product **51** in 78% yield (Scheme 7). The failure of **41** to cyclize to **52** is presumably reflective of the slower rate of addition of the alkyl radical to the enamido $\pi$-bond.[39]

The *strychnos* alkaloids constitute an important class of naturally occurring compounds that has attracted the attention of synthetic chemists due to the interesting biological properties of some of its members.[40] These alkaloids share as part of their structure the pentacyclic strychnan framework in which rings C and E are joined by a bridged juncture and ring E bears an exocyclic olefin. Our general interest in using the [4 + 2]-cycloaddition/rearrangement of indolyl-substituted amidofurans as a synthetic method led us to consider an approach to (±)-dehydrotubifoline (**56**)[41] that makes use of the readily available cycloadduct **54**. To apply this strategy to dehydrotubifoline (**56**), we hoped to form the $C_{15}-C_{20}$ bond by making use of Rawal's elegant intramolecular Heck protocol.[42] Our retrosynthetic analysis of **56** is shown in Scheme 8. Dehydrotubifoline would be obtained from **55**, which, in turn, would be prepared from tetra-

(33) Klein, L. L. *J. Org. Chem.* **1985**, *50*, 1770. Crawford, K. R.; Bur, S. K.; Straub, C. S.; Padwa, A. *Org. Lett.* **2003**, *5*, 3337.

(34) Rashatasakhon, P.; Ozdemir, A. D.; Willis, J.; Padwa, A. *Org. Lett.* **2004**, *6*, 917.

(35) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321. Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. Motherwell, W. B.; Crich, D. *Free Radical Reactions in Organic Synthesis*; Academic Press: London, 1992.

(36) Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525.

(37) Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529.

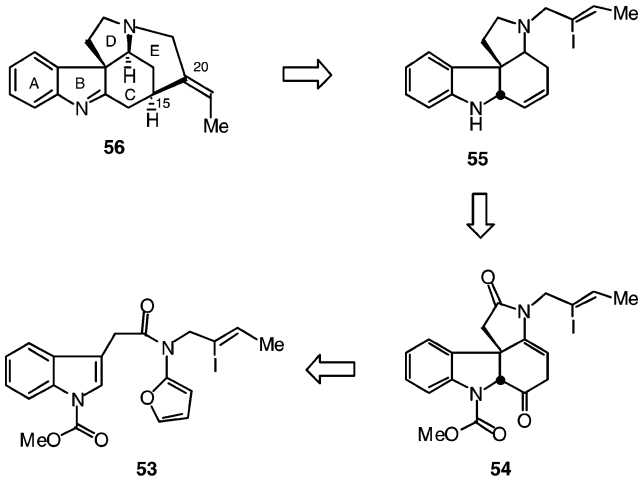
(38) Crich, D.; Hwang, J. T.; Liu, H. *Tetrahedron Lett.* **1996**, *37*, 3105.

(39) Vazquez, A. N.; Garcia, A.; Dominguez, D. *J. Org. Chem.* **2002**, *67*, 3213.

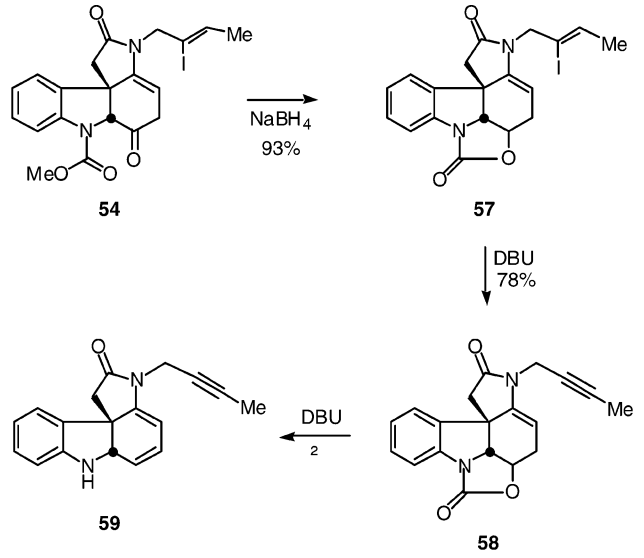
(40) Bosch, J.; Bonjoch, J. Pentacyclic Strychnos Alkaloids. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: Amsterdam, 1988; Vol. 1, p 31. Husson, H. P. In *Indoles: Monoterpenes Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1988; Chapters 1 and 7.

(41) Fevig, J. M.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085. Harley-Mason, J.; Crawley, G. C. *J. Chem. Soc., Chem. Commun.* **1971**, *93*, 685. Takano, S.; Hirama, M.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 881. Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030.

**SCHEME 8**



**SCHEME 9**



cyclic ketone **54**. Indeed, we found that the thermolysis of the easily synthesized indolyl-tethered amidofuran **53** proceeded smoothly at 200 °C and furnished the expected cycloadduct **54** in 87% yield.

Conversion of the keto carbonyl group of **54** into an olefinic $\pi$-bond was our initial goal. Reduction of **54** with sodium borohydride afforded the cyclic carbamate **57** as the major product. Our attempts to introduce the required double bond needed for the Heck reaction only resulted in the elimination of hydrogen iodide giving the propargylic-substituted amide **58** in good yield. In a typical example, the reaction of **57** with DBU gave **58** in 78% yield. Further reaction of **58** with additional base for longer periods of time furnished diene **59** (Scheme 9). Because of this discouraging result, we abandoned further work toward dehydrotubifoline using carbamate **57**. The facility with which hydrogen iodide elimination takes place implies that refunctionalization at the keto carbonyl center is more likely to be accomplished prior to the installation of the (*Z*)-2-iodobut-2-enyl group. Further work to achieve this goal is in progress and will be reported at a later date.

The work reported herein describes a novel approach to the core structure of the aspidosperma alkaloids. As typified in the synthesis of the model compound **40**, the Diels−Alder approach delivers a material in which the *ABCE* tetracyclic core of aspermidine is rapidly assembled. Our studies show that these intramolecular [4 + 2]-cycloaddition reactions are remarkably efficient given that two aromatic systems are compromised in the reaction. This synthetic strategy should prove to be useful for the construction of different members of the Aspidosperma family because the piece-wise construction of the cascade precursor allows for incorporation of varied functionality. Furthermore, the discovery of a facile radical method of closing the D ring may allow for the implementation of synthetic routes to a variety of aspidosperma alkaloids.

## Experimental Section

**Furan-2-ylcarbamic Acid Ethyl Ester (13).** To a solution of 3.0 g (23 mmol) of 2-furoyl chloride in 25 mL of $Et_2O$ at 0 °C was added a solution of 1.8 g (28 mmol) of sodium azide in 15 mL of $H_2O$, and the biphasic mixture was vigorously stirred at room temperature for 4 h. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude white solid was dissolved in 20 mL of EtOH and heated at reflux for 15 h behind a protective shield. The solvent was removed under reduced pressure, and the resulting residue was purified by flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to provide 3.0 g (84%) of **13** as a pale yellow solid: mp 27−28 °C; IR (neat) 1716, 1618, 1552, and 1260 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.29 (t, 3H, $J$ = 6.8 Hz), 4.22 (q, 2H, $J$ = 6.8 Hz), 6.07 (brs, 1H), 6.34 (dd, 1H, $J$ = 3.2 and 1.6 Hz), 6.96 (brs, 1H), and 7.07 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 14.6, 62.1, 95.8, 111.5, 136.6, 145.2, and 153.2. Anal. Calcd for $C_7H_9NO_3$: C, 54.17; H, 5.85; N, 9.03. Found: C, 54.02; H, 6.13; N, 9.12.

