Strategies for the Synthesis of Heterocyclic Natural Products

Stephen F. Martin

Department of Chemistry and Biochemistry, The University of Texas, Austin, TX 78712

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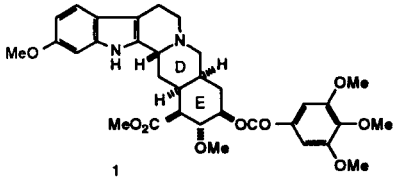
Introduction.

The synthesis of natural products provides an excellent forum for the discovery of new and exciting chemistry, whether by design or by serendipity. In such endeavors, it is necessary to develop general strategies for the assemblage of structural subunits that are common to a variety of complex molecules and to invent methods and reagents for effecting specific transformations in a stereo- and chemoselective fashion. In this context, we have exploited alkaloids as "targets of opportunity" for the development of new applications of intramolecular Diels-Alder and vinylogous Mannich reactions and now wish to describe some of our recent work using such constructions as the key steps in formulating novel approaches to heterocyclic natural products.

Applications of Intramolecular Diels-Alder Reactions to Alkaloid Synthesis.

For a number of years we have been interested in alkaloids that contain hydroisoquinoline or oxahydroisoquinoline rings as key structural elements. For example, the indole alkaloids reserpine (**1**), an alkaloid once prescribed extensively for its antihypertensive properties, and tetrahydroalstonine (**2**), which also exhibits cardiovascular activity, possess hydroisoquinoline and oxahydroisoquinoline rings as the DE ring subunit. More recently we have become intrigued in the novel anticancer agent manzamine A (**3**), which contains a hydroquinoline ring as the AB ring subunit. Given their structural complexities, these alkaloids provide an excellent opportunity to develop new strategies and methods for the synthesis of heterocycles.



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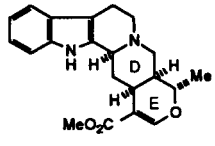

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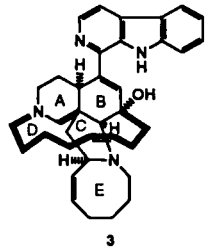
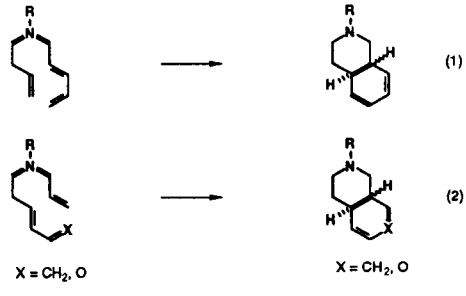


3

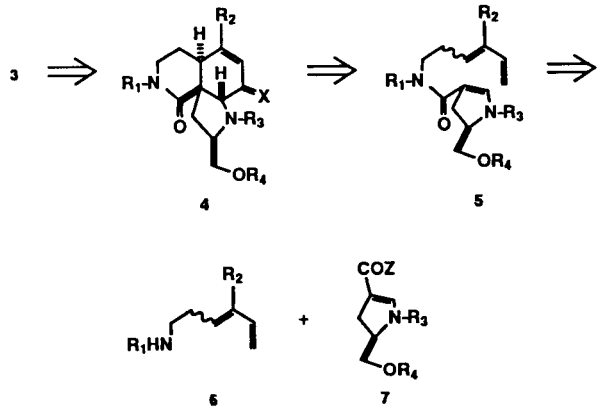
Our successes in the total syntheses of **1** and **2** have already been documented in the literature [1,2] and need not be reiterated here. Suffice it to say that the basic challenge in the syntheses of **1** and **2** was cast as a problem of developing efficient and stereoselective means to form substituted hydroisoquinoline and oxahydroisoquinoline rings. Toward this end, we exploited intramolecular Diels-Alder reactions (equations 1 and 2) as a key constructions in the design of our synthetic strategy [3]. Although the intramolecular Diels-Alder reaction was well known when we first began to investigate transformations such as those depicted in equations 1 and 2, we have tried to examine new issues with each endeavor. For example, in our early work, we were interested in probing the stereochemical issues of those intramolecular cycloadditions that produced simple hydroisoquinolines, as in equations 1 and 2 (X = CH_2), and this work led to the total synthesis of reserpine [1]. In our synthesis of tetrahydroalstonine [2], we raised the new issue of whether simple α,β-unsaturated aldehydes could serve as dienic components in hetero Diels-Alder reactions with simple dienophiles as depicted in equation 2 (X = O). The challenge of exploring novel variants of related intramolecular Diels-Alder reactions to construct the ABC ring system of manzamine A lead to the present investigation.



Progress Toward the Total Synthesis of Manzamine A (3).

Manzamine A (**3**) belongs to a novel class of β-carboline alkaloids that were isolated from marine sponges of genera *Haliclona* and *Pellina* found off the coast of Okinawa [4]. The complex structure of this alkaloid, which is unprecedented in nature, coupled with its antitumor activity has served as an impetus for a number of interesting synthetic investigations, most of which have thus far been focused upon constructing the central pyrrolo[2,3-*i*]iso-quinoline tricyclic core [5]. We were also attracted to manzamine A as an intriguing target of opportunity, and we formulated the strategy that is depicted in

Scheme 1

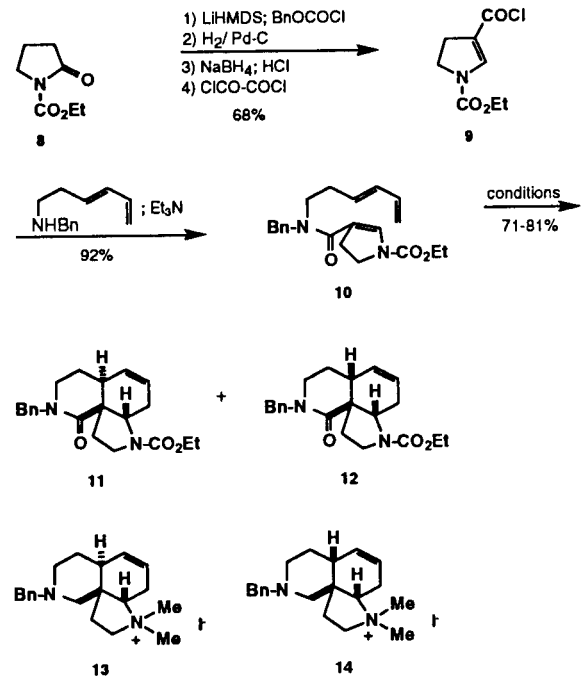


retrosynthetic format in Scheme 1 [6]. Close examination of this plan reveals a number of interesting problems, and these will be considered in turn.

