Acc. Chem. Res. **2002,** *35,* 895−904

Evolution of the Vinylogous Mannich Reaction as a Key Construction for Alkaloid Synthesis

STEPHEN F. MARTIN

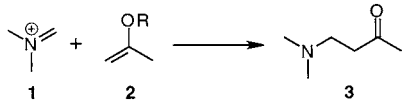
Department of Chemistry and Biochemistry, The University of Texas, Austin, Texas 78712

Received January 18, 2002

ABSTRACT

The vinylogous Mannich reaction is rapidly emerging as an important process for the construction of derivatives of δ-aminocarbonyl compounds. Because the iminium and dienol components employed in this addition may be either acyclic or cyclic, a wide variety of adducts may be quickly assembled. These intermediates may then in turn be converted into a broad array of alkaloids and substituted nitrogen heterocycles. We have developed a number of variations of this reaction and have applied some of them to the concise syntheses of a number of structurally diverse and complex alkaloid natural products. Many of these results are presented in a historical context in this Account.

The venerable Mannich reaction is a classical process that involves addition of the enol derivative of a carbonyl compound **2** to an iminium ion **1** to furnish a β-aminocarbonyl compound **3**, often referred to as a Mannich base (eq 1).[1] This transformation commonly occurs in the

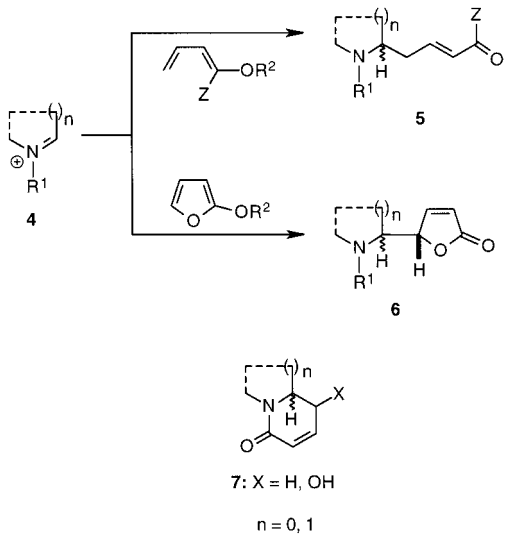


1 **2** **3** (1)

biosynthesis of alkaloids, and together with its variants has been widely used as a key step in the syntheses of nitrogen heterocycles and alkaloid natural products.

More recently, the vinylogue of the Mannich reaction has gained attention as a useful construction for alkaloid synthesis (Scheme 1).[2,3] There are two manifestations of the vinylogous Mannich reaction (VMR) that have been of considerable interest in our group. In the first, an acyclic dienol adds to an iminium ion **4**, which may be acyclic or cyclic, to generate a δ-aminocarbonyl compound **5**. In

Scheme 1



4 **5** **6**

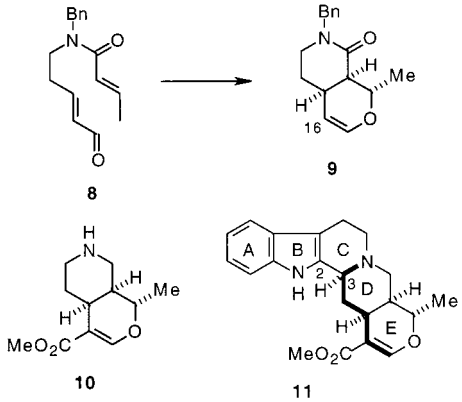
7: X = H, OH

n = 0, 1

the second variation, an alkoxy furan adds to **4** to give an aminoalkyl-substituted butenolide **6**, a structural subunit that is found in a number of alkaloids. Direct cyclization of **5** (R^1 = H) or inducing a lactone−lactam rearrangement of **6** (R^1 = H) leads to functionalized and/or fused piperidines **7**. Such compounds may be useful intermediates for the synthesis of alkaloids belonging to the piperidine, indolizidine, and quinolizidine families. For some years we have exploited VMRs as key steps in the syntheses of a diverse array of alkaloids, and some highlights of our work in this area are summarized in this Account. For a more comprehensive listing of other important syntheses of these alkaloids, the interested reader is directed to the specific citations found in the respective articles referred to herein.