**[2-(1-Acetyl-1*H*-indol-3-yl)-ethyl]furan-2-ylcarbamic Acid Ethyl Ester (16).** To a solution containing 1.2 g (7.6 mmol) of furan-2-yl carbamic acid ethyl ester (**13**) and 150 mL of a 4:1 DMF/THF mixture at room temperature was added 7.4 g (23 mmol) of cesium carbonate. The reaction mixture was stirred at room temperature for 30 min, and 2.2 g (10 mmol) of 3-(2-bromo-ethyl)-indole was added in one portion. The mixture was heated at 90 °C for 12 h and then cooled to room temperature, quenched with $H_2O$, and extracted with ether. The organic layer was washed with $H_2O$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to provide 1.8 g (80%) of furan-2-yl-[2-(1*H*-indol-3-yl)-ethyl]carbamic acid ethyl ester (**15**) as a pale yellow oil: IR (neat) 3416, 1702, 1616, 1460, and 1296 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.25 (t, 3H, $J$ = 7.2 Hz), 3.12 (t, 2H, $J$ = 8.0 Hz), 3.95 (t, 2H, $J$ = 8.0 Hz), 4.21 (q, 2H, $J$ = 7.2 Hz), 6.07 (brs, 1H), 6.41 (dd, 1H, $J$ = 3.2 and 2.4 Hz), 6.99 (d, 1H, $J$ = 2.4 Hz), 7.13−7.24 (m, 2H), 7.28 (dd, 1H, $J$ = 2.0 and 1.2 Hz), 7.35 (d, 1H, $J$ = 8.0 Hz), 7.67 (d, 1H, $J$ = 8.0 Hz), and 8.19 (brs, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 14.5, 24.8, 49.8, 62.4, 101.9, 111.2, 111.3, 112.6, 118.9, 119.4, 122.1, 122.2, 127.6, 136.4, 138.7, 148.3, and 155.3. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.48; H, 6.04; N, 9.32.

To a solution containing 1.0 g (3.4 mmol) of indole **15** in 40 mL of $CH_2Cl_2$ at room temperature was added 0.13 g (0.4

(42) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030. Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685. Birman, V. B.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 7219. Birman, V. H.; Rawal, V. H. *J. Org. Chem.* **1998**, *63*, 9146.
(43) Sato, Y.; Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 371.
(44) Piers, E. *Synthesis* **1998**, 590.

mmol) of tetrabutylammonium hydrogen sulfate followed by 0.67 g (17 mmol) of freshly powdered NaOH. The reaction mixture was stirred at room temperature for 5 min, and then 0.6 g (8 mmol) of acetyl chloride was added dropwise. The reaction mixture was stirred at room temperature for 1 h, quenched with $H_2O$, and extracted with $CH_2Cl_2$. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to afford 1.0 g (90%) of **16** as a colorless oil: IR (neat) 1721, 1612, 1506, and 1457 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.19 (t, 3H, $J$ = 6.8 Hz), 2.56 (s, 3H), 2.99 (t, 2H, $J$ = 7.2 Hz), 3.91 (t, 2H, $J$ = 7.2 Hz), 4.14 (q, 2H, $J$ = 6.8 Hz), 6.05 (brs, 1H), 6.35 (t, 1H, $J$ = 2.0 Hz), 7.21−7.24 (m, 2H), 7.24−7.28 (m, 1H), 7.31−7.35 (m, 1H), 7.53 (d, 1H, $J$ = 7.4 Hz), and 8.40 (d, 1H, $J$ = 6.8 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 14.6, 24.2, 24.6, 48.8, 62.5, 102.3, 111.3, 116.8, 118.9, 119.4, 122.8, 123.7, 125.5, 130.6, 136.0, 138.8, 147.9, 155.1, and 168.6; HRMS calcd for $C_{19}H_{20}N_2O_4$ 340.1423, found 340.1408.

**7-Acetyl-6-oxo-1,2,5,6,6*a*,7-hexahydropyrrolo[2,3-*d*]carbazole-3-carboxylic Acid Ethyl Ester (18).** A solution of 0.5 g (1.3 mmol) of furan **16** in 5 mL of benzene was heated in a sealed tube at 240 °C for 18 h. The solution was concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to provide 0.15 g (30%) of **18** as a yellow solid: mp 174−175 °C; IR (KBr) 1716, 1673, 1595, 1481, and 1403 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.37 (t, 3H, $J$ = 7.2 Hz), 2.03 (dd, 1H, $J$ = 12.0 and 5.6 Hz), 2.16−2.25 (m, 1H), 2.28 (s, 3H), 2.95 (dd, 1H, $J$ = 21.8 and 3.0 Hz), 3.09 (dd, 1H, $J$ = 21.8 and 5.0 Hz), 3.70−3.77 (m, 1H), 3.92 (dd, 1H, $J$ = 10.8 and 8.4 Hz), 4.26−4.34 (m, 2H), 4.45 (s, 1H), 5.81−6.22 (brs, 1H), 6.98−7.04 (m, 2H), 7.19−7.27 (m, 1H), and 8.20 (d, 1H, $J$ = 8.0 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 14.8, 24.0, 36.8, 36.9, 45.9, 62.1, 72.8, 100.2, 115.7, 118.2, 122.0, 123.3, 124.6, 129.4, 134.3, 141.0, 170.0, and 204.6. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.10; H, 6.05; N, 8.38.

**Ethyl-*N*-[3-[1-(4-nitrobenzenesulfonyl)-1*H*-indol]-2-ethyl]-*N*-(2-furyl)-carbamate (17).** To a solution containing 0.25 g (0.84 mmol) of indole **15** and 15 mL of $CH_2Cl_2$ at room temperature were added 0.03 g (0.09 mmol) of tetrabutylammonium hydrogen sulfate and 0.2 g (4.2 mmol) of powdered NaOH. The reaction mixture was stirred at room temperature for 5 min, and then 0.4 g (1.8 mmol) of 4-nitrobenzenesulfonyl chloride in 5 mL of $CH_2Cl_2$ was added dropwise to the solution. The mixture was stirred at room temperature for 2 h, quenched with 10 mL of $H_2O$, and extracted with $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to give 0.13 g (31%) of **17** as a yellow oil: IR (neat) 1716, 1609, 1531, 1445, and 1374 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.12−1.16 (m, 3H), 2.96 (t, 3H, $J$ = 6.8 Hz), 3.85 (t, 2H, $J$ = 7.6 Hz), 4.02−4.12 (m, 2H), 5.93 (brs, 1H), 6.31 (dd, 1H, $J$ = 3.2 and 2.0 Hz), 7.15 (d, 1H, $J$ = 1.2 Hz), 7.24 (t, 1H, $J$ = 7.2 Hz), 7.29−7.32 (m, 1H), 7.33 (s, 1H), 7.51 (d, 1H, $J$ = 7.6 Hz), 7.93 (d, 1H, $J$ = 7.6 Hz), 7.98 (d, 2H, $J$ = 9.2 Hz), and 8.21 (d, 2H, $J$ = 8.8 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 14.5, 24.5, 48.6, 62.5, 102.3, 111.3, 113.7, 120.1, 121.4, 123.3, 124.1, 124.7, 125.6, 128.2, 131.3, 135.2, 138.8, 143.4, 147.9, 150.7, 155.0; HRMS calcd for $C_{23}H_{21}N_3O_7S$ 483.1100, found 483.1111.

