A Cycloaddition Approach toward the Synthesis of Substituted Indolines and Tetrahydroquinolines

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The intramolecular Diels−Alder reaction of 2-substituted aminofurans (IMDAF) results in the formation of various indolines and tetrahydroquinolines. The isolation of these ring systems from the IMDAF reaction can be rationalized in terms of an initial [4 + 2]-cycloaddition that first produces an oxa-bridged cycloadduct, which was not detected since it readily underwent nitrogen-assisted ring opening. Proton exchange followed by an eventual dehydration provides the aromatic product. In certain cases, the intermediate cyclohexadienol can be isolated and independently converted to the final product in high yield. The starting 2-aminofurans were readily prepared from furanyl acyl azide by a Curtius rearrangement in the presence of an alcohol. Alkylation of the resulting *N*-alkyl carbamate with an alkenyl bromide allows for the synthesis of a wide variety of cycloaddition precursors. The scope of the IMDAF reaction was evaluated by using mono- and disubstituted alkenes, electron rich and electron deficient olefins, and acetylenic tethers. Cyclic 2-amidofurans were also synthesized using a related intramolecular Diels−Alder reaction of 2-amido-substituted oxazoles which contain a tethered alkyne. This transformation represents a new route to this rare heterocyclic ring system. The sequential cycloaddition method was used for a formal synthesis of the pyrrolophenanthridone alkaloid hippadine.

Introduction

Functionalized indoles[1] and quinolines,[2] along with their dihydro and tetrahydro derivatives, have been of interest to organic chemists for many years due to the large number of natural products that contain these heterocycles.[3] Indoles display a wide range of biological activities,[4] and an unusually large number of drugs contain this heterocyclic nucleus.[5] This is exemplified by the amino acid tryptophan, the hormones serotonin and melatonin, the antiarthritic indomethacin, and the psychotropic indole LSD.[6] The potent antitumor agent Dynemicin A[7] and the antiviral agent Virantmycin[8] represent important natural products that contain the quinoline core. Accordingly, the synthesis of indoles and quinolines has long been a topic of fundamental interest to organic and medicinal chemists.[6]

The closely related indolines[9] and tetrahydroquinolines[10] have also attracted considerable attention due to their pronounced activity in many physiological processes.[11] These heterocycles are found in numerous commercial products, including pharmaceuticals, fragrances, and dyes.[12] Many strategies have been developed for the preparation of these compounds.[13] One of the major routes involves the partial reduction of the heteroaromatic ring system.[14] Other methods utilize a nucleophilic aromatic cyclization reaction of an *N*-substituted aniline derivative containing a suitable π-acceptor,[15] a 1,5-electrocyclization reaction,[16] and a nucleophilic attack of styrene derivatives onto a transient nitrene species.[17] Recently, Larock has reported that the pal-

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(1) Saxton, J. E. *Nat. Prod. Rep.* **1997**, *14*, 559. Ihara, M.; Fukumoto, K. *Nat. Prod. Rep.* **1997**, *14*, 413. Joshi, K. C.; Chand, P. *Pharm.* **1982**, *37*, 1−12. Gilchrist, T. L. *Heterocyclic Chemistry*; Pitman: London, 1981. Pindur, U.; Adam, R. *J. Heterocycl. Chem.* **1988**, *25*, 1.

(2) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605. Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; McKillop, A., Ed.; Pergamon Press: Oxford, 1996; Vol. 5, Chapter 5.06, pp 246−300. Yates, F. S. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon Press: Oxford, 1984; Vol. 2, part 2A, Chapter 2.09, pp 511−524.

(3) Hesse, M. *Alkaloid Chemistry*; Wiley: New York, 1978. Cordell, G. A. *Introduction to Alkaloids: A Biogenetic Approach*; Wiley: New York, 1981.

(4) Hugel, H. M.; Kennaway, D. *J. Org. Prep. Proc. Int.* **1995**, *27*, 1. Glennon, R. A. *J. Med. Chem.* **1987**, *30*, 1.

(5) Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996; and references therein.

(6) For reviews, see: Gribble, G. W. *Contemporary. Org. Synth.* **1994**, 145−172. Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Bird, C. W., Ed.; Pergamon Press: Oxford, 1996; Vol. 2, Chapter 2.04, pp 207−257.

(7) Isobe, M.; Nishikawa, T.; Yamamoto, N.; Tsukiyama, T.; Ino, A.; Okita, T. *J. Heterocycl. Chem.* **1992**, *29*, 619. Magnus, P.; Parry, D.; IIiadis, T.; Eisenbeis, S. A.; Fairhuist, R. A. *J. Chem. Soc., Chem. Commun.* **1994**, 1543.

(8) Morimoto, Y.; Matsuda, F.; Shirahama, H. *Synlett* **1991**, 202.

(9) Joshi, K. C.; Chand, P. *Pharm.* **1982**, *37*, 1. Somei, M.; Saida, Y.; Funamoto, T.; Ohta, T. *Chem. Pharm. Bull.* **1987**, *35*, 3146. Takahashi, K.; Kametani, T. *Heterocycles* **1979**, *13*, 411. Kamentani, T.; Takahashi, K. *Heterocycles* **1978**, *9*, 293.

(10) De Kimpe, N.; Keppens, M. *Tetrahedron* **1996**, *52*, 3705.

(11) Carling, R. W.; Leeson, P. D.; Moseley, A. M.; Smith, J. D.; Saywell, K.; Tricklebank, M. D.; Kemp, J. A.; Marshall, G. R.; Foster, A. C.; Grimwood, S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 65.

(12) Wright, G. C.; Portlock, D. E. Ger. Offen. 3004370, 1980; *Chem. Abstr.* **1980**, *93*, 239262u. Kurahashi, Y.; Shiokawa, K.; Goto, T.; Kagabu, S.; Kamochi, A.; Moriya, K.; Hayakawa, H. Eur. Patent 173208, 1986; *Chem. Abstr.* **1986**, *105*, 78937s. Rose, D.; Busch, P.; Lieske, E. Ger. Offen. 2714955, 1978; *Chem. Abstr.* **1979**, *90*, 43672w.

(13) Beckwith, A. L. J.; Meijs, G. F. *J. Org. Chem.* **1987**, *52*, 1922. Beckwith, A. L. J.; Gara, W. B. *J. Chem. Soc., Perkin Trans. 2* **1975**, 795. Dittami, J. P.; Ramanathan, H. *Tetrahedron Lett.* **1988**, *29*, 45. Jones, K.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1992**, 1766. Murphy, J. A.; Kizil, M.; Lampard, C. *Tetrahedron Lett.* **1996**, *37*, 2511. Ozlu, Y.; Cladingboel, D. E.; Parsons, P. J. *Synlett* **1993**, 357.

(14) Gribble, G. W.; Heald, P. W. *Synthesis* **1975**, 650. Draper, P. M.; MacLean, D. B. *Can. J. Chem.* **1968**, *46*, 1499. Kikugawa, Y.; Saito, K.; Yamada, S. *Synthesis* **1978**, 447. Ferles, M.; Kocián, O. *Collect. Czech. Chem. Commun.* **1979**, *44*, 3141. Scopes, D. I. C.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2810. Stutz, R. L.; Reynolds, C. A.; McEwen, W. E. *J. Org. Chem.* **1961**, *26*, 1684. Metzger, J.; Larivé, H.; Vincent, E. J.; Dennilauler, R. *Bull. Soc. Chim. Fr.* **1967**, 46.

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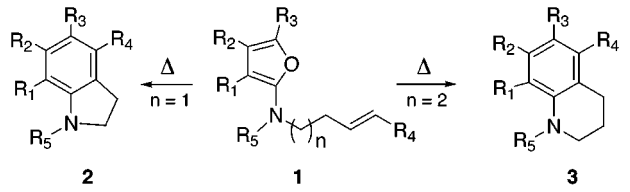
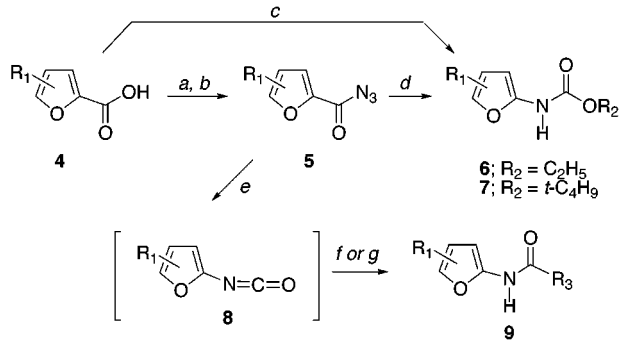
Scheme 1



Scheme 2



Reagents: (a) $SOCl_2$, C_6H_6; (b) NaN_3, Et_2O/H_2O; (c) $N_3PO(OPh)_2$, NEt_3, R_2OH, Δ; (d) Δ, R_2OH; (e) Δ, C_6H_6; (f) $(R_3)_2Cu(CN)Li_2$, H_3O^+; (g) R_3MgX, H_3O^+

ladium-catalyzed cross-coupling of *o*-vinylic and allylic anilides with vinylic halides and triflates produces dihydroindoles and tetrahydroquinolines.[18] In all of these examples, the degree of substitution on the benzenoid portion of the molecule is set prior to the cyclization step. A method that would generate the aromatic portion of an indoline or tetrahydroquinoline ring system by a cycloaddition reaction would be extremely useful and complementary to the existing methods. To date, cycloaddition approaches to these ring systems are limited to the [4 + 2]-cycloaddition of azadienes[19] and *o*-xylylenes[20] which, in turn, are derived from substituted anilines. Our ongoing interest in the synthesis of heterocyclic compounds by the [4 + 2]-cycloaddition of aminofurans[21] coupled with our recent success in the development of an efficient procedure for the synthesis of octahydroindole-based alkaloids[22] by an intramolecular furan Diels−Alder reaction (IMDAF)[23−25] encouraged us to investigate the possible application of this methodology to the synthesis of a variety of substituted indolines (**2**) and tetrahydroquinolines (**3**). Our planned approach is outlined in Scheme 1 and involves an IMDAF reaction of 2-amino-substituted furans. During the course of our studies, we also had the occasion to extend this cycloaddition strategy to include 2-amido-substituted oxazoles that possess tethered alkynes since we were interested in using this reaction as an approach toward the synthesis of the pyrrolophenanthridone alkaloids.[26] The present paper documents the results of this investigation.

Results and Discussion

Synthesis of the 2-aminofuranyl system was accomplished using a number of different procedures depending upon the scale and the specific furan desired (Scheme 2). The most frequently employed method involved converting a 2-furoic acid such as **4** into the corresponding acid chloride with thionyl chloride followed by reaction with sodium azide which provided the acyl azide **5** in good overall yield. A Curtius rearrangement was carried out by heating azide **5** in the appropriate alcohol. This method was used for the large scale preparation (i.e. >50 g) of several of the furanyl carbamate derivatives (*vide infra*). An alternative synthesis that was employed, when smaller quantities of the carbamate (i.e. <1 g) were needed, consisted of heating the 2-furoic acid with diphenyl phosphorylazidate[27] in an alcoholic solvent. A third method that was used to prepare amido-substituted furans such as **9** involved the *in situ* generation of furyl isocyanate **8** from the appropriate acyl azide. Subsequent quenching with either a higher order cyanocuprate or a Grignard reagent afforded the desired 2-amido-substituted furanyl system **9**.[28]

Intramolecular Diels−Alder Reaction of 2-Amidofurans. We began our investigation of the intramolecular [4 + 2]-aminofuran cycloaddition reaction by first preparing the Boc-protected furans **10** and **12** which contain unactivated π-bonds (Scheme 3). Attachment of the alkenyl tether was accomplished by treating furan-2-ylcarbamic acid *tert*-butyl ester (**7**) with potassium carbonate/sodium hydroxide/tetrabutylammonium hydrogen sulfate in benzene followed by the addition of 1-bromo-3-butene or 1-bromo-4-pentene. Furanyl carbamates **10** and **12** were obtained in 77% and 81% yields, respectively. The IMDAF reaction was carried out by heating a benzene solution of the carbamate in a sealed tube at 155−165 °C for 17 h. Disappointingly, under these conditions, indoline **11** was obtained in only 16% yield. The reaction mixture contained a significant amount of a dark tar which was present in even greater quantities when carbamate **10** was heated for longer periods of time. We assume that the thermal instability of the *tert*-butyl carbamate portion of the molecule at the elevated temperatures is responsible for the low yield of product. Another possibility is that the transient cyclo-

(15) Hegedus, L. S.; Allen, G. F.; Bozell, J. T.; Wateman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800. Venkataramu, S. D.; Macdonell, G. D.; Purdum, W. R.; Dilbeck, G. A.; Berlin, K. D. *J. Org. Chem.* **1977**, *42*, 2195. Bringi, N. V.; Deshmukh, P. V. *J. Org. Chem.* **1962**, *27*, 4117. Mortelmans, C.; Van Binst, G. *Tetrahedron* **1978**, *34*, 363. Katritzky, A. R.; Rachwal, B.; Rachwal, R. *J. Org. Chem.* **1995**, *60*, 7631.

(16) Thummel, R. P.; Kohli, D. K. *J. Org. Chem.* **1977**, *42*, 2742.

(17) Sundberg, R. J. In *The Chemistry of Indoles*; Academic Press: New York and London, 1970; pp 142−213. Speckamp, N. W. *Heterocycles* **1984**, *21*, 211.