The Beginning. Our journey began in the mid-1980s, when we completed a formal synthesis of the heteroyohimboid alkaloid tetrahydroalstonine (**11**).[4] A pivotal step in this synthesis was the intramolecular hetero Diels−Alder reaction of **8** to give a mixture (5:1) of **9** and the corresponding trans isomer (Scheme 2). A novel step in

Scheme 2



8 **9** **10** **11**

transforming **9** to **10** was the installation of the vinylogous carbonate function at C(16) by a potentially general

A native of New Mexico, Stephen Martin received his B.S. degree in chemistry in 1968 from the University of New Mexico and his Ph.D. degree in 1972 from Princeton University, where he worked with Professor Edward C. Taylor. After postdoctoral years at the University of Munich with Professor Rudolf Gompper and Massachusetts Institute of Technology with Professor George Büchi, he joined the faculty at The University of Texas at Austin in 1974, where he currently holds the M. June and J. Virgil Waggoner Regents Chair in Chemistry. His current research interests lie generally in the areas of organic and bioorganic chemistry. In the former, his focus has been to develop and apply new tactics and strategies to concise syntheses of complex natural products that exhibit useful biological activity. In the arena of bioorganic chemistry, he has been involved in the design, synthesis, and application of novel peptide mimics as well as the study of the mechanism, structure, and function of enzymes that hydrolyze phospholipids. He has received a number of awards, including an Alexander von Humboldt Award in 1995 and an Arthur C. Cope Scholar Award in 1996, honoring his outstanding accomplishments. He has served on numerous editorial boards, and he is presently a regional editor of *Tetrahedron*.

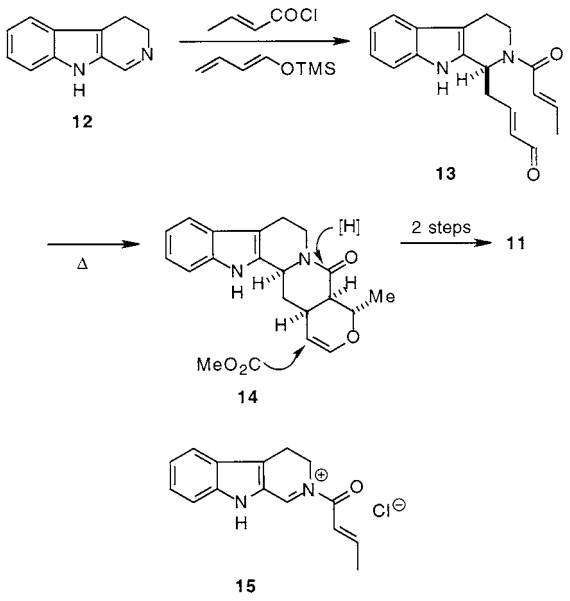
10.1021/ar950230w CCC: $22.00
Published on Web 06/19/2002

process involving trichloroacetylation of the enol ether moiety of **9** followed by methanolysis of the intermediate trichloroacetyl compound by a haloform-type cleavage reaction. The synthesis of **10**, which had previously been converted into **11**,[5] required only 13 steps from commercially available starting materials and was reasonably efficient (18% overall).

At the time this formal synthesis of tetrahydroalstonine was completed, we became aware of the stereochemical and regiochemical uncertainties associated with preparing the pentacyclic ABCDE ring system of heteroyohimboidand yohimboid alkaloids by forming the C(2)−C(3) bond from ABDE precursors that had been assembled from DE ring subunits like **10**.[6] We were thus intrigued by the considerable challenge of devising an even more concise and efficient entry to these important alkaloids. We envisioned that the inadequacies of this ABDE → ABCDE approach could be best addressed by developing an ABC → ABCDE route that featured the hetero Diels−Alder reaction of a substrate like **13**.