The end game of the synthesis will require the development of tactics for constructing the macrocyclic D ring while controlling the stereochemistry of the Z-double bond; there is clearly the issue of timing for the formation of the carbon-carbon and the carbon-nitrogen bonds that join this ring to the AB ring subunit. Elaboration of the eight-membered unsaturated E ring poses another problem; there are few methods for such constructions in the literature. Dismantling the D and E rings thus leads to the intermediate **4**, wherein R^2 is a functional group that may be elaborated into the carboline ring system found in the natural product. At this juncture, it seemed to us that an intramolecular Diels-Alder reaction of a substrate such as **5** was ideally suited to the problem of constructing **4**, which bears the critical tricyclic ABC ring core of manzamine A. The question, however, of whether this cycloaddition would in fact proceed naturally arose, since there is little precedent for the participation of vinylogous imides in Diels-Alder reactions of any type [7]. Whether such dienophiles were electron rich or electron poor must be evaluated in the context of varying the nature of the substituent R^3 on nitrogen and the R^2 group on the diene. The assembly of **5** requires the two fragments **6** and **7**. The preparation of the dienic partner **6** is likely to require the development of novel methods for the stereoselective preparation of functionalized dienes in which the internal double bond is trisubstituted, whereas the synthesis of the dienophile **7** will require the design of procedures for elaborating vinylogous imides and their derivatives. Thus, it is readily apparent that the many challenges posed by manzamine A will require the development of innovative solutions to a number of problems that may be foreseen as well as those that may not be anticipated but would be encountered along the way.

With these considerations in mind, we initiated a model study to determine the underlying viability of the key intramolecular Diels-Alder reaction and to define some of the scope and limitations of the process. We first prepared the triene **10** according to the sequence of reactions depicted in Scheme 2; this protocol for the synthesis of vinylogous imides appears to be general, and we have exploited it in the syntheses of a number of dienophilic partners. When **10** was heated in mesitylene at reflux, a mixture (*ca.* 2:1) of the two cycloadducts **11**, which corresponds to the tricyclic ABC subunit of manzamine A (**3**), and **12** was obtained (81%). The structures of **11** and **12** were initially assigned on the basis of a series of NOE studies, but the veracity of these assignments was later confirmed by single crystal X-ray analyses of the two quaternary salts **13** and **14**, which were prepared from **11** and **12**, respectively, by sequential hydride reduction and methylation [(1) $LiAlH_4$/THF; Δ. (2) MeI/MeOH; 25°C] [8]. This critical experiment convincingly supported the earlier hypothesis that a vinylogous imide array could participate as the dienophile in an intramolecular Diels-Alder reaction with normal electron demand. More importantly this cyclization firmly established the feasibility of the key step **5** → **4** in our strategy for the synthesis of **3**.

Scheme 2

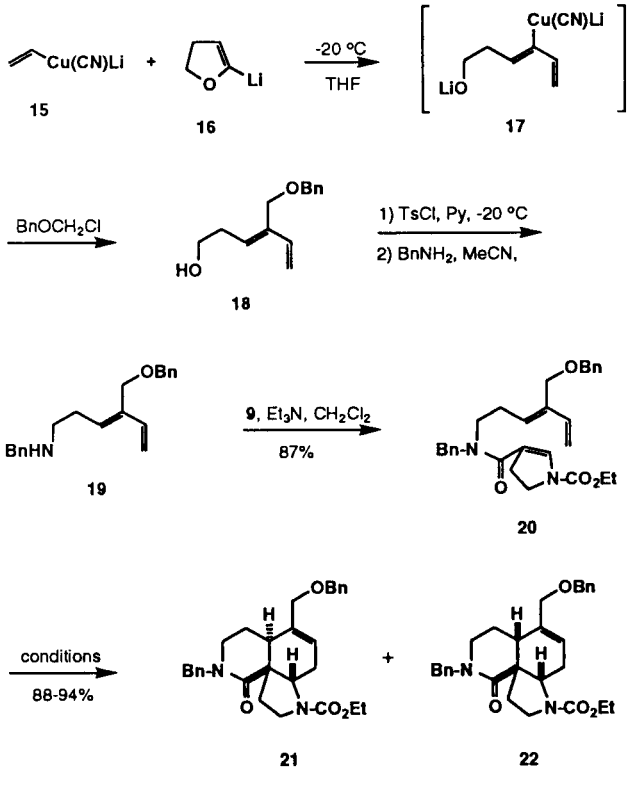


Having established feasibility, we then explored various means to enhance the stereoselectivity of the intramolecular Diels-Alder reaction of **10**. In the event, heating **10** in the presence of $EtAlCl_2$ (1.5 equiv/toluene/110°C; 72 hours; 71%) provided a mixture (5.7:1) of **11** and **12**. That $EtAlCl_2$ served a catalytic role was based upon the observation that the cyclization was markedly slower at this

temperature in the absence of $EtAlCl_2$. Other Lewis acids ($TiCl_4$ and $BF_3{\cdot}Et_2O$) were found to be less effective than $EtAlCl_2$, but Et_2AlCl may also be used. Although the use of Lewis acids to facilitate and to improve the stereoselectivity of Diels-Alder reactions is well documented, this is the first time we have observed that using a Lewis acid enhances an intramolecular Diels-Alder reaction to form a hydroisoquinoline ring.