(18) Larock, R. C.; Yang, H.; Pace, P.; Cacchi, S.; Fabrizi, G. *Tetrahedron Lett.* **1998**, *39*, 1885.

(19) Beifuss, U.; Ledderhose, S. *J. Chem. Soc., Chem. Commun.* **1995**, 2137. Beifuss, U.; Kunz, O.; Ledderhose, S.; Toraschewski, M.; Tonko, C. *Synlett* **1996**, 34. Boger, D. L.; Weinreb, S. N. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. Noland, W. E.; Kim, J. K.; Lee, C. K.; Bae, S. K.; Hahn, C. S. *J. Org. Chem.* **1980**, *45*, 4582. Lucchini, V.; Prato, M.; Scorrano, G.; Stivanello, M.; Valle, G. *J. Chem. Soc., Perkin Trans. 2* **1992**, 259. Crousse, B.; Begue, J. P.; Bonnet-Delphon, D. *Tetrahedron Lett.* **1998**, *39*, 5765.

(20) Wojciechowski, K. *Synlett* **1991**, 571. Letulle, M.; Guenot, P.; Ripoll, J. L. *Tetrahedron Lett.* **1991**, *32*, 2013.

(21) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088; **1998**, *63*, 3986.

(22) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304.

(23) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179.

(24) Sternbach, D. D.; Rossana, D. M.; Onan, K. D. *J. Org. Chem.* **1984**, *49*, 3427.

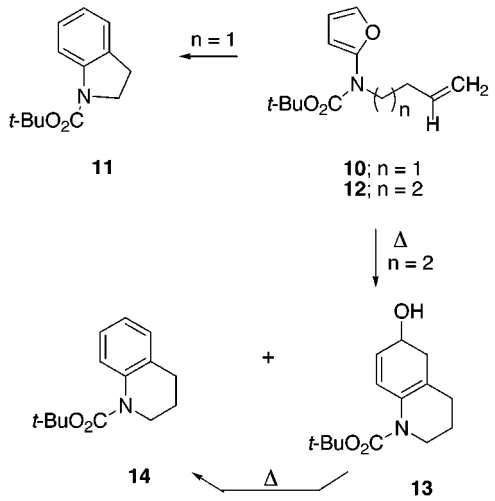
(25) Jung, M. E.; Gervey, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469. Klein, L. L. *J. Org. Chem.* **1985**, *50*, 1770.

(26) For a preliminary report, see: Liu, B.; Padwa, A. *Tetrahedron Lett.* **1999**, *40*, 1645.

(27) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

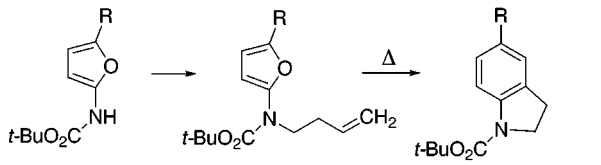
(28) Singleton, H. M.; Edwards, W. R. Jr. *J. Org. Chem.* **1938**, *60*, 540.

Scheme 3



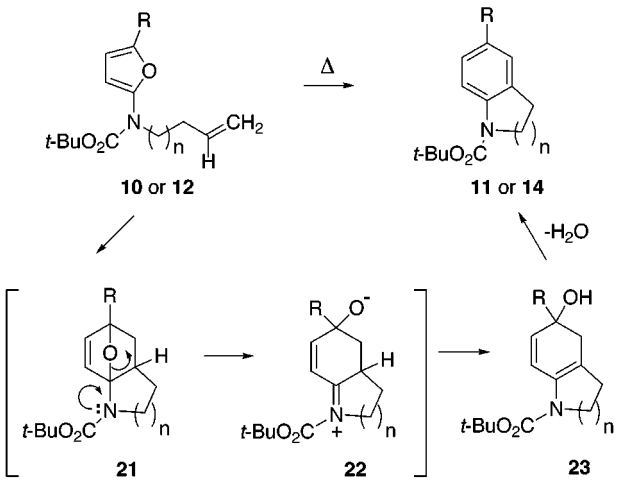
hexadienol that is initially formed (i.e. **23**) may not undergo an easy dehydration in this case and, consequently, alternate pathways may compete with indoline formation. When the homologous carbamate **12** was subjected to the same thermal conditions, cyclohexadienol **13** (28%) and tetrahydroquinoline **14** (33%) were obtained. Alcohol **13** was quantitatively converted to **14** upon further heating in toluene. The overall yield of tetrahydroquinoline **14** corresponded to a respectable 60% by carrying out the thermolysis of **12** at 165 °C for 24 h.

Having established that 2-amino-substituted furans can undergo the IMDAF cycloaddition to produce the indoline and tetrahydroquinoline ring systems, we next examined the effect of placing an aryl or alkyl substituent at the 5-position of the furan ring. These carbamates were synthesized from the corresponding 2-furoic acid derivatives using the one-step protocol of heating the carboxylic acid with diphenyl phosphorylazidate and triethylamine in *tert*-butyl alcohol at 80 °C which resulted in the formation of furans **15** and **18** in 87% and 86% yields, respectively. The carbamates were subjected to the standard alkylation conditions (see Experimental Section) using 1-bromo-3-butene to produce furans **16** and **19** in 68% and 95% yields, respectively. Thermolysis of **16** and **19** at 165 °C for 24 h furnished indolines **17** and **20** in 77% and 57% yields.



The formation of the indoline and tetrahydroquinoline rings from this reaction can be rationalized in terms of an initial Diels−Alder cycloaddition that first produces an oxa-bridged cycloadduct, which was not detected since it readily underwent nitrogen-assisted ring opening (Scheme 4). Proton exchange followed by an eventual dehydration provides the aromatic product. In certain cases, the intermediate cyclohexadienol (i.e. **23**) can be isolated and independently converted to the final product in high yield.

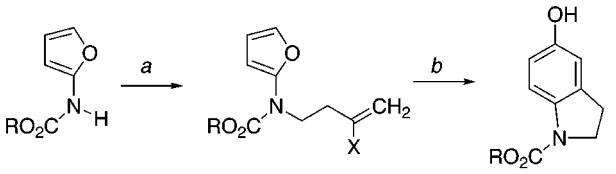
Scheme 4



At this point in our studies we became interested in determining what effect a leaving group on the 2-position of the olefinic tether would have on the cycloaddition reaction. To this end, we treated furan-2-ylcarbamic acid *tert*-butyl ester (**7**) with 2,4-dibromo-1-butene which afforded furan **24** in 90% yield. Unfortunately, the thermolysis of this carbamate provided less than 5% of the desired cycloadduct **25**. Instead, significant quantities of several unindentified decomposition products were obtained. We assume that the low yield of **25** is related to the loss of hydrogen bromide under the thermal conditions which facilitate decomposition of the starting *tert*-butyl carbamate. To overcome this problem, we examined the thermal behavior of furan **26** which contained a thiophenyl-substituted alkenyl group. Heating this carbamate now provided the phenolic indoline **25** in 87% yield by elimination of thiophenol rather than HBr from the initially formed cycloadduct. We also examined the cycloaddition behavior of the thermally more robust *N*-ethyl carbamate derivative **27** which furnished phenol **28** in 80% yield upon heating at 160 °C for 7 h. Isolation of **28**, in such high yield relative to the *tert*-butyl carbamate system, is clearly a reflection of the greater thermal and acid stability of the *N*-ethyl derivative, thereby allowing the [4 + 2]-cycloaddition reaction to occur prior to carbamate decomposition. The phenolic functionality present in the aromatic ring of indolines **25** and **28** has the potential to be transformed into an aryl triflate and used for palladium-catalyzed cross-coupling chemistry to afford more highly functionalized products.[29]

We next investigated the Diels−Alder cycloaddition reaction of 2-amido-substituted furans that contained tethered acetylenic π-bonds. The thermal IMDAF reaction of furan **29** occurred at 170 °C over a 24 h period to give indoline **30** in only 25% yield. Once again, we attribute the low yield of the product to the thermal lability of the *tert*-butyl carbamate portion of the molecule. Simply changing the *tert*-butyl to the *N*-ethyl carbamate (i.e. **31**) had a major effect on the cycloaddition yield. The thermal reaction of **31** gave the 4,5-disubstituted-2,3-indoline **32** in 82% yield. The tetrahydroquinoline ring system could also be easily generated by adjusting the tether length. Thus, furans **33** and **35** were

(29) Arcadi, A.; Cacchi, S.; Marinelli, F.; Morera, E.; Ortar, G. *Tetrahedron* **1990**, *46*, 7151. Barf, T. A.; Boer, P.; Wikström, H.; Peroutka, S. J.; Svensson, K.; Ennis, M. D.; Ghazab, N. B.; McGuire, J. C.; Smith, M. W. *J. Med. Chem.* **1996**, *39*, 4717.



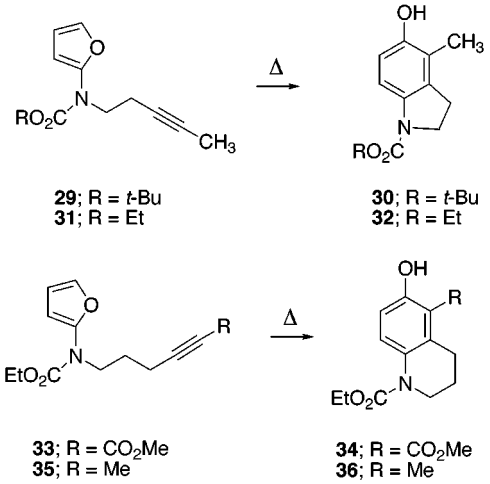
6; R = Et
7; R = *t*-Bu

24; R = *t*-Bu, X = Br
26; R = *t*-Bu, X = SPh
27; R = Et, X = Br

25; R = *t*-Bu
28; R = Et

Reagents: (a) K_2CO_3, $BrCH_2CH_2CX{=}CH_2$; (b) Δ, toluene

readily obtained by alkylation of furan-2-ylcarbamic acid ethyl ester (**6**) with the appropriate acetylenic mesylate. The Diels−Alder reaction of each compound provided 1,2,3,4-tetrahydroquinolines **34** and **36** in 88% and 80% yields, respectively. When the terminal position of the alkyne contained a methyl group, it was necessary to carry out the thermolysis at 240 °C (24 h) in order for the cycloaddition reaction to occur (i.e. **35** → **36**). The



29; R = *t*-Bu
31; R = Et

30; R = *t*-Bu
32; R = Et

33; R = CO_2Me
35; R = Me

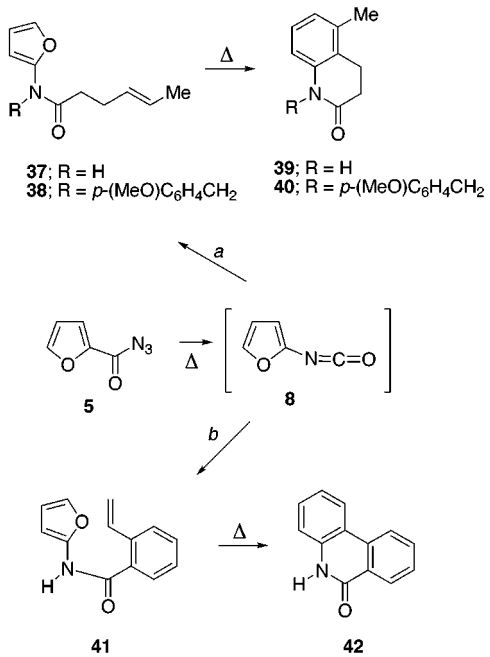
34; R = CO_2Me
36; R = Me

reaction rate and yield were greatly diminished relative to the case where the terminal alkynyl carbon contains the electron-withdrawing carbomethoxy group. This difference in reactivity is consistent with FMO theory.[30] Placement of an electron-withdrawing group on the π-bond lowers the LUMO energy of the dienophile and significantly enhances the rate of the [4 + 2]-cycloaddition reaction.

For comparison purposes, we have also studied the IMDAF chemistry of several 2-substituted furanamides. These compounds were prepared by generating 2-furyl isocyanate **8** as a transient intermediate and allowing it to react with either a Grignard reagent or a higher order cuprate. In the case of (*E*)-5-iodo-2-pentene, the cuprate reagent was utilized, whereas the Grignard reagent was employed with 2-bromostyrene. Using this protocol, we were able to synthesize furans **37** and **41** in 42% and 32% yields, respectively. Furan **37** was also converted to the corresponding *p*-methoxybenzyl amide **38** in 66% yield. When furans **37**, **38**, and **41** were subjected to the IMDAF reaction, the substituted quinolones **39**, **40**, and **42** were obtained in 89%, 80%, and 97% yields (Scheme 5).