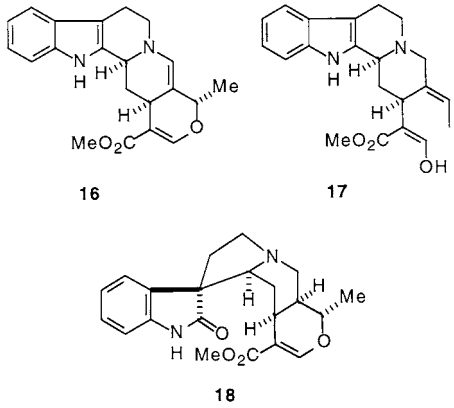
The major hurdle to be overcome in developing this alternative entry to heteroyohimboid alkaloids was developing a short route to **13**, and this proved a difficult task. We eventually discovered, however, that the VMR of **12**, which was prepared in two steps from tryptamine, with 1-trimethylsilyloxybutadiene in the presence of crotonyl chloride gave **13** in excellent yield (Scheme 3).[7] This

Scheme 3



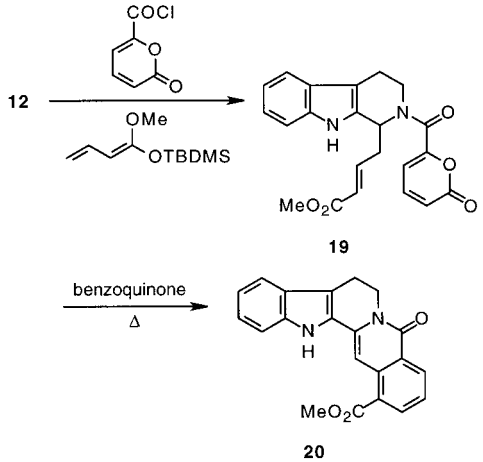
reaction presumably proceeded via the acyl iminium ion **15**, as no reaction was observed in the absence of crotonyl chloride. In contrast to the contemporaneous reports of Pandit[8] and Speckamp,[9] no regioisomers arising from reaction at the α-carbon of the dienol were observed in this VMR. The hetero triene **13** underwent a facile intramolecular [4 + 2] cycloaddition upon heating to give **14** (*cis*/*trans* = 9:1), which was converted into tetrahydroalstonine (**11**) in two steps. Although we did not recognize it at the time, close scrutiny of the structure of **11** reveals the masked δ-aminocarbonyl array that is generated by the VMR (see bold bonds).

The versatility of this remarkably short route to complex indole alkaloids was further established by transforming **14** into cathenamine (**16**), the corynantheoid alkaloid geissoschizine (**17**), and the 2-oxindole alkaloid isopteropidine (**18**).[7,10,11]



Early Extensions of the VMR. These early successes stimulated us to think about the application of the VMR to the synthesis of other alkaloids. For example, a VMR in which a vinyl ketene acetal was used as the nucleophilic dienol partner was implemented in a reaction with **12** to generate **19**; as before, compounds arising from reaction at the α-carbon of the dienol derivative were not observed. Heating **19** in the presence of benzoquinone eventuated in a facile intramolecular Diels−Alder reaction. Oxidation of the resulting adduct thereby completed a concise route to the yohimboid alkaloid oxogambirtannine (**20**) (Scheme 4).[12]

Scheme 4

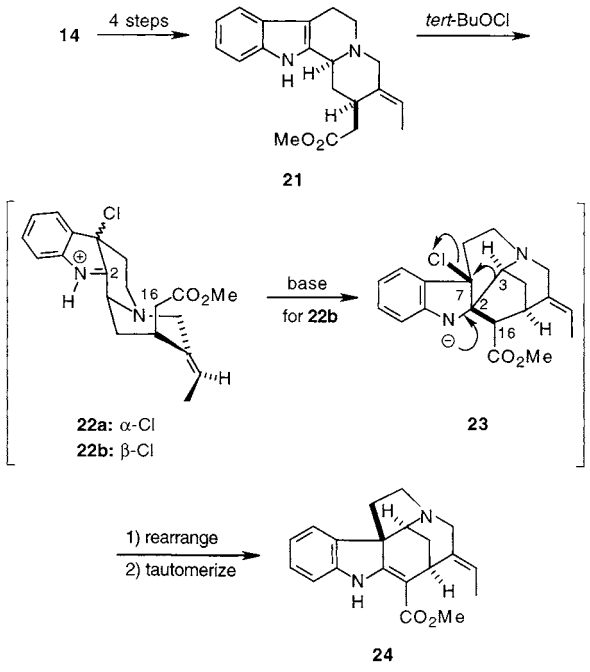


One of the preeminent and more challenging targets in the area of indole alkaloid chemistry is strychnine (**29**), and like others we were attracted by the significant opportunities to develop and apply new chemistry to its synthesis. The genesis of our interest in **29** lay in the knowledge that geissoschizine (**17**) was known to be a biosynthetic precursor of both **29** and the related alkaloid akuammicine (**24**).[13−15] Because we had developed an efficient and concise entry to **17** using sequential vinylo-