**Ethyl-7-(4-nitrobenzenesulfonyl)-6-oxo-1,2,5,6,6*a*,7-hexahydro-pyrrolo[2,3-*d*]-carbazole-3-carboxylate (19).** A solution of 0.05 g (0.10 mmol) of indole **17** in 13 mL of toluene was heated at 200 °C for 18 h in a sealed tube. The solution was concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to give 0.02 g (36%) of **19** as a pale yellow oil: IR (KBr) 2985, 1713, 1522, and 1385 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.34 (t, 3H, $J$ = 7.2 Hz), 1.97−2.03 (m, 1H), 2.89 (dd, 1H, $J$ = 21.0 and 3.0 Hz), 3.04 (dd, 1H, $J$ = 21.0 and 5.2 Hz), 3.56−3.63 (m, 1H), 3.79−3.85 (m, 1H), 4.27 (q, 2H, $J$ = 6.8 Hz), 4.64 (s, 1H), 5.70−6.18 (brs, 1H), 6.99 (d, 1H, $J$ = 7.6 Hz), 7.08 (dt, 1H, $J$ = 7.6 and 0.8 Hz), 7.27−7.31 (m, 1H), 7.45 (d, 1H, $J$ = 8.0 Hz), 8.16 (d, 2H, $J$ = 8.8 Hz), and 8.36 (d, 2H, $J$ = 8.8 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 14.8, 29.9, 36.6, 37.4, 45.6, 62.3, 73.1, 100.5, 116.3, 123.2, 124.6, 125.9, 128.9, 129.7, 135.7, 136.7, 139.2, 145.2, 150.6, and 202.5. Anal. Calcd for $C_{23}H_{21}N_3O_7S$: C, 57.13; H, 4.38; N, 8.70. Found: C, 57.02; H, 4.22; N, 8.83.

**Furan-2-yl-(2-1*H*-indol-3-yl-acetyl)carbamic Acid *tert*-Butyl Ester (22).** To a solution of 0.18 g (1.0 mmol) of furan-2-yl carbamic acid *tert*-butyl ester (**23**) in 4 mL of THF at 0 °C was added dropwise 0.9 mL (1.1 mmol) of *n*-BuLi (1.3 M in hexane). The reaction mixture was stirred at 0 °C for 20 min. In a separate flask, 0.18 g (1.0 mmol) of indole-3-acetic acid was dissolved in 5 mL of THF at 0 °C, and 0.11 mL (1.0 mmol) of 4-methylmorpholine and 0.13 mL (1.0 mmol) of isobutyl chloroformate were added dropwise. After 5 min, the white precipitate that formed was removed via filtration and washed with 2 mL of THF. The filtrate was cooled to 0 °C, and the preformed lithiate was added dropwise via syringe. After stirring at 0 °C for an additional 20 min, the reaction was quenched with $H_2O$ and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to afford 0.23 g (68%) of **22** as a white solid: mp 100−102 °C; IR (neat) 3380, 1772, 1746, 1705, 1603, and 1142 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.46 (s, 9H), 4.28 (s, 2H), 6.15 (dd, 1H, $J$ = 3.2 and 0.8 Hz), 6.42 (dd, 1H, $J$ = 3.2 and 2.0 Hz), 7.03 (d, 1H, $J$ = 2.4 Hz), 7.11−7.20 (m, 2H), 7.27 (d, 1H, $J$ = 7.6 Hz), 7.35 (dd, 1H, $J$ = 2.0 and 1.2 Hz), 7.61 (d, 1H, $J$ = 7.6 Hz), and 8.30 (brs, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 27.9, 34.1, 84.1, 106.2, 107.8, 111.4, 118.9, 119.5, 122.0, 123.9, 127.5, 136.1, 140.7, 144.1, 151.6, and 173.7. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.23; H, 6.04; N, 8.15.

**Furan-2-yl-[2-(1-Acetyl-1*H*-indol-3-yl)acetyl]carbamic Acid *tert*-Butyl Ester (27).** To a solution of 2.0 g (5.9 mmol) of indole **22** in 40 mL of $CH_2Cl_2$ at 0 °C was added 0.2 g (0.6 mmol) of tetrabutylammonium hydrogen sulfate followed by 1.2 g (29 mmol) of freshly powdered NaOH. After the mixture was stirred for 5 min, 1.1 mL (15 mmol) of acetyl chloride was slowly added and the reaction mixture was stirred at 0 °C for 15 min and then at room temperature for 15 min. The reaction was quenched with $H_2O$, and aqueous layer was extracted with $CH_2Cl_2$. The combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to afford 1.97 g (88%) of **27** as a white solid: mp 102−103 °C; IR (neat) 1777, 1751, 1705, 1608, 1454, and 1147 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.43 (s, 9H), 2.60 (s, 3H), 4.27 (s, 2H), 6.15 (dd, 1H, $J$ = 3.2 and 0.8 Hz), 6.42 (dd, 1H, $J$ = 3.2 and 2.0 Hz), 7.26−7.30 (m, 1H), 7.34−7.38 (m, 2H), 7.51−7.53 (m, 2H), and 8.43 (d, 1H, $J$ = 8.0 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 24.2, 27.9, 33.8, 84.4, 106.3, 111.5, 115.0, 116.8, 119.1, 123.8, 124.5, 125.6, 130.5, 135.7, 140.9, 143.7, 151.6, 168.8, and 172.4. Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33. Found: C, 66.17; H, 5.75; N, 7.37.

**2-(1-Acetyl-1*H*-indol-3-yl)-*N*-furan-2-ylacetamide (29).** To a solution of 1.2 g (3.1 mmol) of indole **27** in 30 mL of $CH_3CN$ was added 0.07 g (0.3 mmol) of magnesium perchlorate. The solution was heated to 45 °C for 1.5 h and then cooled to room temperature, and the solvent was removed under reduced pressure. The residue was triturated with EtOAc, and the resultant white solid was collected via filtration to afford 0.25 g of **29**. The filtrate was concentrated and subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to collect an additional 0.44 g (77% total) of **29** as a white solid: mp 164−165 °C; IR (neat) 3257, 1669, 1536, 1449, and 1388 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 2.64

(s, 3H), 3.83 (s, 2H), 6.33−6.36 (m, 2H), 7.00 (dd, 1H, $J$ = 2.0 and 1.2 Hz), 7.31−7.35 (m, 1H), 7.39−7.43 (m, 1H), 7.48 (s, 1H), 7.54 (d, 1H, $J$ = 8.0 Hz), 7.75 (brs, 1H), and 8.43 (d, 1H, $J$ = 8.0 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 24.2, 33.4, 96.1, 111.7, 114.9, 117.1, 118.9, 124.3, 124.7, 126.2, 129.8, 135.8, 136.1, 145.0, 166.5, and 168.7. Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.82; H, 5.01; N, 9.81.

**2-(1-Acetyl-1*H*-indol-3-yl)-*N*-benzyl-*N*-furan-2-ylacetamide (32).** To a solution of 0.16 g (0.6 mmol) of **29** in 8 mL of 4:1 DMF/THF were added 0.36 g (1.1 mmol) of $Cs_2CO_3$ and 0.15 mL (1.2 mmol) of benzyl bromide. The reaction mixture was heated at 80 °C for 1.5 h and then cooled to room temperature, quenched with $H_2O$, and extracted with EtOAc. The combined organic layer was washed with $H_2O$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to provide 0.17 g (80%) of **32** as a pale yellow oil: IR (neat) 1704, 1607, 1501, 1451, and 1384 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.56 (s, 3H), 3.64 (s, 2H), 4.84 (s, 2H), 5.90 (d, 1H, $J$ = 3.2 Hz), 6.35 (dd, 1H, $J$ = 3.2 and 2.0 Hz), 7.24−7.30 (m, 8H), 7.33−7.37 (m, 1H), 7.39 (d, 1H, $J$ = 8.0 Hz), and 8.43 (d, 1H, $J$ = 8.0 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 24.1, 30.8, 52.3, 105.5, 111.5, 115.8, 116.8, 118.9, 123.7, 123.8, 125.5, 127.8, 128.6, 128.7, 130.3, 135.8, 137.0, 140.4, 148.2, 168.6, and 171.2; HRMS calcd for $C_{23}H_{20}N_2O_3$ 372.1474, found 372.1491.