An Approach toward the Amaryllidaceae Class of Alkaloids. The tetrahydroquinoline ring system is a

Scheme 5



37; R = H
38; R = *p*-$(MeO)C_6H_4CH_2$

39; R = H
40; R = *p*-$(MeO)C_6H_4CH_2$

5

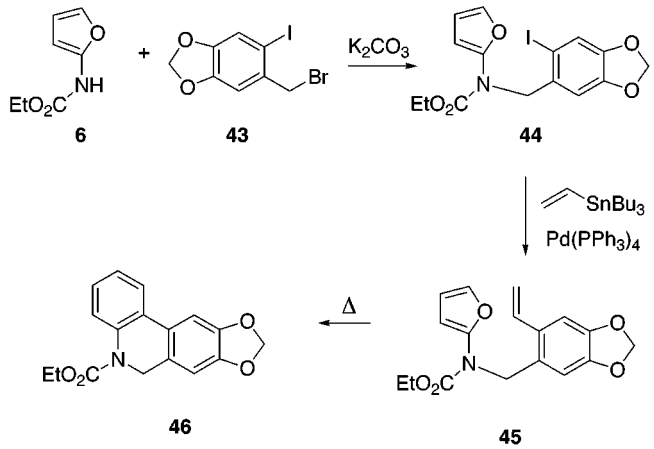
8

41

42

Reagents: (a) $Li_2CNCu(CH_2CH_2CH{=}CHCH_3)_2$, H_3O^+; (b) *o*-$C_6H_4CH{=}CH_2MgBr$, H_3O^+

Scheme 6



6

43

44

46

45

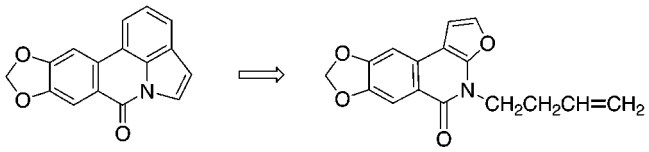
structural feature found in a large number of azapolycycles belonging to the Amaryllidaceae class of alkaloids.[31] One of the goals of our work in this area was to utilize the IMDAF reaction of amidofurans as a method to synthesize this core skeleton. The requisite styryl carbamate (i.e. **45**) necessary for the IMDAF cycloaddition that we were interested in studying was prepared in high yield by treating carbamate **6** with the iodo-substituted benzyl bromide **43** in the presence of base. Stille coupling of the resulting aryl iodide **44** with vinyltributyltin[32] provided the cycloaddition precursor **45** in 72% yield. The intramolecular Diels−Alder reaction of **45** furnished tetrahydroquinoline **46** in 79% yield, thereby demonstrating the efficacy of the method (Scheme 6).

Pyrrolophenanthridone Alkaloid Synthesis. The pyrrolophenanthridone alkaloids[33] are a group of com-

(30) Fleming, I. *Frontier Orbitals and Organic Reactions*; Wiley Science: New York, 1976.

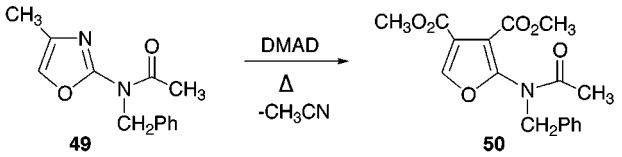
(31) Lewis, J. R. *Nat. Prod. Rep.* **1993**, *10*, 291.
(32) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.

pounds isolated from Amaryllidaceae plants.[34] These alkaloids have attracted the attention of chemists and pharmacologists due to the interesting properties of some of the members.[35] One of the more prevalent members of this family is hippadine (**47**), which is known to inhibit fertility in male rats.[36] While several procedures for the synthesis of individual pyrrolophenanthridones have been developed,[37−40] a short and efficient general method is not yet available. In connection with our work on the IMDAF reaction of 2-aminofurans, we became interested in using the Diels−Alder cycloaddition of a cyclic 2-amidofuran such as **48** as an approach toward hippadine and related structures.[26]



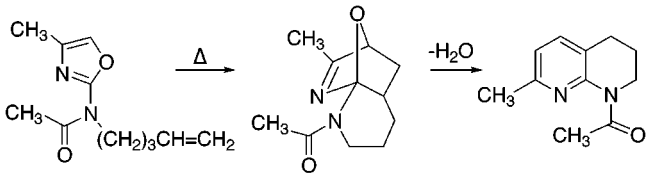
47; (Hippadine) **48**

A synthetic sequence in which cyclic amidofurans would be elaborated from amidooxazoles seemed attractive. Oxazoles have been extensively used as azadienes in cycloadditions,[41] particularly for the synthesis of furans by the Jacobi bis-heteroannulation procedure.[42] The feasibility of this approach clearly hinged upon 2-amidooxazoles undergoing [4 + 2]-cycloaddition chemistry with acetylenic dipolarophiles.[43] Since this tactic was the focal point of our plan, we opted to first verify the viability of this reaction. Unlike the 2-aminofuran system,[44] 2-amino-substituted oxazoles are quite stable and do not undergo ready hydrolysis. Preparation of 2-aminooxazole **49** was easily accomplished by acylation of the readily available amine.[45] We were gratified to find that the reaction of **49** with dimethyl acetylenedicarboxylate proceeded smoothly to give 2-acetamidofuran **50** in 92% yield.



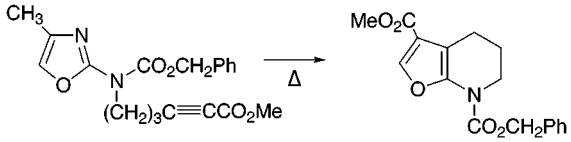
49 **50**

Before investigating the intramolecular cycloaddition behavior of acetylenic aminooxazoles, we decided to first conduct an experiment on a simpler model system. In 1957, Kondrat'eva described the first example of a Diels−Alder cycloaddition of an oxazole with an alkene to produce a pyridine.[46] In a later report, Weinreb and Levin showed that annulated pyridines were formed in good yield by an intramolecular Kondrat'eva cycloaddition of an oxazole with a tethered alkene.[47] This approach was used as a strategy for the synthesis of several azaphenanthrene alkaloids.[48] As a target to test the feasibility of the proposed intramolecular Diels−Alder cycloaddition of a 2-amino-substituted oxazole, we chose to study the thermal behavior of oxazole **51**. Refluxing a solution of **51** in a sealed tube at 180 °C furnished **53** in modest yield. The initially formed bicyclic adduct **52** was not detected as it readily underwent loss of water to give **53**.



51 **52** **53**

To further illustrate the scope and utility of the amidooxazole cycloaddition sequence, we examined the thermal behavior of oxazole **54** where an acetylenic π-bond has been tethered to the amido nitrogen atom. We were pleased to find that heating a sample of **54** at 160 °C provided the expected amidofuran **55** in 85% yield.

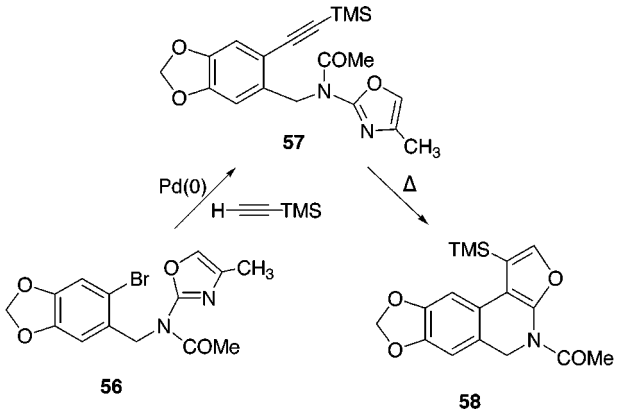


54 **55**

We next focused our attention on the structurally related acetylenic amidooxazole **57** which presented the opportunity to further test the intramolecular cycloaddition/cycloreversion/bis-heteroannulation approach.[42] The preparation of **57** involved a palladium-catalyzed cross-coupling reaction of acetamidooxazole **56** with trimethylsilylacetylene using the Sonogashira catalyst system.[49] Thermolysis of **57** proceeded smoothly at 200 °C to give the desired 2-amidofuran **58** in 93% yield.

Our planned approach toward hippadine involves the preparation of an amidooxazole (i.e. **66**) where the carbonyl group of the amide has been switched from

(33) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: 1987; Vol. 30, pp 252−376.
(34) Llabres, J. M.; Viladomat, F.; Bastida, J.; Codina, C.; Rubiralta, M. *Phytochemistry* **1986**, *25*, 2637.
(35) Ghosal, S.; Rao, P. H.; Jaiswal, D. K.; Kumar, Y.; Frahm, A. W. *Phytochemistry* **1981**, *20*, 2003.
(36) Chattopadhyay, S.; Chattopadhyay, U.; Marthur, P. P.; Saini, K. S.; Ghosal, S. *Planta Med*. **1982**, *49*, 252.
(37) Black, D. St. C.; Keller, P. A.; Kumar, N. *Tetrahedron* **1993**, *49*, 151. Castedo, L.; Guitián, E.; Pérez, D. *Tetrahedron Lett*. **1992**, *33*, 2407. Castedo, L.; Guitián, E.; Meirás, D. P. *Tetrahedron Lett*. **1990**, *31*, 2331.
(38) Grigg, R.; Teasdale, A.; Sridharan, V. *Tetrahedron Lett*. **1991**, *32*, 3859. Snieckus, V.; Siddiqui, M. A. *Tetrahedron Lett*. **1990**, *31*, 1523. Kanematsu, K.; Yasukouchi, T.; Hayakawa, K. *Tetrahedron Lett*. **1987**, *28*, 5895.
(39) Meyers, A. I.; Hutchings, R. H. *Tetrahedron Lett*. **1993**, *34*, 6185. Hutchings, R. H.; Meyers, A. I. *J. Org. Chem*. **1996**, *61*, 1004 and references cited therein.
(40) Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. *J. Chem. Soc., Chem. Commun*. **1995**, 2551.
(41) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev*. **1975**, *75*, 389. Hassner, A.; Fischer, B. *Heterocycles* **1993**, *35*, 1441.
(42) For leading references, see: Jacobi, P. A. *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press: 1992; Vol. 2, pp 251−299.
(43) For an example of an earlier Diels−Alder reaction of a 2-amino-substituted oxazole, see: Crank, G.; Khan, H. R. *J. Heterocycl. Chem*. **1985**, *22*, 1281.
(44) Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Heterocycl. Chem*. **1993**, *30*, 113. Bite, P.; Ramonczai, J.; Vargha, L. *J. Am. Chem. Soc*. **1948**, *70*, 371. Edwards, W. R., Jr.; Singleton, H. M. *J. Am. Chem. Soc*. **1938**, *60*, 540. Marquis, R. *Ann. Chim. Phys*. **1905**, *4*, 196.
(45) Cockerill, A. F.; Deacon, A.; Harrison, R. G.; Osborne, D. J.; Prime, D. M.; Ross, W. J.; Todd, A.; Verge, J. P. *Synthesis* **1976**, 591.
(46) Kondrat'eva, G. Y. *Khim. Nauka Prom*. **1957**, *2*, 666. Kondrat'eva, G. Y. *Izv. Akad. Nauk SSSR, Ser. Khim*. **1959**, 484.
(47) Levin, J. I.; Weinreb, S. M. *J. Am. Chem. Soc*. **1983**, *105*, 1397. Levin, J. I.; Weinreb, S. M. *J. Org. Chem*. **1984**, *49*, 4325.
(48) Subramanyam, C.; Noguchi, M.; Weinreb, S. M. *J. Org. Chem*. **1989**, *54*, 5580.
(49) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, 4467.

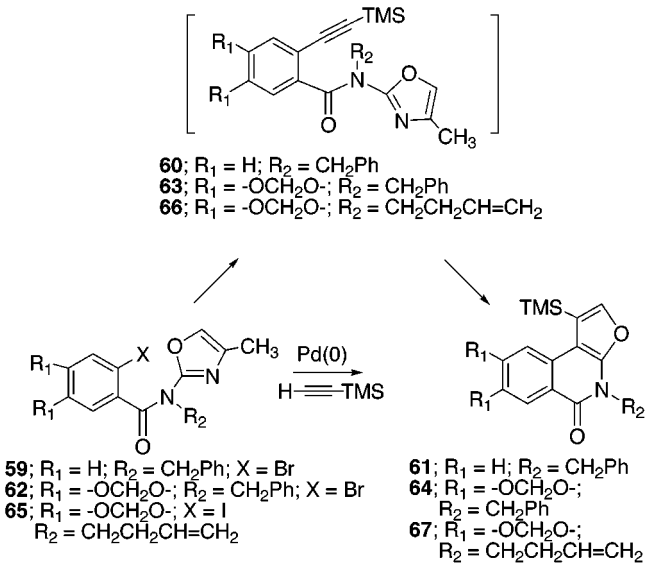


"outside" the tether to the "inside" position. In an attempt to work out the experimental conditions necessary for the preparation of **66**, we opted to first examine a simpler model system. Bromoaryl amide **59** was cross-coupled with TMS-acetylene. The initially formed alkyne **60** was not isolated as it underwent ready intramolecular [4 + 2]-cycloaddition under the cross-coupling conditions (80 °C) to form the cyclic amidofuran **61** in 88% yield (Scheme 7). Similar results were obtained with the corresponding methylenedioxy-substituted aromatic amides **62** and **65** which afforded furano[2,3-*c*]isoquinolones **64** and **67** under the cross-coupling conditions. The accelerating effect encountered by having the carbonyl group *internal* to the tether is probably related to a shortening of the path between the ground state and the corresponding transition state, thereby reducing the activation barrier. Alternatively, the amido carbonyl could act as an electron withdrawing group so as to activate the acetylenic π-bond toward Diels−Alder cycloaddition. This rate enhancement is clearly of synthetic advantage as it offers the opportunity to facilitate the intramolecular [4 + 2]-cycloaddition reaction of these systems.