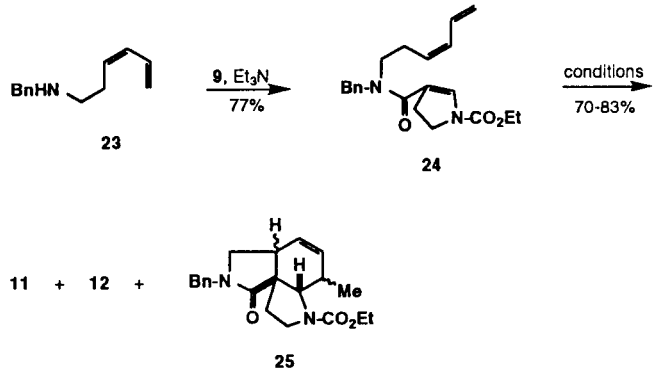
In order to maximize convergency in our synthesis, we reasoned that the maximal number of substitutents should be incorporated onto the triene prior to cyclization. In this context, the cycloadduct **11** lacks a substituent R^2 on the double bond of the B ring that would serve as a handle for the introduction of the carboline ring. Since the cycloadduct **21** does possess such a substituent, we turned to a study of the stereoselectivity of the cyclization of the triene **20** (Scheme 3). In order to synthesize the substituted dienic component, we developed a variant of chemistry previously reported by Kocienski [9]. Namely, treatment of the vinyllithium reagent **16** with **15** leads *via* stereoselective reorganization to the vinylcuprate **17**, which may be trapped with chloromethyl benzyl ether to give **18**. Straightforward exchange of the hydroxyl group for an amino group followed by *N*-acylation of the intermediate secondary amine gave the amide **20** in good overall yield. Although heating **20** in toluene at reflux with or without Lewis acids afforded the cycloadducts in very good yield, the ratio of the desired **21** to the isomeric adduct **22** varied from 2:3 → 3:2, depending upon the conditions. Obviously this cyclization is not suited for application to the total synthesis of manzamine A, and we turned to other tactics to control the stereoselectivity of the critical intramolecular Diels-Alder reaction.

Scheme 3



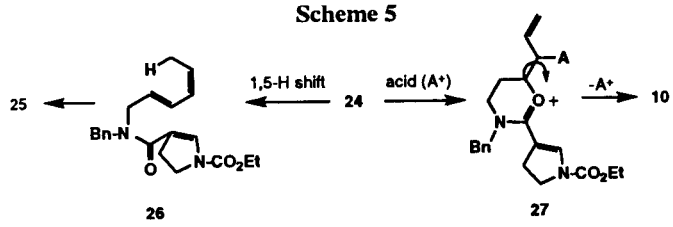
The intramolecular [4+2] cycloadditions of trienes in which the internal double bond is *Z* are more stereoselective than the cyclizations of the corresponding trienes having an *E* internal double bond [10]. We thus set to the task of preparing **24** by straightforward modification of the procedures developed previously for the synthesis of **10**. In the event, the unsaturated amine **23** [3a] was treated with the acid chloride **9** to furnish **24** (Scheme 4). When **24** was heated in refluxing toluene in the presence of $EtAlCl_2$ (1.5 equivalents, 100 hours), a mixture (*ca.* 8:1) of the cycloadducts **11** *and* **12** was obtained in 70% yield; the formation of **12** was completely unexpected. The cyclization of **24** could be induced thermally (180°C, 20 hours), but a mixture of **11**, **12**, and two isomers (*ca.* 3:1) of the cycloadduct **25** was obtained; the adduct **11** was isolated in only about 25-30% yield.

Scheme 4



Based upon our previous work [3a], we anticipated the possible formation of cycloadducts **25**, which arise from the cyclization of the isomeric triene **26** – the product of a 1,5-hydrogen shift of **24** (Scheme 5). However, we did not predict the formation of **12**, since *Z*-dienes are *not* geometrically disposed to give such adducts. We tentatively speculate that those quantities of **12** that were produced upon thermolysis of **24** arose from the cyclization of **10** that is formed under the reaction conditions by isomerization of **24**. Presumably **24** undergoes acid-catalyzed cyclization to an intermediate of type **27** (A = Lewis acid or H); rotation about the C(7)-C(8) bond of the trienic array then leads to **10**. In support of this hypothesis, we found that **24** does undergo partial equilibration to **10** in the presence of catalytic amounts of $EtAlCl_2$ (toluene, 72 hours, 40°C; *ca.* 30% conversion) or

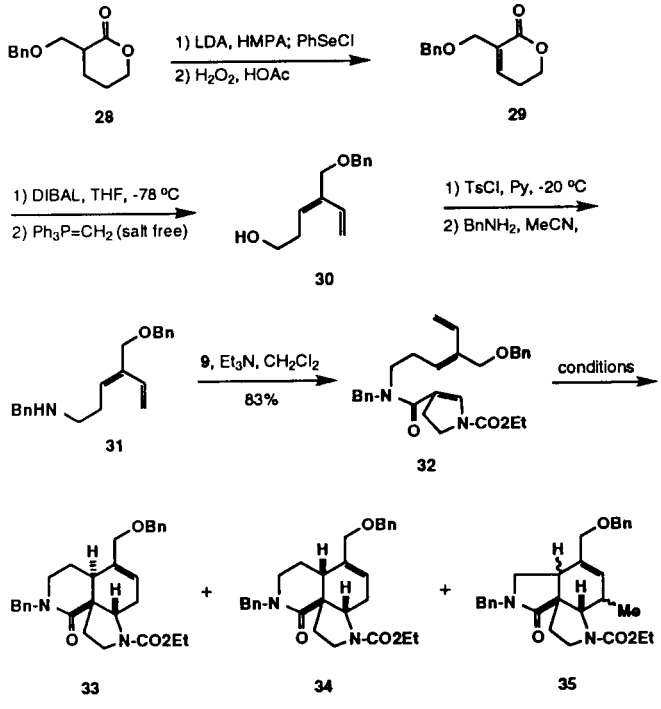
Scheme 5



HCl (room temperature).