**7-Acetyl-3-benzyl-3,5,6a,7-tetrahydropyrrolo[2,3-*d*]carbazole-2,6-dione (39).** A solution of 0.11 g (0.3 mmol) of furan **32** in 2 mL of toluene was heated at 200 °C in a sealed pressure tube for 12 h. The solution was cooled to room temperature; the solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to afford 0.06 g (56%) of **39** as a pale yellow oil: IR (neat) 1724, 1684, 1474, and 1395 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.33 (s, 3H), 2.62 (d, 1H, $J$ = 16.6 Hz), 2.88 (dd, 1H, $J$ = 20.4 and 2.4 Hz), 2.97 (d, 1H, $J$ = 16.6 Hz), 3.01 (dd, 1H, $J$ = 20.4 and 6.0 Hz), 4.13 (dd, 1H, $J$ = 15.6 and 6.0 Hz), 4.38 (dd, 1H, $J$ = 15.6 and 5.6 Hz), 4.53 (s, 1H), 5.10 (dd, 1H, $J$ = 5.6 and 2.4 Hz), 5.28−5.34 (m, 2H), 5.78−5.87 (m, 1H), 7.00−7.05 (m, 2H), 7.23−7.27 (m, 1H), and 8.14 (d, 1H, $J$ = 8.4 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 24.2, 36.9, 44.5, 46.0, 50.2, 71.4, 94.7, 118.2, 121.1, 125.4, 128.2, 128.3, 129.2, 129.8, 134.5, 135.7, 140.9, 141.2, 169.9, 172.1, and 203.0; HRMS calcd for $C_{23}H_{20}N_2O_3$ 372.1474, found 372.1473.

**2-(1-Acetyl-1*H*-indol-3-yl)-*N*-allyl-*N*-furan-2-ylacetamide (33).** To a solution of 0.18 g (0.6 mmol) of **29** in 3 mL of DMF was added 0.03 g (0.7 mmol) of NaH (60% dispersion in mineral oil). The reaction mixture was stirred at room temperature for 30 min, and 0.07 mL (0.8 mmol) of allyl iodide was added dropwise. After an additional 30 min of stirring at room temperature, the reaction was quenched with $H_2O$ and extracted with EtOAc. The organic layer was washed with $H_2O$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to provide 0.1 g (50%) of **33** as a pale yellow oil: IR (neat) 1705, 1680, 1608, 1449, and 1383 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.57 (s, 3H), 3.60 (s, 2H), 4.24 (d, 2H, $J$ = 6.0 Hz), 5.12−5.17 (m, 2H), 5.78−5.88 (m, 1H), 6.10 (dd, 1H, $J$ = 3.2 and 0.8 Hz), 6.41 (dd, 1H, $J$ = 3.2 and 2.0 Hz), 7.22−7.34 (m, 4H), 7.38 (d, 1H, $J$ = 8.0 Hz), and 8.40 (d, 1H, $J$ = 8.0 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 24.1, 30.7, 51.4, 105.3, 111.5, 115.7, 116.7, 118.3, 118.9, 123.7, 123.8, 125.4, 130.3, 132.6, 135.7, 140.4, 148.3, 168.6, and 171.0; HRMS calcd for $C_{19}H_{18}N_2O_3$ 322.1317, found 322.1330.

**7-Acetyl-3-allyl-3,5,6*a*,7-tetrahydropyrrolo[2,3-*d*]carbazole-2,6-dione (40).** A solution of 0.13 g (0.4 mmol) of furan **33** in 2 mL of toluene was heated at 200 °C in a sealed pressure tube for 2 h. The solution was cooled to room temperature; the solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to afford 0.1 g (77%) of **40** as a pale orange solid: mp 202−203 °C; IR (neat) 1726, 1685, 1475, 1393, and 758 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.33 (s, 3H), 2.62 (d, 1H, $J$ = 16.6 Hz), 2.88 (dd, 1H, $J$ = 20.4 and 2.4 Hz), 2.97 (d, 1H, $J$ = 16.6 Hz), 3.01 (dd, 1H, $J$ = 20.4 and 6.0 Hz), 4.13 (dd, 1H, $J$ = 15.6 and 6.0 Hz), 4.38 (dd, 1H, $J$ = 15.6 and 5.6 Hz), 4.53 (s, 1H), 5.10 (dd, 1H, $J$ = 5.6 and 2.4 Hz), 5.28−5.34 (m, 2H), 5.78−5.87 (m, 1H), 7.00−7.05 (m, 2H), 7.23−7.27 (m, 1H), and 8.14 (d, 1H, $J$ = 8.4 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 24.1, 36.7, 43.0, 45.9, 50.1, 71.4, 94.4, 118.1, 119.2, 121.0, 125.4, 129.7, 131.1, 134.5, 140.7, 141.1, 169.8, 171.5, and 203.0. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.54; H, 5.70; N, 8.55.

**2-(1-Acetyl-1*H*-indol-3-yl)-*N*-(3-chloropropyl)-*N*-furan-2-yl-acetamide.** To a solution of 0.6 g (2.2 mmol) of indole **29** in 10 mL of DMF was added 1.0 g (2.4 mmol) of NaH (60% dispersion in mineral oil). The reaction mixture was stirred at room temperature for 30 min, and 0.35 mL (3.3 mmol) of 1-chloro-3-iodopropane was added dropwise. After an additional 30 min of stirring at room temperature, the reaction was quenched with $H_2O$ and extracted with EtOAc. The organic layer was washed with $H_2O$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to provide 0.42 g (54%) of the titled compound as a pale yellow oil: IR (neat) 1710, 1685, 1608, 1449, and 1383 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.01−2.08 (m, 2H), 2.57 (s, 3H), 3.54 (t, 2H, $J$ = 6.8 Hz), 3.58 (s, 2H), 3.79 (t, 2H, $J$ = 6.8 Hz), 6.13 (dd, 1H, $J$ = 3.2 and 0.8 Hz), 6.44 (dd, 1H, $J$ = 3.2 and 2.0 Hz), 7.22−7.27 (m, 2H), 7.31−7.35 (m, 2H), 7.37 (d, 1H, $J$ = 8.0 Hz), and 8.40 (d, 1H, $J$ = 8.0 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 24.1, 30.8, 31.2, 42.3, 46.7, 105.2, 111.6, 115.6, 116.8, 118.9, 123.7, 123.8, 125.5, 130.2, 135.7, 140.5, 148.4, 168.6, and 171.4; HRMS calcd for $C_{19}H_{19}N_2O_3Cl$ 358.1084, found 358.1076.

**2-(1-Acetyl-1*H*-indol-3-yl)-*N*-(3-iodopropyl)-*N*-furan-2-yl-acetamide (34).** A mixture containing of 0.32 g (0.9 mmol) of the above indole, 1.35 g (9.0 mmol) of NaI, and 8 mL of acetone was heated at reflux for 12 h. The reaction mixture was cooled to room temperature, quenched with $H_2O$, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to provide 0.38 g (95%) of **34** as a pale yellow oil: IR (neat) 1705, 1685, 1608, 1454, and 1383 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.07−2.14 (m, 2H), 2.59 (s, 3H), 3.14 (t, 2H, $J$ = 7.2 Hz), 3.58 (s, 2H), 3.72 (t, 2H, $J$ = 7.2 Hz), 6.13 (dd, 1H, $J$ = 3.2 and 0.8 Hz), 6.44 (dd, 1H, $J$ = 3.2 and 2.0 Hz), 7.23−7.27 (m, 2H), 7.31−7.34 (m, 2H), 7.36 (d, 1H, $J$ = 7.6 Hz), and 8.40 (d, 1H, $J$ = 7.6 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 2.2, 24.2, 30.8, 32.3, 49.7, 105.3, 111.7, 115.6, 116.8, 118.9, 123.7, 123.8, 125.5, 130.3, 135.8, 140.6, 148.4, 168.6, and 171.5; HRMS calcd for $C_{19}H_{19}N_2O_3I$ 450.0440, found 450.0445.