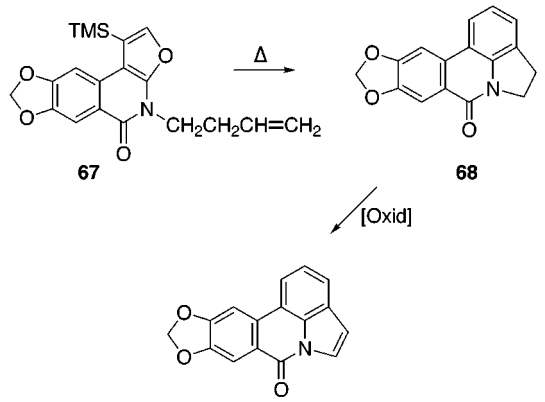
Having established the suitability of the intramolecular [4 + 2]-cycloaddition of 2-amidooxazoles as a method for preparing cyclic 2-amidofurans, we turned our attention to the application of the reaction toward the synthesis of hippadine (**47**). A short route to this alkaloid was achieved by the thermolysis of **67** as depicted in Scheme 8. The IMDAF reaction of furan **67** had to be carried out at 320 °C in order for the [4 + 2]-cycloaddition to take place across the unactivated alkenyl π-bond. The high temperature (320 °C) required for the conversion of **67** to **68** may reflect the fact that, unlike all of the other examples of this reaction, the flat tricyclic system of **67** imposes steric constraints on the orientation of the olefinic side chain which makes it difficult to attain the transition state required for the initial cycloaddition reaction. As a consequence of the elevated temperatures employed, desilylation of the trimethylsilyl group occurred, and indolinone **68** was isolated in only 30% yield. The above sequence constitutes a formal synthesis of hippadine (**47**) based on the successful DDQ oxidation of **68** to **47**.[39,40] Even though the critical IMDAF cycloaddition step proceeded in modest yield, the short number of steps from easily available starting materials suggests that this approach could be useful for the synthesis of other members of the pyrrolophenanthridone class of alkaloids.

In conclusion, this paper describes a versatile new approach toward indolines and tetrahydroquinolines that contain various substitution patterns. The synthetic

Scheme 7



Scheme 8



procedure described here involves an intramolecular Diels−Alder reaction of 2-amidofurans containing a tethered alkenyl group on the nitrogen atom. When the tethered olefin posseses a suitable leaving group or when substituted alkynes are used, phenolic indolines and tetrahydroquinolines are formed. Cyclic 2-amidofurans were synthesized by using a related intramolecular Diels−Alder reaction of 2-amido-substituted oxazoles which contain a tethered alkyne. This transformation represents a new route to this rare heterocyclic ring system, and this protocol was used for a formal synthesis of the pyrrolophenanthridone alkaloid hippadine. Further applications of this cycloaddition approach toward other alkaloids are in progress and will be reported in due course.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry argon. Solutions were evaporated under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column using an ethyl acetate/hexane mixture as the eluent unless specified otherwise. Solid samples were recrystallized from an ethyl acetate/hexane solvent combination unless specified otherwise.

***tert*-Butyl *N*-(3-Butenyl)-*N*-(2-furyl)carbamate (10).** A solution containing 2.0 g (11 mmol) of furan-2-yl carbamic acid

tert-butyl ester (**7**),[21] 2.8 g (11 mmol) of tetrabutylammonium bromide, and 2.5 mL (24 mmol) of 4-bromo-1-butene in 100 mL of CH_2Cl_2 at 0 °C was treated dropwise with a 50% aqueous NaOH solution. The mixture was heated at reflux for 15 h, cooled to room temperature, diluted with water, and extracted with CH_2Cl_2. The combined organic phase was washed with 3 N HCl, water, and brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 2.0 g (77%) of **10** as a colorless oil: IR (neat) 3081, 2981, 1710, and 1614 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9H), 2.32 (dd, 2H, J = 14.4 and 7.2 Hz), 3.59 (m, 2H), 5.06 (m, 2H), 5.79 (m, 1H), 6.00 (brs, 1H), 6.33 (dd, 1H, J = 3.0 and 2.1 Hz), and 7.18 (t, 1H, J = 0.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.1, 33.1, 47.9, 81.0, 101.2, 110.8, 116.6, 135.0, 138.0, 148.4, and 153.8. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.89; H, 8.12; N, 5.81.

***tert*-Butyl 2,3-Dihydroindole-1-carboxylate (11).** A 2.9 g (12 mmol) sample of carbamate **10** in 15 mL of benzene was heated in a sealed tube at 165 °C for 16 h. After cooling to room temperature, the solution was concentrated under reduced pressure and the residue was purified by flash silica gel chromatography to give 0.5 g (16%) of indoline **11** as a white solid: mp 48−49 °C; IR (KBr) 3068, 2932, 1701, and 1481 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.49 (s, 9H), 3.01 (t, 2H, J = 8.8 Hz), 3.86 (t, 2H, J = 8.8 Hz), 6.87 (m, 1H), 7.11 (m, 2H), and 7.58 (brs, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 27.2, 28.4, 47.4, 79.7, 114.6, 122.0, 124.6, 127.2, 130.9, 141.9, and 151.4. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.82; N, 6.38. Found: C, 71.08; H, 7.79; N, 6.37.

Indoline **11** was independently synthesized by treating a 2.0 g (17 mmol) sample of indoline with 0.2 g (1.7 mmol) of dimethylaminopyridine in 75 mL of CH_2Cl_2 at 0 °C. To this mixture was added 4.0 g (18 mmol) of di-*tert*-butyl dicarbonate. After the addition was complete, the mixture was stirred at 0 °C for 1 h and then for an additional 30 min at room temperature. The solution was quenched with 10 mL of a saturated $NaHCO_3$ solution, and the organic phase was washed with water and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by silica gel chromatography gave 2.8 g (72%) of **11** as a white solid whose spectral properties were indentical to those obtained from the Diels−Alder reaction of carbamate **10**.

***tert*-Butyl *N*-(4-Pentenyl)-*N*-(2-furyl)carbamate (12).** A solution containing 2.5 g (14 mmol) of carbamate **7**, 4.4 g (14 mmol) of tetrabutylammonium bromide, and 3.6 mL (30 mmol) of 5-bromo-1-pentene in 100 mL of CH_2Cl_2 at 0 °C was treated dropwise with a 50% aqueous NaOH solution. The mixture was heated at reflux for 18 h, cooled to room temperature, and diluted with water, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with 3 N HCl, water, and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 2.8 g (81%) of **12** as a colorless oil: IR (neat) 3409, 2975, 2925, and 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 9H), 1.66 (p, 2H, J = 7.5 Hz), 2.06 (dd, 2H, J = 14.4 and 6.9 Hz), 3.55 (m, 2H), 5.01 (m, 2H), 5.77 (m, 1H), 5.90 (brs, 1H), 6.32 (dd, 1H, J = 3.0 and 2.1 Hz), and 7.16 (t, 1H, J = 0.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.8, 28.1, 30.7, 48.1, 80.9, 101.0, 110.8, 114.9, 137.8, 137.9, 148.6, and 153.8. Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.85; H, 8.39; N, 5.54.

***tert*-Butyl 1,2,3,4-Tetrahydroquinoline-1-carboxylate (14).** A 1.2 g (4.8 mmol) sample of carbamate **12** in 10 mL of benzene was heated in a sealed tube at 165 °C for 18 h. After cooling to room temperature, the solution was concentrated under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.37 g (33%) of **14** as a pale yellow oil: IR (neat) 3066, 2930, 1704, and 1478 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.52 (s, 9H), 1.92 (m, 2H), 2.77 (t, 2H, J = 6.6 Hz), 3.71 (m, 2H), 6.95−7.12 (m, 3H), and 7.64 (d, 1H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.6, 27.5, 28.4, 44.6, 80.7, 123.2, 124.1, 125.7, 128.5, 129.9, 138.6, and 151.5. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.11; H, 8.18; N, 5.93.

The minor fraction isolated from the column contained 0.33 g (28%) of *tert*-butyl 6-hydroxy-3,4,5,6-tetrahydro-2*H*-quinoline-1-carboxylate (**13**) which showed the following spectral properties: IR (neat) 3415, 2943, 1708, and 1431 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 1.76 (p, 2H, J = 6.0 Hz), 2.11 (m, 2H), 2.34 (m, 3H), 3.35 (m, 1H), 3.59 (m, 1H), 4.20 (m, 1H), 5.77 (dd, 1H, J = 9.8 and 4.5 Hz), and 6.13 (d, 1H, J = 9.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2, 28.0, 28.3, 37.3, 44.0, 63.3, 80.6, 118.9, 124.1, 127.4, 129.5, and 153.9. Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.88; H, 8.36; N, 5.52. Heating a sample of the above alcohol in toluene at 165 °C for 24 h afforded **14** in 96% yield.

***tert*-Butyl *N*-[2-(5-Methylfuryl)]carbamate (15).** A solution of 2.3 g (18 mmol) of 5-methylfuran-2-carboxylic acid, 5.8 g (21 mmol) of diphenylphosphoryl azide,[27] and 2.2 g (22 mmol) of triethylamine in 25 mL of *tert*-butyl alcohol was heated at reflux for 15 h. The reaction mixture was cooled to room temperature and poured into 250 mL of a saturated sodium bicarbonate solution at 0 °C. The resulting precipitate was collected by filtration, washed with 50 mL of H_2O, and dried under reduced pressure to give 3.1 g (87%) of **15** as a white solid: mp 76−77 °C; IR (KBr) 3331, 1710, and 1550 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 2.21 (s, 3H), 5.90 (brs, 2H), and 6.42 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.3, 28.2, 81.0, 97.4, 106.7, 143.1, 146.2, and 152.4; HRMS calcd for $C_{10}H_{15}NO_3$ 197.1052, found 197.1056.

***tert*-Butyl *N*-(3-Butenyl)-*N*-[2-(5-methylfuryl)]carbamate (16).** A solution containing 2.7 g (14 mmol) of furan **15**, 1.9 g (48 mmol) of powdered sodium hydroxide, 3.9 g (28 mmol) of potassium carbonate, and 0.5 g (1.38 mmol) of tetrabutylammonium hydrogen sulfate in 50 mL of benzene was heated at reflux for 30 min, and then 2.8 g (21 mmol) of 4-bromobutene in 25 mL of benzene was added dropwise to the solution. The mixture was heated at reflux for an additional 4 h, quenched with 50 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 to give 2.4 g (68%) of **16** as a colorless oil: IR (neat) 2975, 1709, 1623, and 1573 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 2.24 (s, 3H), 2.32 (m, 2H), 3.57 (t, 2H, J = 7.6 Hz), 5.01 (d, 1H, J = 10.4 Hz), 5.07 (dd, 1H, J = 16.8 and 1.6 Hz), 5.77 (m, 1H), 5.86 (brs, 1H), and 5.90 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 28.1, 33.0, 48.1, 80.6, 102.6, 106.4, 116.5, 135.0, 146.3, 147.7, and 154.0; HRMS calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1520.

***tert*-Butyl 2,3-Dihydro-5-methylindole-1-carboxylate (17).** A solution containing 0.18 g (0.7 mmol) of furan **16** in 12 mL of benzene was heated in a sealed tube at 160 °C for 15 h under an argon atmosphere. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.13 g (77%) of **17** as a white solid: mp 101−102 °C; IR (KBr) 2925, 1701, 1623, and 1573 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56 (s, 9H), 2.28 (s, 3H), 3.04 (t, 2H, J = 8.4 Hz), 3.96 (brs, 2H), 6.96 (brs, 2H), and 7.72 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8, 27.3, 28.4, 47.6, 80.6, 114.3, 125.3, 127.7, 130.9, 131.5, 140.6, and 152.5. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.02; H, 8.31; N, 5.99.

***tert*-Butyl *N*-[2-(5-*p*-Nitrophenylfuryl)]carbamate (18).** A solution of 3.0 g (13 mmol) of 5-(*p*-nitrophenyl)furan-2-carboxylic, 3.9 g (14 mmol) of diphenylphosphoryl azide, and 1.5 g (15 mmol) of triethylamine in 50 mL of *tert*-butyl alcohol was heated at reflux for 16 h. The reaction mixture was quenched with H_2O, washed with 300 mL of a saturated sodium bicarbonate solution, and extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 3.4 g (86%) of **18** as a yellow solid: mp 147−148 °C; IR (KBr) 3407, 1706, 1557, 1331, and 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.53 (s, 9H), 6.22 (brs, 1H), 6.84 (d, 1H, J = 3.6 Hz), 7.10 (brs, 1H), 7.59 (d, 2H, J = 9.2 Hz), and 8.17 (d, 2H, J = 9.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1, 82.0, 96.1, 111.6, 122.6, 124.3, 136.1, 144.3,

145.5, 147.7, and 150.9. Anal. Calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21. Found: C, 59.01; H, 5.31; N, 9.00.

***tert*-Butyl *N*-(3-Butenyl)-*N*-[2-(5-*p*-nitrophenylfuryl)]-carbamate (19).** A solution containing 1.0 g (3.2 mmol) of furan **18**, 0.5 g (13 mmol) of powdered sodium hydroxide, 2.3 g (17 mmol) of potassium carbonate, and 0.1 g (0.3 mmol) of tetrabutylammonium hydrogen sulfate in 25 mL of benzene was heated at reflux for 30 min, and then 0.6 g (4.4 mmol) of 4-bromobutene in 5 mL of benzene was added dropwise to the solution. The mixture was heated at reflux for an additional 2 h, quenched with 25 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 to give 1.0 g (95%) of **19** as a yellow solid: mp 44−45 °C; IR (KBr) 1715, 1514, and 1335 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 2.40 (m, 2H), 3.78 (m, 2H), 5.07 (m, 2H), 5.80 (m, 1H), 6.21 (brs, 1H), 6.85 (d, 1H, J = 3.6 Hz), 7.64 (d, 2H, J = 8.8 Hz), and 8.18 (d, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.0, 33.2, 47.2, 81.8, 102.2, 111.0, 117.0, 122.8, 124.2, 134.7, 136.2, 145.7, 145.8, 150.1, and 152.7. Anal. Calcd for $C_{19}H_{22}N_2O_5$: C, 63.68; H, 6.19; N, 7.82. Found: C, 63.63; H, 6.13; N, 7.76.