In a parallel series of reactions, we examined the cyclization of the substituted triene **32** (Scheme 6). Synthesis of the requisite diene **31** commenced with a deprotonation of **28** followed by phenylselenylation of the intermediate enolate; oxidation and elimination gave **29** in 30-40% overall yield. This conversion is noteworthy since the intermediate enolate did not suffer complete fragmentation by β-elimination of benzyloxide to give the α-methylene lactone. The conversion of **29** into **31** follows from previous work in our laboratory [3a], *N*-acylation of **31** as before furnished **32**. Unfortunately, heating **32** at 200°C gave **35** as the major product (80% yield). Although heating **32** in toluene at reflux in the presence of $EtAlCl_2$ did give **33** as the only isolable product, the yield was only about 15%, and substantial quantities (*ca*

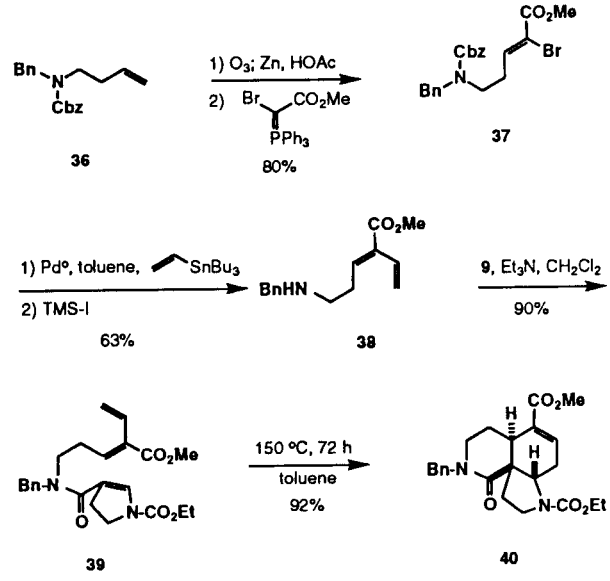
Scheme 6



60%) of starting material were recovered. Thus, the added substituent on the double bond of the diene moiety of **32** adversely affected its cyclization by an intramolecular Diels-Alder reaction relative to **24**.

To this point we have considered only those Diels-Alder reactions that are of the "normal" electron demand type, and it was now appropriate to evaluate some of the electronic features of the Diels-Alder reactions of vinylogous imides. If the vinylogous imide array functioned as an electron rich dienophile, then an inverse electron demand Diels-Alder reaction was indicated. Toward this end, we prepared the dienic partner **38** exploiting a highly stereoselective Wittig reaction involving the aldehyde derived from **36** followed by a Stille coupling reaction; subsequent reaction of **38** with **9** gave the cyclization substrate **39** in excellent overall yield (Scheme 7). When **39** was heated at 150°C in toluene, **40** was obtained as the *only* cycloadduct in 92% yield; the reaction also proceeds at 110°C, albeit more slowly. The structure of **40**, whose *relative* configuration at each stereogenic center corresponds that in manzamine A, was verified by an X-ray analysis of a derivative. Thus, the stereochemistry of the internal carbon-carbon double bond of the diene *combined* with activation of the diene using an electron withdrawing group resulted in a highly efficient and stereoselective intramolecular Diels-Alder reaction.

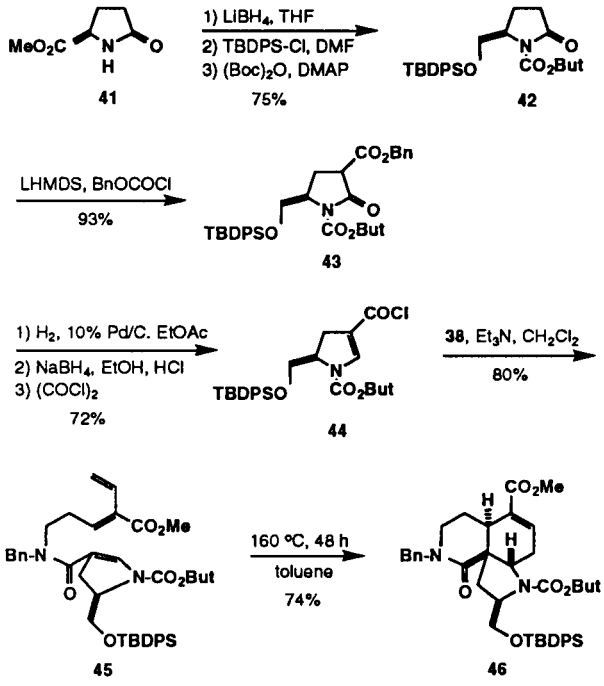
Scheme 7



In order to complete the assembly of an ABC ring core that could realistically be elaborated into manzamine A, it remained to incorporate substitution that would provide for the introduction of the eight-membered E ring; an asymmetric synthesis would further necessitate the preparation of this intermediate in optically pure form. Toward this end the dienophilic partner **44** was produced in good overall yield from methyl pyro-D-glutamate (**41**) by a straightforward sequence of reactions that follow the tactics previously outlined for the synthesis of **9** (Scheme 8).

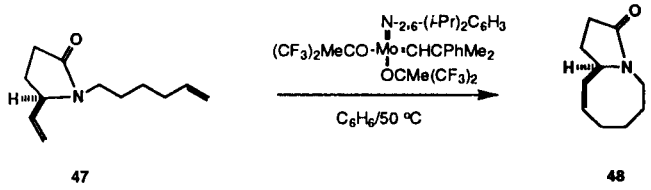
Coupling **44** with the dienic partner **38** gave **45**, which underwent a facile intramolecular Diels-Alder reaction to give **46** as the *only* isolated product. That the cyclization proceeded as expected from the less hindered face of the dienophile was supported by NOE experiments. With the preparation of **46**, a fully competent synthetic intermediate is in hand.