**7-Acetyl-3-(3-iodopropyl)-3,5,6*a*,7-tetrahydropyrrolo-[2,3-*d*]carbazole-2,6-dione (41).** A solution of 0.36 g (0.8 mmol) of furan **34** in 3 mL of toluene was heated at 200 °C in a sealed pressure tube for 1.5 h. The solution was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to afford 0.27 g (74%) of **41** as a pale orange solid: IR (neat) 1721, 1680, 1475, 1393, and 1224 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.17−2.26 (m, 2H), 2.33 (s, 3H), 2.61 (d, 1H, $J$ = 16.4 Hz), 2.90 (dd, 1H, $J$ = 20.4 and 2.8 Hz), 2.95 (d, 1H, $J$ = 16.4 Hz), 3.03 (dd, 1H, $J$ = 20.4 and 6.0 Hz), 3.19−3.29 (m, 2H), 3.54−3.61 (m, 1H), 3.82−3.89 (m, 1H), 4.53 (s, 1H), 5.19 (dd, 1H, $J$ = 5.6 and 2.0 Hz), 6.93−7.05 (m, 2H), 7.24−7.28 (m, 1H), and 8.14 (d, 1H, $J$ = 8.4 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 2.0, 24.1, 30.8, 36.7, 41.0, 45.8, 50.2, 71.3, 93.7, 118.2, 120.7, 125.4, 129.8, 134.4, 140.9, 141.1, 169.8, 171.9, and 202.8; HRMS calcd for $C_{19}H_{19}N_2O_3I$ 450.0440, found 450.0438.

**2-(1-Acetyl-1*H*-indol-3-yl)-*N*-furan-2-yl-*N*-[(*Z*)-3-iodoallyl]-acetamide (35).** To a solution of 0.57 g (2.0 mmol) of indole **29** in 8 mL of DMF was added 0.09 g (2.2 mmol) of NaH (60% dispersion in mineral oil). The reaction mixture was stirred at room temperature for 30 min, and 0.9 g (2.6 mmol) of (*Z*)-1-iodo-3-methane sulfonyloxy-1-propene[42,43] in 2.0 mL of DMF was added dropwise. After an additional 30 min of stirring at room temperature, the reaction was quenched with $H_2O$ and extracted with EtOAc. The organic layer was washed with $H_2O$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to provide 0.37 g (41%) of **35** as a pale yellow oil: IR (neat) 1695, 1608, 1454, 1378, and 1219 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 2.58 (s, 3H), 3.61 (s, 2H), 4.35 (dd, 2H, $J$ = 6.0 and 1.2 Hz), 6.13 (d, 1H, $J$ = 2.0 Hz), 6.32 (dt, 1H, $J$ = 7.6 and 6.0 Hz), 6.41 (dt, 1H, $J$ = 7.6 and 1.2 Hz), 6.43 (dd, 1H, $J$ = 3.2 and 2.0 Hz), 7.23−7.27 (m, 2H), 7.31−7.37 (m, 2H), 7.38 (d, 1H, $J$ = 8.0 Hz), and 8.40 (d, 1H, $J$ = 8.0 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 24.2, 30.6, 52.8, 85.5, 105.7, 111.7, 115.5, 116.8, 118.9, 123.7, 123.9, 125.5, 130.3, 135.7, 136.0, 140.7, 147.9, 168.6, and 171.3; HRMS calcd for $C_{19}H_{17}N_2O_3I$ 448.0284, found 448.0285.

**7-Acetyl-3-[(*Z*)-3-iodoallyl]-3,5,6*a*,7-tetrahydropyrrolo-[2,3-*d*]carbazole-2,6-dione (42).** A solution of 0.37 g (0.8 mmol) of furan **35** in 3.0 mL of toluene was heated at 200 °C in a sealed pressure tube for 2.0 h. The solution was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to afford 0.31 g (84%) of **42** as a pale yellow oil: IR (neat) 1726, 1690, 1475, and 1398 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 2.33 (s, 3H), 2.65 (d, 1H, $J$ = 16.8 Hz), 2.90 (dd, 1H, $J$ = 20.4 and 2.4 Hz), 2.98 (d, 1H, $J$ = 16.8 Hz), 3.03 (dd, 1H, $J$ = 20.4 and 5.2 Hz), 4.22 (ddd, 1H, $J$ = 16.0, 6.4, and 1.6 Hz), 4.48−4.54 (m, 1H), 4.53 (s, 1H), 5.12 (dd, 1H, $J$ = 5.6 and 2.4 Hz), 6.29 (dt, 1H, $J$ = 7.6 and 6.0 Hz), 6.60 (dt, 1H, $J$ = 7.6 and 2.0 Hz), 6.98−7.06 (m, 2H), 7.24−7.28 (m, 1H), and 8.15 (d, 1H, $J$ = 8.0 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 24.1, 36.8, 45.0, 46.0, 50.1, 71.3, 86.4, 94.9, 118.2, 120.9, 125.4, 129.8, 134.4, 134.8, 140.5, 141.1, 169.8, 171.6, and 202.9. Anal. Calcd for $C_{19}H_{17}N_2O_3I$: C, 50.91; H, 3.82; N, 6.25. Found: C, 50.96; H, 4.08; N, 5.97.

**3-[2-(*tert*-Butoxycarbonylfuran-2-yl-amino)-2-oxoethyl]indole-1-carboxylic Acid Methyl Ester (28).** To a solution of 2.3 g (6.8 mmol) of indole **22** in 40 mL of THF was added 1.1 g (8.2 mmol) of dimethyl pyrocarbonate followed by 0.08 g (0.7 mmol) of 4-(dimethyl-amino)pyridine. The reaction mixture was stirred at room temperature for 3 h and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to afford 1.9 g (70%) of **28** as a white solid: mp 90−91 °C; IR (neat) 1787, 1746, 1613, 1260, and 1152 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.44 (s, 9H), 4.01 (s, 3H), 4.25 (s, 2H), 6.14 (d, 1H, $J$ = 3.2 Hz), 6.41 (t, 1H, $J$ = 2.0 Hz), 7.26 (t, 1H, $J$ = 7.2 Hz), 7.32−7.36 (m, 2H), 7.54 (d, 1H, $J$ = 7.2 Hz), 7.64 (s, 1H), and 8.18 (d, 1H, $J$ = 7.2 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 27.9, 33.8, 53.9, 84.3, 106.2, 111.4, 114.1, 115.2, 119.4, 123.1, 124.6, 124.9, 130.4, 135.4, 140.7, 143.7, 151.5, 151.6, and 172.3. Anal. Calcd for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.39; H, 5.65; N, 7.00.