***tert*-Butyl 2,3-Dihydro-5-(*p*-nitrophenyl)indole-1-carboxylate (20).** A solution of 0.1 g (0.3 mmol) of furan **19** in 12 mL of benzene was heated in a sealed tube at 165 °C for 15 h under an argon atmosphere. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.06 g (57%) of **20** as yellow needles: mp 121−122 °C; IR (KBr) 1700, 1520, and 1349 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.58 (s, 9H), 3.16 (t, 2H, J = 8.8 Hz), 4.03 (t, 2H, J = 8.8 Hz), 7.41 (s, 1H), 7.43 (d, 1H, J = 8.4 Hz), 7.67 (d, 2H, J = 8.8 Hz), 7.94 (brs, 1H), and 8.23 (d, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.1, 28.4, 47.8, 80.9, 114.9, 123.5, 124.0, 126.9, 127.0, 132.3, 132.4, 144.0. 146.4, 147.3, and 152.4. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.03; H, 5.93; N, 8.23. Found: C, 67.06; H, 5.91; N, 8.18.

***tert*-Butyl *N*-(3-Bromo-3-butenyl)-*N*-(2-furyl)carbamate (24).** To a solution containing 0.2 g (1.0 mmol) of carbamate **7** and 15 mL of CH_2Cl_2 at room temperature was added 0.1 g (3 mmol) of sodium hydroxide, 0.2 g (2 mmol) of potassium carbonate, 0.4 g (1.3 mmol) of tetrabutylammonium bromide, and 0.8 g (3.8 mmol) of 2,4-dibromo-1-butene.[50] The mixture was heated at reflux for 12 h, quenched with 25 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 to give 0.07 g (90%) of **24** as a pale yellow oil: IR (neat) 2979, 2117, 1717, 1631, and 1614 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H), 2.70 (t, 2H, J = 6.8 Hz), 3.78 (t, 2H, J = 7.2 Hz), 5.45−5.45 (m, 1H), 5.62−5.63 (m, 1H), 6.02 (brs, 1H), 6.34−6.35 (m, 1H), and 7.18−7.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.2, 28.4, 47.4, 81.7, 101.7, 111.2, 118.9, 130.6, 138.4, 148.4, and 153.9; HRMS calcd for $C_{13}H_{18}NO_3Br$ 315.0471, found 315.0470.

***tert*-Butyl *N*-(3-Phenylthio-3-butenyl)-*N*-(2-furyl)carbamate (26).** To a solution containing 1.0 g (5.6 mmol) of 3-phenylthio-3-butenol[51] and 0.9 mL (6.7 mmol) of triethylamine in 20 mL of CH_2Cl_2 was added dropwise 0.5 mL (6.1 mmol) of methanesulfonyl chloride at 0 °C. After the addition, the mixture was stirred overnight at room temperature and quenched with brine, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give 1.4 g (100%) of the crude mesylate as an oil which was used in the next step without further purification.

To a solution containing 0.9 g (4.6 mmol) of carbamate **7** in 8 mL of DMF was added 4.5 g (14 mmol) of $CsCO_3$. The mixture was stirred for 30 min at 60 °C, and 1.4 g (5.6 mmol) of the above mesylate in 2 mL of THF was added. The resulting mixture was heated at 60 °C for 7 h, quenched with 20 mL of H_2O, and extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.7 g (44%) of **26** as a light yellow oil: IR (neat) 1713, 1610, 1391, and 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H), 2.51 (t, 2H, J = 7.2 Hz), 3.79 (t, 2H, J = 7.2 Hz), 4.96 (s, 1H), 5.22 (s, 1H), 5.98 (s, 1H), 6.33 (dd, 1H, J = 7.2 and 2.0 Hz), 7.16 (dd, 1H, J = 2.0 and 0.8 Hz), 7.29−7.35 (m, 3H), and 7.40−7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.4, 35.8, 48.0, 81.4, 101.2, 111.1, 115.0, 128.0, 129.3, 133.0, 133.3, 138.1, 142.6, 148.6, and 153.8; HRMS calcd for $C_{19}H_{23}NO_3S$ 345.1399, found 345.1399.

***tert*-Butyl 5-Hydroxy-2,3-dihydroindole-1-carboxylate (25).** A solution containing 0.15 g (0.4 mmol) of furan **26** in 10 mL of benzene was heated in a sealed tube at 160 °C for 6 h under an argon atmosphere. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.09 g (87%) of **25** as a white solid after recrystallization: mp 162−163 °C; IR (KBr) 3370, 1655, 1487, 1365, and 1132 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.49 (s, 9H), 2.96 (t, 2H, J = 6.4 Hz), 3.84 (t, 2H, J = 6.4 Hz), 6.53 (d, 1H, J = 6.4 Hz), 6.62 (s, 1H), and 7.22−7.42 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 26.7, 27.9, 47.2, 79.4, 112.0, 112.9, 114.4, 128.8, 131.5, 151.5, and 152.6. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.38; H, 7.33; N, 5.92.

A small amount (<5%) of phenol **25** was also obtained from the thermolysis of carbamate **24**.

Ethyl *N*-(3-Bromo-3-butenyl)-*N*-(2-furyl)carbamate (27). A solution containing 0.5 g (3.2 mmol) of carbamate **6**, 0.45 g (11 mmol) of powdered sodium hydroxide, 0.9 g (6.4 mmol) of potassium carbonate, and 0.2 g (0.6 mmol) of tetrabutylammonium hydrogen sulfate in 50 mL of benzene was heated at reflux for 30 min, and then 0.8 g (3.9 mmol) of 2,4-dibromo-1-butene[50] in 5 mL of benzene was added dropwise to the solution. The mixture was heated for an additional 4 h at reflux, quenched with 40 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 to give 0.02 g (40%) of **27** as a pale yellow oil: IR (neat) 2982, 1716, 1609, 1410, and 1203 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (brs, 3H), 2.71 (dt, 2H, J = 7.2 and 0.8 Hz), 3.82 (t, 2H, J = 7.2 Hz), 4.18 (q, 2H, J = 6.4 Hz), 5.45 (d, 1H, J = 1.6 Hz), 5.62−5.63 (m, 1H), 6.05 (brs, 1H), 6.36 (dd, 1H, J = 3.4 and 1.8 Hz), and 7.20−7.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 40.7, 47.8, 62.6, 102.8, 111.2, 118.9, 130.5, 138.9, 147.8, 155.0; HRMS calcd for $C_{11}H_{14}NO_3Br$ 287.0158, found 287.0156.

Ethyl 5-Hydroxy-2,3-dihydroindole-1-carboxylate (28). A solution of 0.08 g (0.3 mmol) of furan **27** in 10 mL of benzene was heated in a sealed tube at 160 °C for 7 h under an argon atmosphere. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.07 g (80%) of **28** as a white solid: mp 126−127 °C; IR (KBr) 3514, 1743, 1708, 1600, and 1507 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.24 (brs, 3H), 2.99 (t, 2H, J = 8.4 Hz), 3.88 (t, 2H, J = 8.4 Hz), 4.14 (brs, 2H), 6.34 (d, 1H, J = 8.8 Hz), 6.62 (s, 1H), 7.49 (s, 1H), and 9.07 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 14.6, 27.1, 47.1, 60.6, 112.1, 113.0, 114.4, 132.5, 134.5, 152.9, and 153.0. Anal. Calcd for $C_{11}H_{13}O_3N$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.73; H, 6.38; N, 6.73.

***tert*-Butyl *N*-(3-Pentynyl)-*N*-(2-furyl)carbamate (29).** To a solution containing 2.5 g (14 mmol) of carbamate **7** and 100 mL of a 4:1 DMF/THF mixture at room temperature was added 6.2 g (19 mmol) of $CsCO_3$. The mixture was stirred at room temperature for 45 min and then charged with 5.0 g (34 mmol) of 5-bromo-2-pentyne.[52] The solution was heated at 70 °C for 6 h, quenched with 50 mL of H_2O, and extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.9 g (78%)

(50) Barton, T. J.; Lin, J.; Ijadi-Maghsoodi, S.; Power, M. D.; Zhang, X.; Ma, Z.; Shimizu, H.; Gordon, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 11695.

(51) Perron, F.; Albizati, K. F. *J. Org. Chem.* **1987**, *52*, 4128.

(52) Flahaut, J.; Miginiac, P. *Helv. Chim. Acta* **1978**, *61*, 2275.

of **29** as a colorless oil: IR (neat) 2975, 1709, 1609, and 1367 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 1.74 (t, 3H, J = 2.6 Hz), 2.37−2.42 (m, 2H), 3.66 (t, 2H, J = 7.6 Hz), 6.02 (brs, 1H), 6.32 (t, 1H, J = 2.4 Hz), and 7.16−7.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.7, 19.1, 28.4, 48.0, 75.9, 77.2, 81.4, 101.5, 111.1, 138.3, 148.5, and 153.8. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.54; H, 7.74; N, 5.55.

***tert*-Butyl 5-Hydroxy-4-methyl-2,3-dihydroindole-1-carboxylate (30).** A solution of 0.7 g (2.6 mmol) of furan **29** in 15 mL of benzene was heated in a sealed tube at 170 °C for 24 h under an argon atmosphere. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.17 g (25%) of **30** as a white solid: mp 213-214 °C; IR (KBr) 3267, 2975, 1645, 1602, and 1481 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.49 (s, 9H), 2.00 (s, 3H), 2.91 (t, 2H, J = 8.4 Hz), 3.85 (t, 2H, J = 8.4 Hz), 6.55 (d, 1H, J = 8.8 Hz), 7.21 (s, 1H), and 8.67 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 12.1, 26.2, 28.4, 47.6, 79.7, 111.8, 112.9, 113.0, 120.8, 131.7, 150.9, and 151.9. Anal. Calcd for $C_{14}H_{19}O_3N$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.33; H, 7.74; N, 5.64.

Ethyl *N*-(3-Pentynyl)-*N*-(2-furyl)carbamate (31). A solution containing 0.5 g (3.2 mmol) of carbamate **6**, 0.45 g (11 mmol) of sodium hydroxide, 0.9 g (6.4 mmol) of potassium carbonate, and 0.2 g (0.6 mmol) of tetrabutylammonium hydrogen sulfate in 50 mL of benzene was heated at reflux for 30 min, and then 1.1 g (7.8 mmol) of 5-bromo-2-pentyne[52] in 5 mL of benzene was added dropwise to the solution. The mixture was heated at reflux for 5 h, quenched with 50 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 to give 0.44 g (72%) of **31** as a colorless oil: IR (neat) 2918, 1716, 1609, 1410, and 1296 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, 3H, J = 6.0 Hz), 1.75 (t, 3H, J = 2.4 Hz), 2.39−2.45 (m, 2H), 3.71 (t, 2H, J = 8.0 Hz), 4.18 (q, 2H, J = 6.0 Hz), 6.07 (brs, 1H), 6.35 (dd, 1H, J = 3.2 and 2.4 Hz), and 7.19 (d, 1H, J = 0.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.5, 14.5, 18.9, 48.3, 62.3, 75.7, 77.4, 102.6, 111.0, 138.7, 147.8, and 154.8; HRMS calcd for $C_{12}H_{15}NO_3$ 231.1052, found 231.1057.

Ethyl 5-Hydroxy-4-methyl-2,3-dihydroindole-1-carboxylate (32). A solution of 0.4 g (1.7 mmol) of furan **31** in 12 mL of benzene was heated in a sealed tube at 210 °C for 8 h under an argon atmosphere. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.3 g (82%) of **32** as a white solid: mp 184−185 °C; IR (KBr) 3288, 2975, 1680, 1602, and 1488 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.26 (t, 3H, J = 7.2 Hz), 2.01 (s, 3H), 2.94 (t, 2H, J = 8.8 Hz), 3.91 (t, 2H, J = 8.8 Hz), 4.16 (q, 2H, J = 7.2 Hz), 6.58 (d, 1H, J = 8.4 Hz), 7.27 (s, 1H), and 8.74 (s, 1H); ^{13}C NMR (DMSO-d_6, 60 °C, 100 MHz) δ 11.7, 14.3, 25.9, 46.9, 60.3, 111.3, 112.6, 120.4, 131.2, 133.7, 150.7, and 152.2. Anal. Calcd for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.90; H, 6.85; N, 6.23.

Ethyl *N*-(2-Furyl)-*N*-(5-carbomethoxy-4-pentynyl)carbamate (33). To a solution containing 2.0 g (14.1 mmol) of methyl 6-hydroxy-2-hexynoate[53] in 100 mL of CH_2Cl_2 at 0 °C were added 2.1 g (21 mmol) of triethylamine and 1.8 g (16 mmol) of methanesulfonyl chloride. The solution was stirred at 0 °C for 1 h, quenched with 25 mL of H_2O, and extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give 3.2 g (100%) of 6-methanesulfonylhex-2-ynoic acid methyl ester as a pale yellow oil which was used in the next step without further purification.