Scheme 8



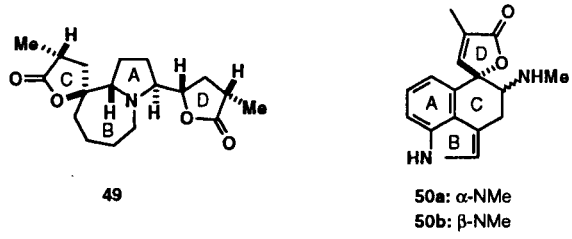
It is now necessary to address the issue of constructing the eight-membered ring. Although the numerous possibilities include an intramolecular Wittig or reductive coupling reaction, we were attracted to a recent report of Grubbs who described a novel route to monocyclic amines and lactams via an olefin metathesis reaction [11]. In order to ascertain whether such a tactic could be employed to form the E-ring of manzamine A, we conducted a simple model study in which **47** was converted into **48**, albeit in modest yield. We have not optimized this reaction, but it clearly establishes the potential of an olefin metathesis for the elaboration of the ABCE ring subunit of manzamine A.

Scheme 9



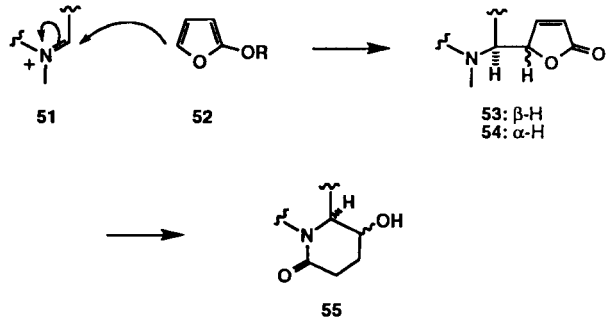
Novel Applications of Vinylogous Mannich Reactions.

Several years ago we noted the presence of a 5-aminoalkyl butenolide or butyrolactone ring as a key skeletal feature in a number of alkaloids. For example, in croomine (**49**) [12,13], which is a representative member of the *Stemona* family of alkaloids, the C and D rings are γ-butyrolactones that bear an aminoalkyl group alpha to the ring oxygen. Furthermore, the *Ergot* alkaloids rugulovasines A and B (**50a,b**) [14,15] possess a spirocyclic CD ring array in which there is an alkyl amino substituent on a butenolide ring. A general entry to these and other alkaloids might be developed if a simple means of constructing such finctionalized heterocyclic arrays were in hand.



Toward this end, we queried whether a vinylogous Mannich reaction of the 2-alkoxy furans **52** with the acyliminium ions **51** would give adducts **53** and/or **54** according to Scheme 10. In addition to constructing the targeted 5-aminoalkyl butenolide motif, we recognized that subsequent elaboration of these adducts could then lead to the functionalized piperidone **55**; such intermediates could also be widely exploited in alkaloid synthesis. A preliminary examination of the literature provided a measure of confidence that the addition reaction of **52** to **51** itself was feasible, since the acid-catalyzed reactions of furans **52** with aldehydes was already well established [16,17].

Scheme 10



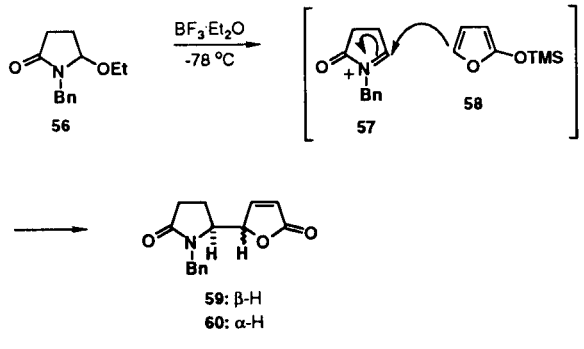
Model Studies of Nucleophilic Additions of Furans to Acyliminium Salts.

To address the key issue of whether vinylogous Mannich reactions of the general type depicted in Scheme

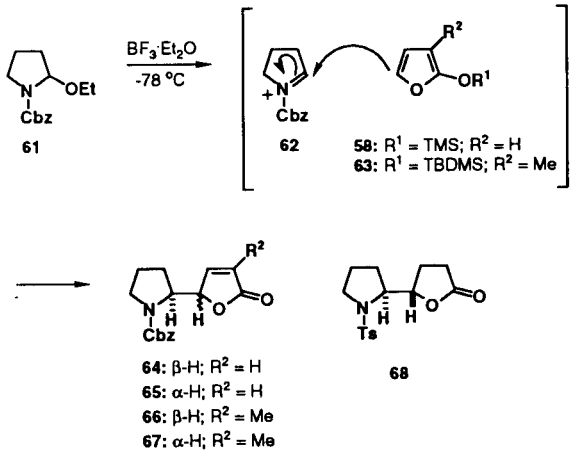
10 might be implemented in a synthesis of croomine, it was first necessary to confirm our hypothesis that the reaction would proceed. Having answered this question, it would remain to elucidate the stereochemical outcome of the reaction by determining the relative configuration at the two newly constructed stereogenic centers. Toward these objectives, we embarked on several simple model studies as outlined in Schemes 11 and 12. We first found that the addition of the furan **58** to the iminium ion **57** gave a mixture (1.6:1) of the *threo* and *erythro*-adducts **59** and **60**, respectively. Although this experiment confirmed that the key addition occurred, the stereoselectivity of the process was not encouraging.