**3-[2-(*N*-Furan-2-yl-amino)-2-oxoethyl]indole-1-carboxylic Acid Methyl Ester (30).** To a solution of 0.3 g (0.75 mmol) of indole **28** in 5 mL of $CH_3CN$ was added 0.02 g (0.09 mmol) of magnesium perchlorate. The solution was heated to 45 °C for 1.5 h and then cooled to room temperature, and the solvent was evaporated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to afford 0.18 g (81%) of **30** as a white solid: mp 138−139 °C; IR (neat) 3242, 1736, 1654, 1557, 1454, and 1383 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.75 (s, 2H), 3.97 (s, 3H), 6.31−6.32 (m, 2H), 6.97 (t, 1H, $J$ = 1.4 Hz), 7.24−7.28 (m, 1H), 7.34−7.38 (m, 1H), 7.52 (d, 1H, $J$ = 7.6 Hz), 7.59 (s, 1H), 8.16 (d, 1H, $J$ = 7.6 Hz), and 8.35 (brs, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 33.2, 54.0, 95.8, 111.6, 114.1, 115.5, 119.1, 123.5, 124.8, 125.4, 129.8, 135.6, 135.7, 145.2, 151.3, and 167.0. Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.24; H, 4.77; N, 9.27.

**3-[(Allyl-furan-2-ylcarbamoyl)methyl]indole-1-carboxylic Acid Methyl Ester (36).** To a solution of 0.24 g (0.8 mmol) of indole **30** in 8 mL of 4:1 DMF/THF were added 0.5 g (1.6 mmol) of $Cs_2CO_3$ and 0.15 mL (1.8 mmol) of allyl bromide. The reaction mixture was heated at 80 °C for 1 h and then cooled to room temperature, quenched with $H_2O$, and extracted with EtOAc. The combined organic layer was washed with $H_2O$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to provide 0.22 g (80%) of **36** as a colorless oil: IR (neat) 1736, 1685, 1608, 1378, and 1260 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.59 (s, 2H), 4.00 (s, 3H), 4.24 (d, 2H, $J$ = 6.4 Hz), 5.12−5.17 (m, 2H), 5.79−5.89 (m, 1H), 6.10 (d, 1H, $J$ = 3.2 Hz), 6.40 (dd, 1H, $J$ = 3.2 and 2.0 Hz), 7.21−7.25 (m, 1H), 7.30−7.34 (m, 2H), 7.43−7.45 (m, 2H), and 8.14−8.16 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 30.8, 51.3, 53.9, 105.3, 111.4, 114.9, 115.3, 118.2, 119.3, 123.0, 124.0, 124.8, 130.3, 132.7, 135.5, 140.4, 148.4, 151.5, and 171.1; HRMS calcd for $C_{19}H_{18}N_2O_4$ 338.1267, found 338.1278.

**3-Allyl-2,6-dioxo-1,2,3,5,6,6a-hexahydropyrrolo[2,3-*d*]-carbazole-7-carboxylic Acid Methyl Ester (43).** A solution of 0.05 g (0.16 mmol) of furan **36** in 1.5 mL of toluene was heated at 200 °C in a sealed pressure tube for 2 h. The solution was cooled to room temperature; the solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to afford 0.05 g (91%) of **43** as a colorless oil: IR (neat) 1726, 1690, 1480, 1388, and 1065 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 2.57 (d, 1H, $J$ = 16.4 Hz), 2.94 (dd, 1H, $J$ = 20.4 and 2.8 Hz), 2.96 (d, 1H, $J$ = 16.4 Hz), 3.04 (dd, 1H, $J$ = 20.4 and 4.8 Hz), 3.84 (brs, 3H), 4.12 (dd, 1H, $J$ = 15.6 and 6.4 Hz), 4.41 (dd, 1H, $J$ = 15.6 and 5.6 Hz), 4.73 (brs, 1H), 5.11 (dd, 1H, $J$ = 4.8 and 3.2 Hz), 5.28−5.34 (m, 2H), 5.79−5.89 (m, 1H), 6.94−7.01 (m, 2H), 7.23−7.27 (m, 1H), and 7.91 (brs, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 36.6, 43.0, 46.3, 50.6, 53.2, 70.7, 95.7, 116.1, 119.1, 121.0, 124.3, 129.7, 131.2, 134.3, 140.0, 140.7, 154.0, 171.7, and 202.3; HRMS calcd for $C_{19}H_{18}N_2O_4$ 338.1267, found 338.1263.

**3-{[(2-Bromo-allyl)-furan-2-ylcarbamoyl]methyl}-indole-1-carboxylic Acid Methyl Ester (37).** To a solution of 0.18 g (0.6 mmol) of indole **30** in 8 mL of 4:1 DMF/THF were added 0.38 g (1.2 mmol) of $Cs_2CO_3$ and 0.17 mL (1.3 mmol) of 2,3-dibromopropene. The reaction mixture was heated at 80 °C for 1 h and then cooled to room temperature, quenched with $H_2O$, and extracted with EtOAc. The combined organic layer was washed with $H_2O$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to provide 0.18 g (74%) of **37** as a pale yellow oil: IR (neat) 1741, 1690, 1613, 1372, and 1255 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.63 (s, 2H), 4.01 (s, 3H), 4.51 (s, 2H), 5.54 (d, 1H, $J$ = 2.0 Hz), 5.72 (d, 1H, $J$ = 2.0 Hz), 6.21 (d, 1H, $J$ = 3.2 Hz), 6.41 (dd, 1H, $J$ = 3.2 and 2.0 Hz), 7.21−7.25 (m, 1H), 7.30−7.34 (m, 2H), 7.42−7.45 (m, 2H), and 8.14 (d, 1H, $J$ = 6.4 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 30.8, 53.9, 55.6, 105.9, 111.5, 114.5, 115.3, 119.3, 119.4, 123.1, 124.1, 124.9, 127.8, 130.2, 135.5, 140.6, 147.5, 151.5, and 171.2; HRMS calcd for $C_{19}H_{17}N_2O_4Br$ 416.0372, found 416.0361.

**3-(2-Bromoallyl)-2,6-dioxo-1,2,3,5,6,6*a*-hexahydropyrrolo[2,3-*d*]carbazole-7-carboxylic Acid Methyl Ester (44).** A solution of 0.16 g (0.4 mmol) of furan **37** in 1.5 mL of toluene was heated at 200 °C in a sealed pressure tube for 2 h. The solution was cooled to room temperature; the solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography using a 5% ethyl

acetate−hexane mixture to afford 0.08 g (50%) of **44** as a pale yellow oil: IR (neat) 1731, 1690, 1485, 1383, and 1311 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 2.62 (d, 1H, $J$ = 16.6 Hz), 2.95 (dd, 1H, $J$ = 20.8 and 3.2 Hz), 3.00 (d, 1H, $J$ = 16.6 Hz), 3.05 (dd, 1H, $J$ = 20.8 and 4.8 Hz), 3.84 (brs, 3H), 4.40 (d, 1H, $J$ = 16.0 Hz), 4.63 (d, 1H, $J$ = 16.0 Hz), 4.74 (brs, 1H), 5.17 (dd, 1H, $J$ = 5.2 and 3.2 Hz), 5.72 (d, 1H, $J$ = 2.0 Hz), 5.90 (d, 1H, $J$ = 2.0 Hz), 6.98 (t, 1H, $J$ = 7.2 Hz), 7.20−7.28 (m, 2H), and 7.91 (brs, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 36.6, 46.1, 48.3, 50.5, 53.2, 70.8, 96.1, 116.1, 120.6, 121.6, 124.4, 126.3, 129.8, 134.0, 139.6, 140.7, 153.9, 171.9, and 202.1. Anal. Calcd for $C_{19}H_{17}N_2O_4Br$: 416.0372. Found: 416.0363.