A solution containing 0.3 g (1.7 mmol) of carbamate **6**, 0.01 g (2.5 mmol) of sodium hydroxide, 0.5 g (3.4 mmol) of potassium carbonate, and 0.1 g (0.4 mmol) of tetrabutylammonium hydrogen sulfate in 35 mL of benzene was heated at reflux for 30 min, and then 0.8 g (3.5 mmol) of the above mesylate in 5 mL of benzene was added dropwise to the solution. The mixture was heated at reflux for 5 h, quenched with 25 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 to give 0.04 g (9%) of **33** as a colorless oil: IR (neat) 3127, 2953, 2234, 1732, and 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24−1.25 (m, 3H), 1.87 (pent, 2H, J = 7.2 Hz), 2.39 (t, 2H, J = 7.2 Hz), 3.69 (t, 2H, J = 7.2 Hz), 3.75 (s, 3H), 4.18 (q, 2H, J = 6.4 Hz), 6.06 (brs, 1H), 6.36 (dd, 1H, J = 3.2 and 2.0 Hz), and 7.20 (d, 1H, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 16.3, 26.9, 52.8, 62.6, 73.4, 77.5, 88.7, 102.2, 111.3, 138.9, 147.8, 154.3, and 155.5; HRMS calcd for $C_{14}H_{17}NO_5$ 279.1107, found 279.1103.

6-Hydroxy-1,2,3,4-tetrahydroquinoline-1,5-dicarboxylic Acid 1-Ethyl 5-Methyl Diester (34). A solution containing 0.1 g (0.4 mmol) of furan **33** in 12 mL of benzene was heated in a sealed tube at 175 °C for 8 h under an argon atmosphere. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.08 g (88%) of **34** as a white solid: mp 106−107 °C; IR (KBr) 1697, 1655, 1592, and 1446 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, 3H, J = 6.8 Hz), 1.89 (p, 2H, J = 6.4 Hz), 3.04 (t, 2H, J = 6.8 Hz), 3.68 (t, 2H, J = 6.0 Hz), 3.96 (s, 3H), 4.21 (q, 2H, J = 7.2 Hz), 6.84 (d, 1H, J = 8.8 Hz), 7.60 (d, 1H, J = 8.8 Hz), and 10.35 (s, 1H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 14.8, 24.1, 26.9, 44.0, 52.5, 62.1, 111.5, 115.5, 131.3, 132.5, 133.6, 155.4, 159.4, and 171.9. Anal. Calcd for $C_{14}H_{17}O_5N$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.11; H, 6.08; N, 4.91.

Ethyl *N*-(4-Hexynl)-*N*-(2-furyl)carbamte (35). To a solution containing 5.0 g (51 mmol) of 4-hexyn-1-ol[54] in 200 mL of CH_2Cl_2 at 0 °C were added 7.7 g (76 mmol) of triethylamine and 6.4 g (56 mmol) of methanesulfonyl chloride. The solution was stirred at 0 °C for 1 h, quenched with 50 mL of H_2O, and extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give 8.9 g (100%) of methanesulfonic acid hex-4-ynyl ester as a colorless oil which was used in the next step without further purification.

A solution containing 4.0 g (26 mmol) of carbamate **6**, 21 g (52 mmol) of sodium hydroxide, 7.1 g (52 mmol) of potassium carbonate, and 1.8 g (5.2 mmol) of tetrabutylammonium hydrogen sulfate in 300 mL of benzene was heated at reflux for 30 min, and then 6.8 g (40 mmol) of the above mesylate in 25 mL of benzene was added dropwise to the solution. The mixture was heated for 3 h at reflux, quenched with 120 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 to give 3.7 g (61%) of **35** as a colorless oil: IR (neat) 3120, 2939, 1711, 1613, and 1397 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (t, 3H, J = 6.8 Hz), 1.68−1.76 (m, 5H), 2.11−2.16 (m, 2H), 3.64 (t, 2H, J = 7.6 Hz), 4.14 (q, 2H, J = 6.8 Hz), 6.02 (brs, 1H), 6.32 (dd, 1H, J = 3.2 and 2.4 Hz), and 7.16−7.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.6, 14.6, 16.3, 28.1, 48.5, 62.3, 76.0, 78.1, 102.2, 111.1, 138.7, 148.1, and 155.1. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.60; H, 7.21; N, 5.88.

6-Hydroxy-5-methyl-1,2,3,4-tetrahydroquinoline-1-carboxylic Acid Ethyl Ester (36). A solution of 1.2 g (5 mmol) of furan **35** in 12 mL of benzene was heated in a sealed tube at 210 °C for 8 h under an argon atmosphere. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.4 g (80%) of **36** as a white solid: mp 115−116 °C; IR (KBr) 3336, 2939, 1662, 1585, and 1488 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (t, 3H, J = 7.2 Hz), 1.95 (pent, 2H, J = 6.0 Hz), 2.11 (s, 3H), 2.66 (t, 2H, J = 6.8 Hz), 3.69−3.73 (m, 2H), 4.23 (q, 2H, J = 7.2 Hz), 6.56 (brs, 1H), 6.63 (d, 1H, J = 8.4 Hz), and 7.24 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$,100 MHz) δ 11.4, 14.7, 23.6,

(53) Kita, Y.; Okunaka, R.; Honda, T.; Shindo, M.; Taniguchi, M.; Kondo, M.; Sasho, M. *J. Org. Chem.* **1991**, *56*, 119.

(54) Semmelhack, M. F.; Bozell, J. J.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W.; Zask, A. *Tetrahedron* **1985**, *41*, 5803.

25.0, 44.1, 62.1, 112.7, 122.2, 122.7, 130.1, 131.1, 150.8, and 155.6. Anal. Calcd for $C_{13}H_{17}O_3N$: C, 66.35; H, 7.29; N, 5.96. Found: C, 66.67; H, 7.30; N, 5.97.

Hex-4-enoic Acid Furan-2-yl Amide (37). To a solution containing 1.2 g (6.0 mmol) of (*E*)-5-iodo-2-pentene[55] in 10 mL of ether at − 78 °C was added 8.1 mL (13.0 mmol) of 1.6 M *t*-BuLi. The mixture was stirred at −78 °C for 30 min and then allowed to warm to room temperature. The resulting mixture was transferred via cannula through a pad of glass wool to a suspension of 0.25 g (2.8 mmol) of CuCN in 6 mL of THF at −78 °C. The organocopper reagent was stirred at −78 °C for 1 h, and then 2-furoyl isocyanate (**8**) was transferred via cannula to the solution at −78 °C. The 2-furyl isocyanate (**8**) was prepared by heating 0.6 g (2.8 mmol) of 2-furoyl azide (**5**) in 30 mL of a 2:1-benzene−toluene mixture at reflux for 2 h. After cannulation, the mixture was warmed to room temperature and stirred for 1 h. The mixture was diluted with ether, quenched with 10 mL of NH_4Cl, and extracted with ether. The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.2 g (42%) of **37** as a white solid: mp 65−66 °C; IR (KBr) 3203, 3063, 1667, and 1560 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.66 (d, 3H, J = 6.0 Hz), 2.41 (m, 4H), 5.44−5.55 (m, 2H), 6.31 (d, 1H, J = 3.2 Hz), 6.34 (m, 1H), 7.04 (d, 1H, J = 0.8 Hz), and 7.61 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.9, 28.2, 36.5, 95.2, 111.5, 127.0, 129.0, 135.2, 145.0, and 168.8. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.30; H, 7.32; N, 7.68.

5-Methyl-1,2,3,4-tetrahydroquinolin-2-one (39). A solution of 0.2 g (0.8 mmol) of furan **37** in 10 mL of toluene was heated in a sealed tube at 200 °C for 36 h under an argon atmosphere. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.12 g (89%) of **39** as a white solid: mp 163−164 °C; IR (KBr) 3438, 3196, 1676, and 1393 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.29 (s, 3H), 2.64 (t, 2H, J = 7.6 Hz), 2.92 (t, 2H, J = 7.6 Hz), 6.69 (d, 1H, J = 8.0 Hz), 6.86 (d, 1H, J = 7.6 Hz), 7.07 (t, 1H, J = 7.6 Hz), and 9.03 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3, 21.9, 30.3, 113.5, 121.9, 124.9, 127.0, 136.0, 137.2, and 171.9. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.25; H, 6.90; N, 8.62.

Hex-4-enoic Acid Furan-2-yl(4-methoxybenzyl)amide (38). A suspension containing 0.2 g (1.1 mmol) of **37**, 0.2 g (4.0 mmol) of powdered potassium hydroxide, 0.15 g (1.1 mmol) of potasium carbonate, and 0.2 g (0.5 mmol) of tetrabutylammonium hydrogen sulfate in 5 mL of benzene was stirred at room temperature for 1 h. To the above mixture was added 0.3 mL (2.2 mmol) of 4-methoxybenzyl chloride. After stirring at room temperature for 4 h, the mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.2 g (66%) of **38** as a colorless oil: IR (neat) 2931, 1680, 1611, and 1513 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.60 (d, 3H, J = 5.5 Hz), 2.18−2.20 (m, 2H), 2.24−2.29 (m, 2H), 3.78 (s, 3H), 4.71 (s, 2H), 5.30−5.40 (m, 2H), 5.84 (d, 1H, J = 3.2 Hz), 6.31 (m, 1H), 6.80−6.82 (m, 2H), 7.13−7.16 (m, 2H), and 7.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.9, 28.1, 33.9, 51.0, 55.2, 105.0, 111.0, 113.6, 125.8, 129.4, 129.6, 129.9, 140.0, 148.3, 158.9, and 173.5; HRMS calcd for $C_{18}H_{21}NO_3$ 299.1521, found 299.1520.

1-(4-Methoxybenzyl)-5-methyl-1,2,3,4-tetrahydroquinolin-2-one (40). A solution of 0.2 g (0.7 mmol) of **39** in 10 mL of toluene was heated in a sealed tube at 160 °C for 24 h. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.2 g (80%) of **40** as a white solid: mp 136−137 °C; IR (KBr) 1666, 1513, and 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3H), 2.75 (m, 2H), 2.91 (m, 2H), 3.77 (s, 3H), 5.11 (s, 2H), 6.77−6.86 (m, 4H), 7.01 (t, 1H, J = 7.6 Hz), and 7.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.7, 21.7, 31.5, 45.8, 55.2, 113.7, 114.1, 124.9, 126.8, 127.6, 129.2, 135.5, 139.5, 140.0, 158.6, and 170.4. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.57; H, 6.86; N, 4.91.

***N*-(Furan-2-yl)-2-vinylbenzamide (41).** To a mixture containing 0.2 g (6 mmol) of magnesium metal in 10 mL of ether at room temperature were added 0.5 mL (4.0 mmol) of 2-bromostyrene and 10 mg (0.04 mmol) of 1,2-diiodoethane. The suspension was heated at reflux for 30 min and then stirred at room temperature for 8 h. The phenyl Grignard reagent was transferred via cannula through a pad of glass wool into a flask at 0 °C. To this Grignard solution was added via cannula a sample of 2-furyl isocyanate (**8**) at 0 °C which was prepared by heating 0.5 g (4.0 mmol) of 2-furoyl azide (**5**) in 40 mL of a 2:1-benzene−toluene mixture for 2 h. The solution was allowed to warm to room temperature and was stirred for an additional 1 h. The resulting mixture was diluted with ether, quenched with aqueous NH_4Cl, and extracted with ether. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.27 g (32%) of **41** as an orange solid: mp 92−93 °C; IR (KBr) 3241, 1656, and 1551 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.40 (d, 1H, J = 11.2 Hz), 5.73 (dd, 1H, J = 9.4 and 1.0 Hz), 6.41 (t, 1H, J = 2.4 Hz), 6.46 (d, 1H, J = 3.2 Hz), 7.05−7.12 (m, 2H), 7.30 (t, 1H, J = 7.6 Hz), 7.43 (t, 1H, J = 7.4 Hz), 7.52−7.58 (m, 2H), and 8.16 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 95.3, 111.5, 117.6, 126.7, 127.6, 127.8, 130.9, 133.5, 134.3, 135.4, 136.4, 145.2, and 164.9. Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.53; H, 5.25; N, 6.52.

5*H*-Phenanthridin-6-one (42). A solution containing 0.18 g (0.8 mmol) of benzamide **41** in 10 mL of toluene in a sealed tube was heated at 160 °C for 4 days. Removal of the solvent under reduced pressure followed by silica gel chromatography gave 0.16 g (97%) of **42** as a white solid: mp 290−292 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.50 (brs, 1H), 7.27 (m, 1H), 7.37 (dd, 1H, J = 8.0 and 1.2 Hz), 7.49 (m, 1H), 7.65 (m, 1H), 7.86 (dt, 1H, J = 7.4 and 1.2 Hz), 8.32 (dd, 1H, J = 8.0 and 1.2 Hz), 8.40 (m, 1H) and 8.51 (d, 1H, J = 8.0 Hz). Structure **42** was unequivocally established by comparison with an authentic sample acquired from Aldrich Chemical Co.