In a parallel series of experiments, we studied the additions of substituted furans to the *N*-acyliminium salt derived from **61** (Scheme 12) [18]. These reactions proceeded with significantly higher stereoselectivity; the addition of **58** to **62** gave a mixture (8.5:1) of the *threo*- and *erythro*-adducts **64** and **65**, respectively, whereas the addition of **63** to **62** gave a mixture (6:1) of the corresponding adducts **66** and **67** in good yields. The stereochemical outcome of the reaction of **58** and **62** was verified by the X-ray analysis of **68**, which was readily derived from **64** by reduction and *N*-tosylation.

Scheme 11



Scheme 12

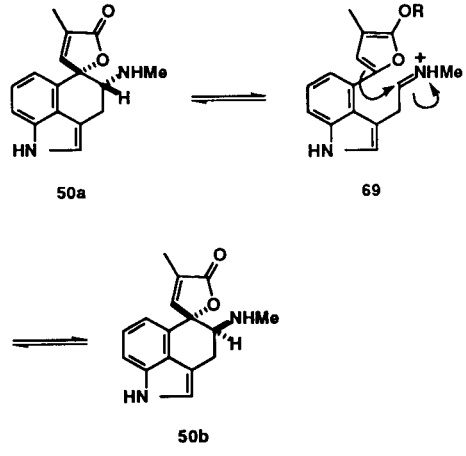


Significantly, the relative stereochemistry at the new stereogenic centers of the major adducts **64** and **66** correspond to that found in croomine (**49**) thereby establishing the viability of using vinylogous Mannich reactions as a key construction in formulating a strategy for the total synthesis. We are presently working toward that goal and probing such additions in more highly substituted systems.

Total Synthesis of Rugulovasines A and B (**50a,b**).

Rugulovasines A and B (**50a,b**) were isolated together *and* in racemic form; moreover, they interconvert upon heating [14]. To account for these facts, the mechanism depicted in Scheme 13 was proposed in which **50a** and **50b** underwent interconversion via the achiral intermediate **69**. That this hypothesis was indeed feasible was convincingly demonstrated by Rebek, who completed the first and only total synthesis of rugulovasine A (**50a**) and then studied its equilibration to form a mixture of **50a** and **50b** [15].

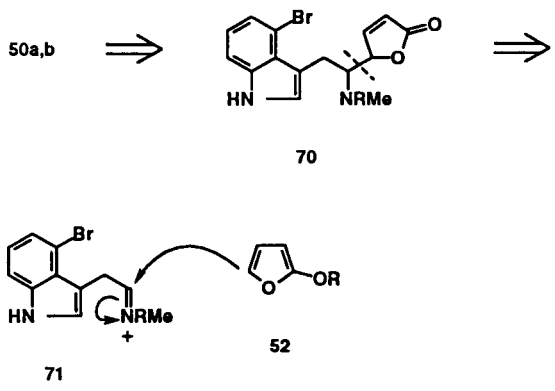
Scheme 13



The conversion of **69** into **50a** and **50b** is an example of a vinylogous Mannich reaction, and a biomimetic approach to the rugulovasines A and B might then be envisioned as proceeding *via* the intermediacy of **69** – a possibility we are currently exploring. We have also devised an alternate approach to these and related *Ergot* alkaloids that features an intermolecular addition of the 2-alkoxyfuran **52** to the iminium ion **71** to give the 5-aminoalkyl butenolide **70**, cyclization of which *via* a photostimulated $S_{RN}1$ reaction [19] would deliver the natural products **50a,b** (Scheme 14).

The first step of the synthesis involved the introduction of a functionalized side chain onto the 3-position of commercially available 4-bromoindole **72** by classical methods to give the 3-indolylacetonitrile derivative **73** in 71% overall yield (Scheme 15) [20]. After converting **73** into

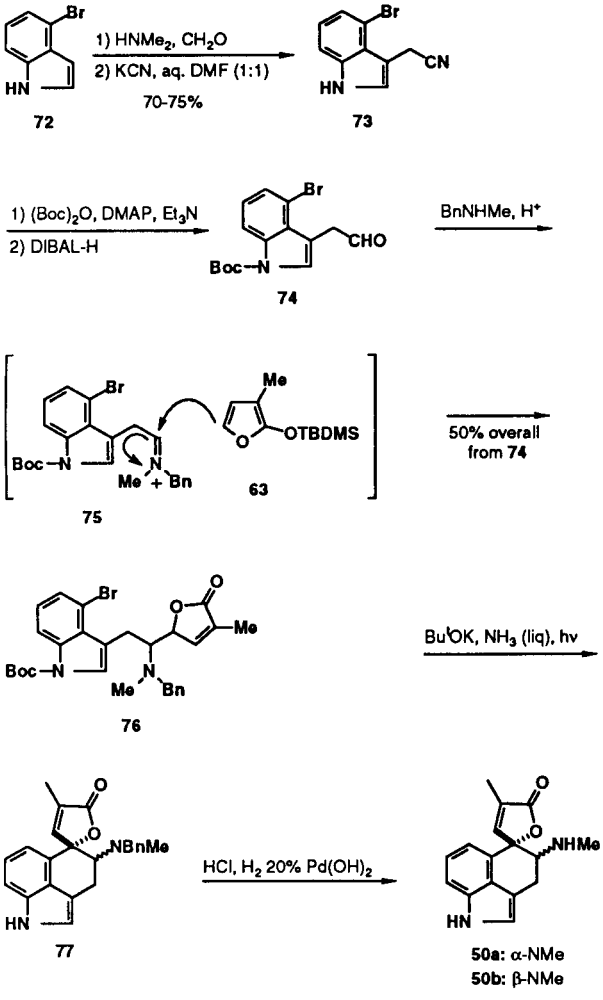
Scheme 14



its derived *tert*-butyl carbamate, the nitrile function was reduced with diisobutylaluminum hydride to give the aldehyde **74**, which was used in subsequent steps without purification. If the indole N-H was not protected prior to reduction, the resultant aldehyde was too unstable [21] and could not be efficiently elaborated further. Condensation of **74** with methylamine followed by exposure of the intermediate imine to the silyloxyfuran **63** in the presence of acids under a variety of conditions afforded no detectable quantities of the desired adduct. However, the reaction of crude **74** with *N*-benzyl-*N*-methylamine in the presence of the the silyloxyfuran **63** and camphorsulphonic acid in refluxing benzene provided a mixture (1:2) of diastereomeric adducts **76** in 40-45% overall yield from **73**.