**7-Acetyl-3-allyl-6-(*tert*-dimethyl-silanyloxy)-5,6,6*a*,7-tetrahydro-*3H*-pyrrolo-[2,3-*d*]carbazol-2-one (47).** To a solution of 0.5 g (1.5 mmol) of the tetracyclic ketone **40** in 40 mL of EtOH was added 0.06 g (1.5 mmol) of $NaBH_4$. The reaction mixture was stirred for 10 min at room temperature; $H_2O$ was added, and this was followed by extraction with $CH_2Cl_2$. The combined organic layers were washed with $H_2O$ and dried over $MgSO_4$. After removing the solvent under reduced pressure, the resulting residue was dissolved with 20 mL of $CH_2Cl_2$ and cooled to 0 °C. To this mixture was added 0.35 mL (3.0 mmol) of 2,6-lutidine, followed by the addition of 0.5 mL (2.3 mmol) of TBSOTf via syringe. After stirring for 20 min, the reaction mixture was warmed to 25 °C and stirred for an additional 2 h. The reaction was quenched by the addition of water, and the mixture was extracted with $CH_2Cl_2$. The combined organic layers were washed with 0.1 N HCl, water, and brine, respectively. The solution was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to give 0.43 g (60%) of **47** as a pale yellow oil: IR (neat) 1726, 1677, 1395, and 751 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 400 MHz) $\delta$ 0.06 (s, 3H), 0.09 (s, 3H), 0.83 (s, 9H), 1.78 (ddd, 1H, $J$ = 15.0, 9.6, and 3.2 Hz), 2.22 (dddd, 1H, $J$ = 15.0, 7.6, 4.4, and 0.8 Hz), 2.27 (s, 3H), 2.48 (d, 1H, $J$ = 17.0 Hz), 2.97 (d, 1H, $J$ = 17.0 Hz), 4.06−4.13 (m, 2H), 4.26 (ddt, 1H, $J$ = 16.0, 5.2, and 1.6 Hz), 4.70 (d, 1H, $J$ = 5.6 Hz), 4.97 (dd, 1H, $J$ = 7.6 and 3.2 Hz), 5.44 (dq, 1H, $J$ = 10.6 and 1.6 Hz), 5.30 (dq, 1H, 17.0 and 1.6 Hz), 5.83−5.93 (m, 1H), 6.97−7.01 (m, 2H), 7.17−7.24 (m, 1H), and 7.89 (brs, 1H); $^{13}C$ NMR ($CD_3CN$, 100 MHz) $\delta$ −3.9, −3.7, 19.0, 25.5, 26.6, 30.7, 43.5, 47.1, 49.8, 68.4, 71.2, 96.6, 117.4, 118.6, 121.9, 125.6, 129.4, 133.2, 138.8, 144.3, 144.5, 171.2, and 173.5; HRMS calcd for $[(C_{25}H_{34}N_2O_3Si) + Li]^+$ 445.2499, found 445.2513.

**7-Acetyl-3-allyl-4-bromo-6-(*tert*-dimethyl-silanyloxy)-5,6,6*a*,7-tetrahydro-*3H*-pyrrolo[2,3-*d*]carbazol-2-one (48).** To a solution of 0.43 g (1.0 mmol) of **47** in 25 mL of $CH_2Cl_2$ was added 0.19 g (1.0 mmol) of NBS at 25 °C. After stirring for 2 h, the reaction mixture was quenched with $H_2O$ and extracted with $CH_2Cl_2$. The combined organic layers were washed with $H_2O$, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to afford 0.37 g (66%) of **48** as a clear oil: IR (neat) 1725, 1667, 1215, and 769 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 400 MHz) $\delta$ −0.04 (s, 3H), −0.06 (s, 3H), 0.71 (s, 9H), 2.27 (s, 3H), 2.38 (d, 1H, 16.0 Hz), 2.40 (dd, 1H, 16.2 and 7.2 Hz), 2.68 (dd, 1H, 16.2 and 3.6 Hz), 2.97 (d, 1H, 16.0 Hz), 4.31 (ddd, 1H, 7.2, 5.2 and 3.6 Hz), 4.63 (dt, 2H, 5.6, and 1.6 Hz), 4.65 (brs, 1H), 5.28 (dq, 1H, 10.0, and 1.6 Hz), 5.78 (dq, 1H, 16.8, and 1.6 Hz), 6.02−6.12 (m, 1H), 6.95−7.02 (m, 2H), 7.20 (ddd, 1H, 7.8, 7.4, and 2.0 Hz), and 7.86 (brs, 1H); $^{13}C$ NMR ($CD_3CN$, 150 MHz) $\delta$ −4.6, −4.1, 18.7, 24.8, 26.2, 44.0, 45.1, 47.8, 53.7, 67.6, 70.5, 91.6, 117.7, 118.5, 121.3, 125.4, 129.6, 134.7, 138.1, 139.1, 144.1, 170.5, and 174.2.

**6-Acetyl-5-(*tert*-dimethyl-silanyloxy)-2,3,4,5,5*a*,6-hexahydro-1*H*-6,12*a*-diaza-indeno[7,1-*cd*]fluoren-12-one (50).** To a solution of 0.2 g (0.39 mmol) of **48** in 40 mL of anhydrous benzene were added 0.18 g (0.6 mmol) of $Bu_3SnH$ and 7 mg (0.039 mmol) of AIBN. The resultant mixture was placed in a preheated oil bath at 90 °C, and the mixture was heated at reflux for 12 h. The solvent was removed under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography to afford 0.16 g (91%) of **50** as a white solid: mp 152−154 °C; IR (neat) 1697, 1659, 1479, 1397, and 750 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 400 MHz) $\delta$ −0.03 (s, 3H), 0.05 (s, 3H), 0.73 (s, 9H), 1.80 (m, 1H), 1.88 (m, 2H), 2.03 (m, 2H), 2.14 (dd, 1H, 15.6 and 4.0 Hz), 2.27 (s, 3H), 2.34 (d, 1H, 16.4 Hz), 2.81 (d, 1H, 16.4 Hz), 3.47 (ddd, 1H, 13.0, 8.0, and 3.6 Hz), 3.70 (ddd, 1H, 13.0, 6.4, and 6.4 Hz), 4.23 (ddd, 1H, 7.2, 6.4, and 4.0 Hz), 4.61 (d, 1H, 4.4 Hz), 6.96 (ddd, 1H, 7.6, 7.2 and 0.8 Hz), 7.05 (dd, 1H, 7.6 and 1.2 Hz), 7.16 (ddd, 1H, 8.0, 7.2, and 1.2 Hz), and 7.85 (brs, 1H); $^{13}C$ NMR ($CD_3CN$, 100 MHz) $\delta$ −4.3, −3.9, 18.8, 22.4, 25.1, 26.1, 26.3, 26.4, 35.6, 40.0, 48.6, 68.4, 70.7, 106.9, 117.6, 121.6, 125.3, 129.0, 135.9, 139.6, 144.1, 170.8, and 172.5; HRMS calcd for $C_{25}H_{33}N_2O_3Si$ 438.2339, found 438.2334.