Ethyl *N*-(6-Iodobenzo[1,3]dioxolo-5-ylmethyl)-*N*-(2-furyl)carbamate (44). A solution containing 1.1 g (7.3 mmol) of carbamate **6**, 1.0 g (26 mmol) of sodium hydroxide, 2.0 g (14.7 mmol) of potassium carbonate, and 0.5 g (1.5 mmol) of tetrabutylammonium hydrogen sulfate in 125 mL of benzene was heated at reflux for 30 min, and then 3.0 g (9 mmol) of 5-bromomethyl-6-iodobenzo[1,3]dioxole[56] in 20 mL of benzene was added dropwise to the solution. The mixture was heated at reflux for an additional 3 h, quenched with 50 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 to give 2.0 g (67%) of **44** as a white solid: mp 67−68 °C; IR (KBr) 2987, 1725, 1585, 1523, and 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, 3H, J = 6.8 Hz), 4.21 (q, 2H, J = 6.8 Hz), 4.75 (s, 2H), 5.95 (s, 2H), 5.96 (brs, 1H), 6.30−6.31 (m, 1H), 6.89 (s, 1H), 7.17 (d, 1H, J = 0.8 Hz), and 7.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 57.5, 62.8, 86.3, 101.9, 103.1, 108.6, 111.2, 118.7, 133.0, 138.9, 147.4, 147.9, 148.8, and 155.3. Anal. Calcd for $C_{15}H_{14}NO_5$: C, 43.39; H, 3.40; N, 3.37. Found: C, 43.13; H, 3.38; N, 3.38.

Ethyl *N*-(6-Vinylbenzo[1,3]dioxolo-5-ylmethyl)-*N*-(2-furyl)carbamate (45). To a solution containing 0.1 g (0.2 mmol) of iodide **44** in 10 mL of dry THF were added 0.06 g (0.05 mmol) of tetrakis(triphenylphosphine)palladium and 0.12 g (0.4 mmol) of tributyl(vinyl)tin. The solution was heated at reflux for 8 h and quenched with 10 mL of a saturated KF solution. The mixture was allowed to stir for 8 h at room temperature, 25 mL of water was added, and the mixture was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to

(55) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1990**, *55*, 1447.

(56) Fuchs, P. L.; Jin, Z. *Tetrahedron Lett.* **1993**, *34*, 5205.

give 0.06 g (72%) of **45** as a colorless oil: IR (neat) 2981, 1718, 1606, 1481, and 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, 3H, $J = 7.2$ Hz), 4.20 (q, 2H, $J = 7.2$ Hz), 4.79 (s, 2H), 5.16 (dd, 1H, $J = 11.0$ and 1.2 Hz), 5.46 (dd, 1H, $J = 17.2$ and 1.2 Hz), 5.87 (brs, 1H), 5.93 (s, 2H), 6.27 (dd, 1H, $J = 3.4$ and 2.0 Hz), 6.72 (s, 1H), 6.78 (dd, 1H, $J = 17.2$ and 11.0 Hz), 6.94 (s, 1H), and 7.16 (dd, 1H, $J = 2.0$ and 0.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 49.8, 62.7, 101.3, 105.8, 109.2, 111.2, 114.9, 120.2, 128.4, 131.2, 133.5, 138.9, 139.0, 147.6, 149.8, and 155.4; HRMS calcd for $C_{17}H_{17}NO_5$ 315.1107, found 315.1105.

6*a*,11*a*-Dihydro-6*H*-[1,3]dioxolo[4,5-*j*]phenanthridine-5-carboxylic Acid Ethyl Ester (46). A solution of 0.1 g (0.3 mmol) of furan **45** in 15 mL of toluene was heated at reflux for 24 h under an argon atmosphere. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.08 g (79%) of **46** as a colorless oil: IR (neat) 2904, 1697, 1620, 1481, and 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, 3H, $J = 7.2$ Hz), 4.20 (q, 2H, $J = 7.2$ Hz), 4.69 (s, 2H), 5.95 (s, 2H), 6.73 (s, 1H), 7.16−7.19 (m, 2H), 7.22−7.26 (m, 1H), and 7.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6, 47.9, 63.2, 102.3, 105.1, 107.4, 124.4, 125.8, 126.2, 127.1, 128.1, 129.4, 129.8, 137.6, 148.3, 148.8, and 154.9; HRMS calcd for $C_{17}H_{15}NO_4$ 297.1001, found 297.1005.

2-(Acetylbenzylamino)furan-3,4-dicarboxylic Acid Dimethyl Ester (50). A solution containing 0.07 g (0.3 mmol) of the known amidooxazole **49**[45] and 0.04 g (0.3 mmol) of dimethyl acetylenedicarboxylate in 3 mL of toluene was stirred in a sealed tube at 150 °C for 18 h. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.09 g (92%) of **50** as a yellow oil: IR (neat) 1736, 1694, 1551, 1289, and 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.96 (s, 3H), 3.57 (s, 3H), 3.77 (s, 3H), 4.75 (s, 2H), 7.10−7.21 (m, 5H), and 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.1, 51.4, 52.2, 52.4, 112.6, 119.1, 128.0, 128.6, 129.1, 135.9, 144.9, 151.3, 161.4, 161.6, and 170.8. Anal. Calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.60; H, 5.19; N, 4.23.

***N*-(4-Methyloxazol-2-yl)-*N*-(pent-4-enyl)acetamide (51).** A mixture containing 0.4 g (3.0 mmol) of 2-acetamidooxazole,[45] 2.6 g (7.8 mmol) of $CsCO_3$ in 8 mL of DMF, and 4 mL of THF was stirred at 60 °C for 30 min. To this mixture was added 0.5 mL (3.9 mmol) of 5-bromo-1-pentene,[57] and the solution was stirred at 60 °C for 4 h. The reaction mixture was quenched with 25 mL of water and extracted with ether. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 0.4 g (70%) of **51** as a light yellow oil: IR (neat) 1693, 1577, 1399, 1275, and 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.64−1.72 (m, 2H), 2.07 (q, 2H, $J = 6.8$ Hz), 2.17 (s, 3H), 2.22 (s, 3H), 3.80 (t, 2H, $J = 7.6$ Hz), 4.94−5.03 (m, 2H), 5.73−5.83 (m, 1H), and 7.25 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.9, 23.6, 27.4, 30.8, 46.4, 115.2, 132.4, 137.0, 137.6, 155.8, and 170.2. Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.25; H, 7.78; N, 13.25.

1-Acetyl-7-methyl-1,2,3,4-tetrahydro-1,8-naphthyridine (53). A solution containing 0.1 g (0.5 mmol) of **51** and 0.06 g (0.4 mmol) of DBU in 2 mL of toluene was heated in a sealed tube at 180 °C for 20 h under an argon atmosphere. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.3 g (39%) of **53** as a pale yellow oil: IR (neat) 1662, 1571, 1460, 1369, and 1009 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.92 (m, 2H), 2.46 (s, 3H), 2.49 (s, 3H), 2.73 (t, 2H, $J = 6.4$ Hz), 3.88 (t, 2H, $J = 6.4$ Hz), 6.86 (d, 1H, $J = 7.4$ Hz), and 7.32 (d, 1H, $J = 7.4$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2, 24.1, 25.8, 26.7, 43.1, 119.3, 121.9, 137.6, 154.6, and 171.8; HRMS calcd for $C_{11}H_{14}N_2O$ 190.1106, found 190.1102.

Oxazol-2-ylcarbamic Benzyl Ester. To a solution containing 2.8 g (30 mmol) of 2-aminooxazole, 0.7 g (6 mmol) of (dimethylamino)pyridine, and 8 mL (60 mmol) of triethylamine in 40 mL of THF was added dropwise 4.5 mL (30 mmol) of benzyl chloroformate at 0 °C. The resulting mixture was heated at reflux for 24 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 2.9 g (43%) of the above carbamate as a white solid: mp 138−139 °C; IR (neat) 3140, 1750, 1641, 1236, and 1082 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.92 (s, 3H), 5.22 (s, 2H), 7.12 (s, 1H), 7.35−7.41 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.2, 67.9, 128.7, 128.8, 129.0, 130.6, 135.1, 135.6, and 154.3; HRMS calcd for $C_{12}H_{12}N_2O_3$ 232.0848, found 232.0855.

Oxazol-2-ylpent-4-ynylcarbamic Acid Benzyl Ester. A mixture containing 1.7 g (7 mmol) of the above carbamate, 7.0 g (22 mmol) of $CsCO_3$, 0.9 mL (9 mmol) of 5-chloropentyne, and 0.05 g of potassium iodide in 16 mL of DMF and 4 mL of THF was stirred at 60 °C for 36 h. The mixture was diluted with water and extracted with ether, and the combined ether layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 1.5 g (71%) of the above carbamate as a yellow oil: IR (neat) 3298, 1728, 1578, 1402, and 1098 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.88 (p, 2H, $J = 7.2$ Hz), 1.92 (t, 1H, $J = 2.8$ Hz), 2.15 (d, 3H, $J = 1.2$ Hz), 2.24 (dt, 2H, $J = 7.2$ and 2.8 Hz), 3.90 (t, 2H, $J = 7.2$ Hz), 5.24 (s, 2H), 7.22 (p, 1H, $J = 1.2$ Hz), and 7.33−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.0, 16.0, 27.5, 48.1, 68.4, 69.1, 83.2, 128.2, 128.4, 128.7, 132.5, 135.8, 136.7, 153.8, and 154.7; HRMS calcd for $C_{17}H_{18}N_2O_3$ 298.1317, found 298.1312.

6-(Benzyloxycarbonyloxazol-2-ylamino)hex-2-ynoic Acid Methyl Ester (54). To a solution containing 1.0 g (3 mmol) of the above carbamate in 20 mL of THF at −78 °C was added dropwise 4.0 mL (4.0 mmol) of a 2.0 M lithium bis-(trimethylsilyl)amide/THF solution. The solution was stirred at −78 °C for 1 h, and then 0.4 mL (5.0 mmol) of methyl chloroformate was added. The resulting mixture was stirred at −78 °C for 1 h and then at room temperature for 20 h and was then partitioned between brine and ether. The ether layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.8 g (72%) of **54** as a light yellow oil: IR (neat) 2234, 1717, 1577, 1400, and 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.94 (p, 2H, $J = 7.2$ Hz), 2.15 (s, 3H), 2.39 (t, 2H, $J = 7.2$ Hz), 3.75 (s, 3H), 3.89 (t, 2H, $J = 7.2$ Hz), 5.24 (s, 2H), 7.22 (s, 1H), and 7.33−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1, 16.4, 26.8, 48.1, 52.8, 68.6, 73.4, 88.3, 128.0, 128.4, 128.7, 132.5, 135.6, 136.6, and 153.6; HRMS calcd for $C_{19}H_{20}N_2O_5$ 356.1372, found 356.1372.

4,5,6,7-Tetrahydrofuro[2,3-*b*]pyridine-3,7-dicarboxylic Acid 7-Benzyl Methyl Diester (55). A solution containing 0.2 g (0.6 mmol) of **54** in 8 mL of toluene was heated in a sealed tube at 160 °C for 30 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 0.15 g (85%) of **55** as a colorless oil: IR (neat) 1720, 1634, 1551, 1394, 1256, and 1124 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.92 (p, 2H, $J = 6.4$ Hz), 2.68 (t, 2H, $J = 6.4$ Hz), 3.76−3.78 (m, 2H), 3.80 (s, 3H), 5.26 (s, 2H), 7.31−7.42 (m, 5H), and 7.72 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.2, 22.9, 45.4, 51.4, 67.9, 103.4, 118.4, 127.9, 128.2, 128.6, 136.0, 142.0, 145.5, 152.7, and 163.9; HRMS calcd for $C_{17}H_{17}NO_5$ 315.1107, found 315.1107.

***N*-(6-Bromo-3,4-methylenedioxybenzyl)-*N*-(4-methyloxazol-2-yl)acetamide (56).** A mixture containing 0.6 g (4.3 mmol) of 2-acetamidooxazole[45] and 4.2 g (13.0 mmol) of $CsCO_3$ in 4 mL of DMF and 2 mL of THF was stirred at 60 °C for 30 min. To this mixture was added 1.4 g (4.7 mmol) of 6-bromopiperonyl bromide,[58] and the solution was heated at 60 °C for 2 h. The reaction mixture was quenched with 25 mL of water and extracted with ether. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography to give 1.3 g (89%) of **56** as a white solid: mp 106−107 °C; IR (neat) 1694, 1578,

(57) Nico, J. L. M.; Broekholf, N.; Wittevenn, J. G.; Weerdt, A. J. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 436.

(58) Barthel, W. F.; Alexander, B. H. *J. Org. Chem.* **1958**, *23*, 1012.

1480, 1396, and 932 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.14 (d, 3H, J = 1.2 Hz), 2.27 (s, 3H), 4.98 (s, 2H), 5.94 (s, 2H), 6.83 (s, 1H), 6.95 (s, 1H), and 7.23 (d, 1H, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.0, 23.3, 50.3, 101.9, 109.0, 112.8, 113.7, 129.0, 133.0, 137.3, 147.7, 147.9, 155.2, and 170.4. Anal. Calcd for $C_{14}H_{13}BrN_2O_4$: C, 47.61; H, 3.71; N, 7.93. Found: C, 47.81; H, 3.73; N, 7.84.