The stage was now set to explore cyclization of **76** by an intramolecular $S_{RN}1$ reaction to create the spirocyclic lactone moiety and complete the skeletal construction of the rugulovasines. Although such processes have experienced only limited application in the synthesis of natural products [22], irradiation of **76** in refluxing ammonia in the presence of sublimed potassium *tert*-butoxide proceeded smoothly to deliver an inseparable mixture (1:2) of the protected rugulovasines **77** in 51% yield; the desired cyclization proceeded with concomitant removal of the *tert*-butyl carbamate group thereby obviating the need for a separate deprotection step. Debenzylation of **77** proceeded smoothly by hydrogenolysis of the hydrochloride salt of **77** over Pearlman's catalyst to give a mixture (1:2) of the rugulovasines A and B (**50a,b**), whose spectral characteristics correspond to those of an authentic sample [23], in 74% yield.

Scheme 15



Conclusions.

We have shown that intramolecular Diels-Alder reactions and bimolecular, vinylogous Mannich reactions may be exploited for the assembly of heterocyclic subunits that are common to a variety of alkaloid natural products. The ABC ring tricyclic core of manzamine A (**3**) has been constructed in optically pure form as evidenced by the synthesis of **46**. Significantly, **46** is endowed with functionality that is well suited for subsequent elaboration. During the course of this work, we have elucidated some of the electronic features of the Diels-Alder reactions of vinylogous imides and have developed some useful methods for the stereoselective synthesis of dienes bearing trisubstituted internal double bonds. Moreover, we have identified a novel plan for the elaboration of the E ring of **3** that entails an olefin metathesis reaction. It now remains to develop a tactic to introduce the 14-membered ring and complete the total synthesis.

On another front, we have begun to investigate the stereochemical control elements in the additions of 2-alkoxy furans to *N*-acyliminium salts, but more work needs to be done before making any generalizations. Since such reactions proceed preferentially to give the relative stereochemistry present in the *Stemona* alkaloid croomine (**49**), these preliminary experiments verify the key step in our strategy for the total synthesis of this alka-

loid. Finally, we have completed a concise total synthesis of the *Ergot* alkaloids rugulovasines A and B **(50a,b)** exploiting a vinylogous Mannich reaction in tandem with an intramolecular $S_{NR}1$ reaction.

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REFERENCES AND NOTES

[1] S. F. Martin, H. Rüeger, S. A. Williamson, and S. Grzejszczak, *J. Am. Chem. Soc.* **109**, 6124 (1987).

[2a] S. F. Martin, B. Benage, S. A. Williamson, and S. P. Brown, *Tetrahedron*, **42**, 2903 (1986); [b] S. F. Martin, B. Benage, L. S. Geraci, J. E. Hunter, and M. P. Mortimore, *J. Am. Chem. Soc.*, **113**, 6161 (1991).

[3] For example, see: [a] S. F. Martin, S. A. Williamson, R. P. Gist, and K. M. Smith, *J. Org. Chem.*, **48**, 5170 (1983); [b] S. F. Martin, in Strategies and Tactics in Organic Synthesis, T. Lindberg, ed., Academic Press, NY, 1989, p 291; [c] S. F. Martin, W. Li, *J. Org. Chem.*, **56**, 642 (1991).

[4a] R. Sakai, T. Higa, C. W. Jefford, and G. Bernardinelli,*J. Am. Chem. Soc.* **108**, 6404 (1986); [b] R. Sakai, S. Kohmoto, T. Higa, C. W. Jefford, and G. Bernardinelli, *Tetrahedron Letters*, **28**, 5493 (1987); (c) H. Nakamura, S. Deng, J. Kobayashi, Y. Ohizumi, Y. Tomotake, T. Matsuzaki, Y. and Hirata, *Tetrahedron Letters*, **28**, 621 (1987); [d] T. Ichiba, R. Sakai, S. Kohmoto, G. Saucy, and T. Higa, *Tetrahedron Letters*, **29**, 3083 (1988).

[5] For leading references, see: [a] D. J. Hart, and J. A. McKinney, *Tetrahedron Letters*, **30**, 2611 (1989); [b] K. M. J. Brands, and U. K. Pandit, *Tetrahedron Lett.*, **30**, 1423 (1989); *Heterocycles* , **30**, 257 (1990); [c] Y. Torisawa, A. Hashimoto, M. Nakagawa, and T. Hino, *Tetrahedron Letters*, **30**, 6549 (1989); [d] M. Nakagawa, Z. Lai, Y. Torisawa, and T. Hino, *Heterocycles*, **31**, 999 (1990); [e] Y. Torisawa, M. Nakagawa, H. Arai, Z. Lai, T. Hino, T. Nakata, T. Oishi, *Tetrahedron Letters*, **31**, 3195 (1990); [f] K. M. J. Brands, A. A. P. Meekel, and U. K. Pandit, *Tetrahedron*, **47**, 2005 (1991); [g] D. de Oliveira Imbroisi, and N. S. Simpkins, *Tetrahedron Letters*, **30**, 4309 (1989); *J. Chem. Soc., Perkin Trans I*, 1815 (1991); [h] Y. Torisawa, M. Nakagawa, T. Hosaka, K. Tanabe, Z. Lai, K. Ogata, T. Nakata, T. Oishi, and T. Hino, *J. Org. Chem.*, **57**, 5741; [i] I. E. Markó, J. M. Southern, and H. Adams, *Tetrahedron Letters*, **33**, 4657 (1992); [j] J. A. Campbell, and D. J. Hart, *Tetrahedron Letters*, **33**, 6247 (1992); [k] J. Leonard, S. P. Fearnley, and D. M. B. Hickey, *SynLetters*, 272 (1992); [l] I. E.Markó, and A. Chesney, *SynLetters*, 275 (1992).