**Methyl 3-((*N*-(Furan-2-yl)-*N*-((*Z*)-2-iodobut-2-enyl)carbamoyl)methyl)-1*H*-indole-1-carboxylate (53).** To a solution containing 0.3 g (1.0 mmol) of 2-amidofuran **30** and 15 mL of a 4:1 DMF/THF mixture at room temperature was added 0.7 g (2.1 mmol) of cesium carbonate. The reaction mixture was stirred at room temperature for 30 min, and 0.5 g (2.1 mmol) of (*Z*)-1-bromo-2-iodobut-2-ene was added in one portion. The reaction mixture was heated at 80 °C for 2 h and then cooled to room temperature, quenched with $H_2O$, and extracted with EtOAc. The organic layer was washed with $H_2O$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to provide 0.34 g (76%) of methyl 3-((*N*-(furan-2-yl)-*N*-((*Z*)-2-iodobut-2-enyl)carb-amoyl)methyl)-1*H*-indole-1-carboxylate (**53**)-as a pale yellow oil: IR (neat) 1734, 1689, 1456, 1257, and 735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.70 (d, 3H, $J$ = 6.4 Hz), 3.62 (s, 2H), 4.01 (s, 3H), 4.59 (s, 3H), 4.72 (q, 1H, $J$ = 6.4 Hz), 6.19 (d, 1H, $J$ = 2.4 Hz), 6.38 (dd, 1H, $J$ = 3.6 and 2.4 Hz), 7.23 (t, 1H, $J$ = 7.6 Hz), 7.30−7.34 (m, 2H), 7.45 (d, 1H, $J$ = 7.6 Hz), 7.47 (s, 1H), and 8.14 (brs, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 21.8, 30.9, 53.8, 103.0, 106.2, 111.4, 115.2, 119.3, 122.9, 124.0, 124.8, 130.2, 134.0, 135.4, 140.4, 147.3, 151.4, and 171.1; HRMS calcd for $[(C_{20}H_{19}IN_2O_4) + Li]^+$ 485.0550, found 485.0547.

**Methyl 2,3,9,10-Tetrahydro-1-((*Z*)-2-iodobut-2-enyl)-2,9-dioxo-1*H*-pyrrolo[2,3-*d*]carbazole-8-(8a*H*)-carboxylate (54).** A solution of 0.3 g (0.6 mmol) of amide **53** in 1 mL of toluene was heated at 200 °C for 2 h, cooled to room temperature, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to provide 0.26 g (87%) of ketone **54** as a pale yellow oil: IR (neat) 1728, 1685, 1477, 1386, and 731 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 600 MHz) $\delta$ 1.79 (d, 3H, $J$ = 6.6 Hz), 2.58 (d, 1H, $J$ = 16.8 Hz), 2.89 (dd, 1H, $J$ = 19.8 and 3.0 Hz), 2.94 (d, 1H, $J$ = 16.8 Hz), 2.98 (dd, 1H, $J$ = 19.8 and 5.4 Hz), 3.84 (s, 3H), 4.47 (d, 1H, $J$ = 16.2 Hz), 4.62 (d, 1H, $J$ = 16.2 Hz), 4.72 (brs, 1H), 5.11 (dd, 1H, $J$ = 5.4 and 3.0 Hz), 5.96 (q, 1H, $J$ = 6.6 Hz), 6.95 (t, 1H, $J$ = 7.8 Hz), 7.22 (t, 2H, $J$ = 7.8 Hz), and 7.78 (brs, 1H); $^{13}C$ NMR ($CDCl_3$, 150 MHz) $\delta$ 21.9, 36.6, 46.3, 50.4, 52.2, 53.2, 70.9, 88.5, 95.9, 101.4, 116.1, 122.0, 124.3, 129.7, 134.5, 140.2, 140.5, 154.0, 171.9, and 201.9.

**Preparation of Carbamate 57.** To the solution of 0.05 g (0.1 mmol) of ketone **54** in 1 mL of MeOH was added 4.5 mg (0.1 mmol) of $NaBH_4$. The reaction was stirred at room temperature for 5 min, quenched with $H_2O$, and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to provide 0.04 g (93%) of **57** as a clear oil: IR (neat) 1770, 1673, 1275, 1001, and 729 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 600 MHz) $\delta$ 1.77 (d, 3H, $J$ = 6.6 Hz), 1.83−1.89 (m,1H), 2.58−2.63 (m, 1H), 2.90 (s, 2H), 4.33 (d, 1H, $J$ = 15.6 Hz), 4.66 (d, 1H, $J$ = 15.6 Hz), 4.77 (dt, 1H, $J$ = 10.8 and 6.0

Hz), 4.81 (d, 1H, $J$ = 6.0 Hz), 4.89 (dd, 1H, $J$ = 7.8 and 3.0 Hz), 4.93 (q, 1H, $J$ = 6.6 Hz), 7.08 (t, 1H, $J$ = 7.8 Hz), 7.29 (d, 1H, $J$ = 7.8 Hz), 7.30 (t, 1H, $J$ = 7.8 Hz), and 7.42 (d, 1H, $J$ = 7.8 Hz); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 22.0, 26.0, 29.9, 47.1, 47.5, 51.8, 67.5, 94.1, 101.4, 114.2, 123.2, 125.5, 129.9, 134.6, 136.8, 141.9, 143.2, 158.4, and 172.3.

**Preparation of Alkyne 58.** To a solution of 0.1 g (0.2 mmol) of carbamate **57** in 3 mL of toluene was added 0.07 mL (1.2 mmol) of DBU. The mixture was heated at reflux for 12 h, cooled to room temperature, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using a 5% ethyl acetate−hexane mixture to provide 0.06 g (78%) of **58** as a white solid: mp 210−212 °C; IR (neat) 1770, 1727, 1675, and 752 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 1.78 (t, 3H, $J$ = 2.4 Hz), 1.89−1.94 (m,1H), 2.66−2.71 (m, 1H), 2.83 (d, 1H, $J$ = 16.8 Hz), 2.88 (d, 1H, $J$ = 16.8 Hz), 4.24 (dq, 1H, $J$ = 16.8 and 2.4 Hz), 4.36 (dq, 1H, $J$ = 16.8 and 2.4 Hz), 4.81 (d, 1H, $J$ = 6.0 Hz), 4.83 (dt, 1H, $J$ = 12.0 and 6.0 Hz), 5.06 (dd, 1H, $J$ = 7.8 and 3.0 Hz), 7.06 (d, 1H, $J$ = 7.8 Hz), 7.08 (t, 1H, $J$ = 7.8 Hz), 7.31 (t, 1H, $J$ = 7.8 Hz), and 7.44 (d, 1H, $J$ = 7.8 Hz); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 3.7, 26.0, 30.1, 46.9, 47.7, 67.2, 71.8, 77.6, 80.4, 93.9, 114.3, 122.2, 125.6, 130.0, 137.0, 141.9, 142.7, 158.5, and 171.5. Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.08; H, 5.06; N, 8.72.

**1-(But-2-ynyl)-8,8*a*-dihydro-1*H*-pyrrolo[2,3-*d*]carbazol-2(3*H*)-one (59).** To a solution of 0.03 g (0.09 mmol) of the above alkyne **58** in 1 mL of toluene was added 0.5 mL of DBU. The reaction mixture was heated at reflux for 12 h, quenched with water, and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give 0.02 g (70%) of **59** as a pale yellow oil: $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 1.80 (t, 3H, $J$ = 2.4 Hz), 2.55 (d, 1H, $J$ = 16.8 Hz), 2.72 (d, 1H, $J$ = 16.8 Hz), 3.90 (brs,1H), 4.20 (dq, 1H, $J$ = 16.8 and 2.4 Hz), 4.53 (dq, 1H, $J$ = 16.8 and 2.4 Hz), 5.54 (m,1H), 5.20 (dd, 1H, $J$ = 9.6 and 2.4 Hz), 5.33 (d, 1H, $J$ = 6.0 Hz), 5.97 (ddd, 1H, $J$ = 9.6, 6.0, and 2.4 Hz), 6.70 (d, 1H, $J$ = 7.8 Hz), 6.71 (t, 1H, $J$ = 7.8 Hz), 6.92 (dd, 1H, $J$ = 7.8 and 1.2 Hz), and 7.07 (td, 1H, $J$ = 7.8 and 1.2 Hz).

**Acknowledgment.** This research was supported by the National Science Foundation (Grant CHE-0132651).

**Supporting Information Available:** Spectroscopic and experimental procedures for compounds **20**, **21**, **31**, **38**, **45**, and **46** and $^1$H and $^{13}$C NMR spectra for new compounds lacking elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049808I