***N*-(4-Methyloxazol-2-yl)-*N*-(6-trimethylsilylethynyl-3,4-methylenedioxybenzyl)acetamide (57).** To a solution containing 0.4 g (1.1 mmol) of **56** in 10 mL of triethylamine were added 0.02 g (0.03 mmol) of bis(triphenylphosphine)palladium(II) chloride, 0.04 g (0.02 mmol) of triphenylphosphine, 0.02 g (0.01 mmol) of copper(I) iodide, and 0.6 mL (4 mmol) of trimethylsilylacetylene. The mixture was heated at reflux for 24 h, cooled to room temperature, diluted with ether, and filtered through a pad of Celite. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 0.28 g (60%) of **57** as a light yellow oil: IR (neat) 2148, 1694, 1578, and 1481 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.22 (s, 9H), 2.12 (d, 3H, J = 1.2 Hz), 2.25 (s, 3H), 5.08 (s, 2H), 5.92 (s, 2H), 6.80 (s, 1H), 6.83 (s, 1H), and 7.21 (d, 1H, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.2, 12.0, 23.2, 48.4, 97.8, 101.6, 102.5, 107.8, 111.9, 115.3, 133.0, 134.1, 137.2, 146.6, 148.6, 155.3, and 170.5; HRMS calcd for $C_{19}H_{22}N_2O_4Si$ 370.1349, found 370.1350.

4-Acetyl-4,5-dihydro-7,8-methylenedioxy-1-trimethylsilylfurano[2,3-*c*]isoquinoline (58). A solution containing 0.05 g (0.13 mmol) of **57** in 5 mL of toluene was heated in a sealed tube at 200 °C for 17 h under an argon atmosphere. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 0.04 g (93%) of **58** as a yellow oil: IR (neat) 1683, 1586, 1507, 1238, and 839 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.37 (s, 9H), 2.31 (s, 3H), 4.93 (s, 2H), 5.96 (s, 2H), 6.74 (s, 1H), 6.92 (s, 1H), and 7.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −0.1, 23.3, 47.6, 101.3, 104.3, 107.7, 111.1, 117.1, 124.3, 124.6, 143.6, 145.8, 146.6, 147.4, and 168.8; HRMS calcd for $C_{17}H_{19}NO_4Si$ 329.1083, found 329.1081.

***N*-Benzyl-2-bromo-*N*-(4-methyloxazol-2-yl)benzamide (59).** To a stirred suspension containing 1.0 g (5.0 mmol) of 2-bromobenzoic acid in 25 mL of CH_2Cl_2 was added 3 drops of DMF followed by 4.0 mL (8.0 mmol) of a 2.0 M oxalyl chloride−CH_2Cl_2 solution. The mixture was stirred at room temperature for 2 h and concentrated under reduced pressure to give the expected acid chloride as a yellow oil. This material was used in the next step without further purification.

To a solution containing the above benzoyl chloride and 0.9 g (5.0 mmol) of 2-benzylaminooxazole[45] in 20 mL of benzene was added 1.4 mL (10.0 mmol) of triethylamine. The mixture was heated at reflux for 4 days, cooled to room temperature, diluted with ether, quenched with brine, and extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.8 g (40%) of **59** as a yellow oil: IR (neat) 1685, 1574, 1397, 1284, and 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.98 (s, 3H), 5.22 (s, 2H), 6.88 (s, 1H), 7.17−7.33 (m, 6H), 7.42 (d, 2H, J = 7.6 Hz), and 7.50 (d, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.9, 51.0, 119.7, 127.2, 127.9, 128.4, 128.6, 128.7, 131.0, 132.7, 132.9, 136.3, 136.9, 137.7, 154.6, and 168.1; HRMS calcd for $C_{18}H_{15}BrN_2O_2$ 370.0317, found 370.0319.

4-Benzyl-1-trimethylsilylfurano[2,3-*c*]isoquinol-5-one (61). To a solution containing 0.7 g (1.8 mmol) of **59** in 10 mL of triethylamine were added 0.01 g (0.01 mmol) of bis(triphenylphosphine)palladium(II) chloride, 0.03 g (0.01 mmol) of triphenylphosphine, 0.03 g (0.01 mmol) of copper(I) iodide, and 0.6 mL (4.5 mmol) of trimethylsilylacetylene. The resulting mixture was heated at reflux for 24 h, cooled to room temperature, diluted with ether, and filtered through a pad of Celite. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.62 g (88%) of **61** as a yellow oil: IR (neat) 1657, 1551, 1518, 1446, and 839 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.01 (s, 9H), 5.05 (s, 2H), 6.76 (s, 1H), 6.79−6.82 (m, 1H), 6.86 (t, 2H, J = 7.2 Hz), 6.98 (t, 1H, J = 7.2 Hz), 7.08 (d, 2H, J = 7.2 Hz), 7.26 (t, 1H, J = 7.2 Hz), 7.41 (d, 1H, J = 8.0 Hz), and 8.14 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −0.4, 46.9, 102.9, 117.1, 123.0, 123.6, 124.8, 127.8, 128.5, 128.6, 130.0, 132.7, 133.5, 136.5, 143.1, 150.0, and 161.0; HRMS calcd for $C_{21}H_{21}NO_2Si$ 347.1342, found 347.1342.

***N*-Benzyl-6-bromo-*N*-(4-methyloxazol-2-yl)-3,4-methylenedioxybenzamide (62).** To a stirred suspension containing 1.0 g (4.3 mmol) of 6-bromopiperonylic acid in 25 mL of CH_2Cl_2 was added 3 drops of DMF followed by 3.2 mL (6.4 mmol) of a 2.0 M oxalyl chloride/CH_2Cl_2 solution. The mixture was stirred at room temperature for 2 h and concentrated under reduced pressure to give the expected acid chloride as a yellow oil. This material was used in the next step without further purification.

To a stirred suspension containing 0.3 g (6.4 mmol) of 60% NaH in 20 mL of THF was added dropwise a solution containing 0.8 g (4 mmol) of 2-benzylaminooxazole[45] in 10 mL of THF at 0 °C. After 15 min of stirring, a solution containing the above acid chloride in 20 mL of THF was added dropwise. The resulting mixture was stirred at room temperature for 12 h and then heated at reflux for 1.5 h. The mixture was cooled to room temperature, quenched with 5 mL of brine, and extracted with ether. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 1.0 g (56%) of **62** as a white solid: mp 186−187 °C; IR (KBr) 1790, 1711, 1507, 1491, and 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.02 (s, 3H), 5.18 (s, 2H), 5.96 (s, 2H), 6.76 (s, 1H), 6.91 (s, 1H), 6.95 (s, 1H, J = 1.6 Hz), 7.25−7.32 (m, 3H), and 7.40 (d, 2H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.9, 51.2, 102.3, 108.7, 111.3, 113.0, 127.9, 128.4, 128.7, 130.7, 132.7, 136.3, 136.9, 147.2, 149.5, 154.6, and 167.7; HRMS calcd for $C_{19}H_{15}BrN_2O_4$ [M^+ − Br] 335.1032, found 335.1030.

4-Benzyl-7,8-methylenedioxy-1-trimethylsilylfurano-[2,3-*c*]isoquinol-5-one (64). To a solution containing 0.8 g (1.9 mmol) of amide **62** in 10 mL of triethylamine were added 0.04 g (0.05 mmol) of bis(triphenylphosphine)palladium(II) chloride, 0.08 g (0.03 mmol) of triphenylphosphine, 0.08 g (0.4 mmol) of copper(I) iodide, and 0.5 mL (4 mmol) of trimethylsilylacetylene. The resulting mixture was heated at reflux for 18 h, cooled to room temperature, diluted with ether, and filtered through a pad of Celite. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 0.36 g (48%) of **64** as a yellow solid: mp 178−179 °C; IR (KBr) 1650, 1575, 1497, 1469, and 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.41 (s, 9H), 5.60 (s, 2H), 6.08 (s, 2H), 7.16 (s, 1H), 7.18 (s, 1H), 7.26−7.30 (m, 3H), 7.49 (d, 2H, J = 7.2 Hz), and 7.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −0.3, 46.0, 101.7, 101.9, 103.2, 107.9, 116.9, 118.6, 127.9, 128.6, 128.7, 130.8, 136.6, 143.0, 146.2, 149.5, 152.4, and 160.2; HRMS calcd for $C_{22}H_{21}NO_4Si$ 391.1240, found 391.1235.

2-(But-3-enylamino)oxazole. To a suspension containing 7.2 g (68 mmol) of cyanogen bromide and 19 g (140 mmol) of potassium carbonate in 100 mL of dry ether was added dropwise a solution containing 4.8 g (70 mmol) of 4-amino-1-butene[59] in 20 mL of ether at −10 °C. The mixture was stirred at −10 °C for 2 h and then allowed to warm to 0 °C. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was taken up in 50 mL of THF and 50 mL of water and then treated with 5 mL (70 mmol) of 90% acetol, followed by the dropwise addition of 8 mL of a 2 M NaOH solution. The resulting mixture was stirred at 50 °C for 2 h, diluted with water, and extracted with ether. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 3.9 g (38%) of the above oxazole as a light yellow oil: IR (neat) 3218, 1637, 1603, 1328, and 916 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.04 (s, 3H), 2.35 (q, 2H, J = 6.4 Hz), 3.39 (q, 2H, J = 6.4 Hz), 4.64 (brs, 1H), 5.08−5.15 (m, 2H), 5.73−5.84 (m, 1H), and 6.87 (s,

(59) Koziara, A.; Osowska, P.; Zawadzki, S.; Zwierzak, A. *Synthesis* **1985**, 202.

1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.1, 34.2, 42.3, 117.7, 127.5, 135.2, 136.0, and 161.0; HRMS calcd for $C_8H_{12}N_2O$ 152.0950, found 152.0955.

***N*-(But-3-enyl)-6-iodo-*N*-(4-methyloxazol-2-yl)-3,4-methylenedioxybenzamide (65).** To a stirred suspension containing 1.0 g (3.4 mmol) of 6-iodopiperonylic acid in 25 mL of CH_2Cl_2 was added 3 drops of DMF followed by 2.6 mL (5.2 mmol) of a 2.0 M oxalyl chloride/CH_2Cl_2 solution. The mixture was stirred at room temperature for 2 h and concentrated under reduced pressure, to give the expected acid chloride as a yellow solid. This material was used in the next step without further purification.

To a suspension containing 0.20 g of 60% of sodium hydride/mineral oil in 20 mL of THF was added dropwise a solution containing 0.52 g (3.4 mmol) of 2-(but-3-enylamino)oxazole in 5 mL of THF at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and was added to a solution containing the above acid chloride in 20 mL of THF at 0 °C. The resulting mixture was stirred at room temperature for 36 h, quenched by the slow addition of 10 mL of brine, and extracted with ether. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.72 g (49%) of **65** as a colorless oil: IR (neat) 1678, 1574, 1477, 1237, and 1034 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03 (d, 3H, J = 1.2 Hz), 2.46 (q, 2H, J = 7.2 Hz), 4.00 (t, 2H, J = 7.2 Hz), 5.00−5.09 (m, 2H), 5.71−5.81 (m, 1H), 5.94 (s, 2H), 6.68 (s, 1H), 6.97 (d, 1H, J = 1.2 Hz), and 7.11 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.9, 32.6, 47.4, 81.7, 102.1, 108.4, 117.4, 118.8, 132.6, 134.4, 135.1, 136.9, 147.9, 149.1, 154.6, and 168.9; HRMS calcd for $C_{16}H_{15}IN_2O_4$ 426.0078, found 426.0075.

4-(But-3-enyl)-7,8-methylenedioxy-1-trimethylsilylfurano[2,3-*c*]isoquinol-5-one (67). To a solution containing 0.3 g (0.7 mmol) of **65** in 5 mL of diisopropylamine were added 0.01 g (0.01 mmol) of bis(triphenylphosphine)palladium(II) chloride, 0.02 g (0.01 mmol) of triphenylphosphine, 0.02 g (0.01 mmol) of copper(I) iodide, and 0.14 mL (1.0 mmol) of trimethylsilylacetylene. The resulting mixture was heated at reflux for 20 h, cooled to room temperature, diluted with ether, and filtered through a pad of Celite. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.2 g (77%) of **67** as a yellow oil: IR (neat) 1655, 1576, 1467, 1239, and 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.44 (s, 9H), 2.59 (q, 2H, J = 7.6 Hz), 4.35 (t, 2H, J = 7.6 Hz), 5.03−5.13 (m, 2H), 5.83−5.92 (m, 1H), 6.10 (s, 2H), 7.18 (s, 1H), 7.19 (s, 1H), and 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −0.2, 32.9, 42.3, 101.6, 101.8, 102.9, 107.7, 116.8, 117.4, 118.5, 130.5, 134.5, 142.7, 146.0, 149.5, 152.1, and 159.9; HRMS calcd for $C_{19}H_{21}NO_4Si$ 355.1240, found 355.1238.

Anhydrolycorin-7-one (68). A solution containing 0.08 g (0.2 mmol) of **67** in 5 mL of 1,2,4-trichlorobenzene was heated in a sealed tube at 320 °C for 24 h. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.02 g (30%) of **68** as a yellow solid: mp 230−231 °C; IR (neat) 1655, 1576, 1467, 1239, and 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.42 (t, 2H, J = 8.0 Hz), 4.46 (t, 2H, J = 8.0 Hz), 6.13 (s, 2H), 7.19 (t, 1H, J = 8.0 Hz), 7.28 (dd, 1H, J = 7.2 and 0.8 Hz), 7.52 (s, 1H), 7.73 (d, 1H, J = 7.2 Hz) and 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.6, 46.7, 101.0, 102.2, 106.9, 116.9, 119.6, 123.1, 123.4, 123.9, 130.8, 131.0, 139.5, 148.5, 152.0, and 159.6; HRMS calcd for $C_{16}H_{11}NO_3$ 265.0739, found 265.0734.

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

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