[6] S. F. Martin, T. Rein, and Y.-S. Liao,*Tetrahedron Letters*, **32**, 6481 (1991).

[7] For examples of intramolecular [4+2] cycloadditions of vinylogous imides in which the imide nitrogen is located in the chain linking the dienophilic and dienic partners, see: [a] D. J. Morgans, Jr., and G. Stork, *Tetrahedron Letters*, 1959 (1979); [b] M. E. Kuehne, W. G. Bornmann, W. G. Earley, and I. Marko, *J. Org. Chem.*, **51**, 2913 (1986); [c] G. A. Kraus, J. Raggon, P. J. Thomas, and D. Bougie, *Tetrahedron Letters*, **29**, 5605 (1988).

[8] V. M. Lynch, Y. Liao, S. F. Martin, and B. E. Davis, *Acta Cryst.*, **C48**, 1703 (1992).

[9] P. Kocienski, S. Wadman, and K. Cooper, *J. Am. Chem. Soc.*, **111**, 2363 (1989).

[10a] H. O. House, and T. H. Cronin, *J. Org. Chem.*, **30**, 1061 (1965); [b] W. Oppolzer, C. Fehr, and J. Warneke, *Helv. Chim. Acta*, **60**, 48 (1977); [c] R. K. Boeckman, Jr., and T. R. Alessi, *J. Am. Chem. Soc.*, **104**, 3216 (1982); [d] S. G. Pyne, M. J. Hensel, and P. L. Fuchs, *J. Am. Chem. Soc.*, **104**, 5719 (1982); [e] M. Yoshioka, H. Nakai, and M. Ohno, *J. Am. Chem. Soc.*, **106**, 1133 (1984); [f] S. Wattanasin, F. G. Kathawala, and R. K. Boeckman, Jr., *J. Org. Chem.*, **50**, 3810 (1985).

[11] G. C. Fu, and R. H. Grubbs, *J. Am. Chem. Soc.*, **114**, 7324 (1992).

[12a] H. Lizuka, H. Irie, N. Masaki, K. Osaki, and S. Uyeo, *J. Chem. Soc., Chem. Commun.*, 125 (1973); [b] K. Sakata, K. Aoki, C.-F. Chang, A. Sakaurai, S. Tamura, and S. Mukakoshi, *Agric. Biol. Chem.*, **42**, 457 (1978); [c] T. Noro, S. Fukushima, A. Ueno, Y. Litaka, and Y. Saiki, *Chem. Pharm. Bull.*, **27**, 1495 (1979); [d] R.-S. Xu, Y.-J. Lu, J.-H. Chu, T. Iwashita, H. Naoki, Y. Naya, and K. Nakanishi, *Tetrahedron*, **38**, 2667 (1982).

[13] For the total synthesis of croomine, see: D. R. Williams, D. L. Brown, and J. W. Benbow, *J. Am. Chem. Soc.*, **111**, 1923 (1989).

[14a] M. Abe, S. Ohmono, T. Ohashi, and T. Tabuchi, *Agric. Biol. Chem.*, **33**, 469 (1969). [b] R. J. Cole, J. W. Kirksey, J. Clardy, N. Eickman, S. M. Weinreb, P. Singh, and D. Kim, *Tetrahedron Letters*, 3849 (1976).

[15] For a synthesis of rugulovasines A and B, see: [a] J. Rebek, and Y.-K. Shue, *J. Am. Chem. Soc.*, **102**, 5426 (1980); [b] J. Rebek, Y.-K. Shue, and D. F.Tai, *J. Org. Chem.*, **49**, 3540 (1984).

[16] For leading references to accounts of the related additions of 2-trialkylsilylfurans to aldehydes, see: [a] C. W. Jefford, D. Jaggi, and J. Boukouvalas, in Studies of Natural Products Chemistry, Stereoselective Synthesis (Part B), Vol 3, Atta-ur-Rahman, ed.; Elsevier, Amsterdam, 1989, p 163; [b] G. Casiraghi, and G. Rassu, in Studies of Natural Products Chemistry, Vol 11, Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1992, p 429.

[17] For recent examples of the reactions of furans with iminium electrophiles reported after our initial work, see: [a] K. E. Harding, M. T. Coleman, and L. T. Liu, *Tetrahedron Letters*, **32**, 3795 (1991). [b] G. Casiraghi, G. Rassu, P. Spanu, L. Pinna, and F. Ulgheri, *J. Org. Chem.*, **58**, 3397 (1993).

[18] S. F. Martin, and J. W. Corbett, *Synthesis*, 55 (1992).

[19] For reviews on the $S_{RN}1$, see: [a] J. F. Bunnett, *Acc. Chem. Res.*, **11**, 413 (1978). [b] J. F. Wolfe, and D. R. Carver, *Org. Prep. Proced. Int.*, **10**, 225 (1978). [c] R. A. Rossi, and R. H. de Rossi, in Aromatic Substitution by the $S_{RN}1$ Mechanism; American Chemical Society: Washington, DC, ACS Monograph Series No. 178, 1983.

[20] M. Somei, K. Kizu, M. Kunimoto, and F. Yamada, *Chem. Pharm. Bull.*, **33**, 3996 (1985).

[21] For example, see: S. Burkard, and H.-J. Borschberg, *Helv. Chim. Acta*, **72**, 254 (1989).

[22a] M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, and L. D. Jones, *J. Am. Chem. Soc.*, **97**, 2507 (1975). [b] R. R. Goehring, *Tetrahedron Letters*, **33**, 6045 (1992).

[23] We thank Professor Julius Rebek (Massachusetts Institute of Technology) for spectra of rugulovasines A and B.Strategies for the Synthesis of Heterocyclic Natural Products