gous Mannich and intramolecular hetero Diels–Alder reactions, we had a unique opportunity to explore the feasibility of inducing a putative biosynthetic transformation to convert either geissoschizine or related corynantheoid intermediates into **24** and **29**.

The first step in the effort toward our initial target akuammicine involved converting the readily available pentacyclic intermediate **14** into deformylgeissoschizine (**21**) (Scheme 5).[16,17] We had already developed some

Scheme 5

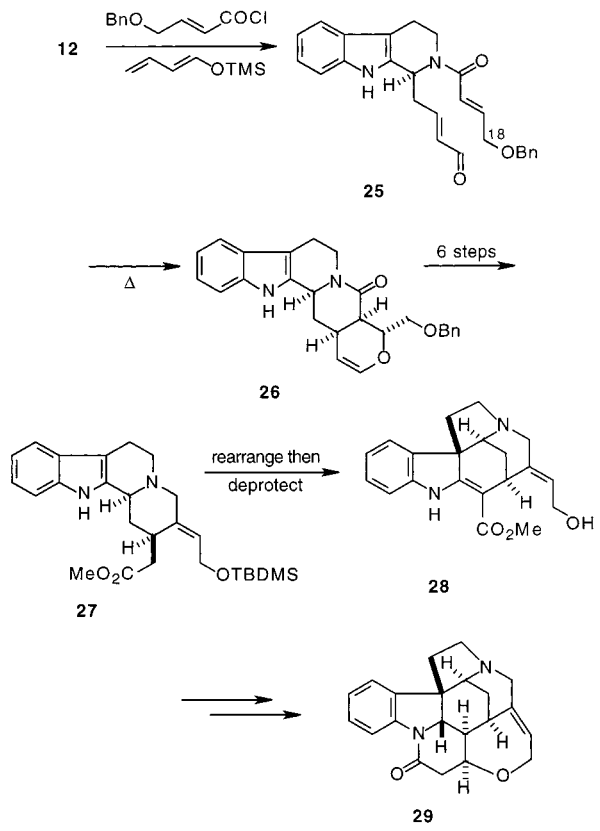


expertise in inducing rearrangements of compounds related to **21** in work involving the synthesis of the oxindole alkaloid **18**.[11] However, early experiments directed toward converting **21** into **24** via the epimeric chloroindolinines **22a,b** gave complex reaction mixtures that were almost intractable. Indeed, the TLC plates of those initial reactions resembled DNA sequencing gels rather than typical reaction mixtures! Fortunately, we had obtained an authentic sample of akuammicine from Professor Larry Overman at the University of California, Irvine, and we were able to detect a faint spot on a TLC plate that had an R_f corresponding to that of **24**. After considerable effort and experimentation requiring a period of some months, we were able optimize this complex transformation and obtain **24** in 52% overall yield from **21** and in only 10 steps from commercially available tryptamine. Paramount to this success was the finding that complexation of **21** with Lewis acids, especially $SnCl_4$, prior to reaction with *tert*-butylhypochlorite gave predominantly the requisite β-chloroindolinine **22b**.

The mechanistic course of this novel biogenetically patterned transformation has not been established. However, we presently envision that a likely pathway for forming **24** involves deprotonation of the β-chloroindolinine **22b** to furnish an enolate that cyclizes spontaneously onto C(2), giving **23**. Subsequent skeletal reorganization of **23** via 1,2-migration of C(3) from C(2) to C(7), perhaps by an S_N2-like process, followed by tautomerization would then deliver **24**.

Given the success in implementing the biomimetic conversion **21** → **24**, we used a VMR to prepare **25**, which bears the protected alcohol function at C(18) that is necessary for the synthesis of strychnine (**29**) (Scheme 6). When **25** was heated, it predictably underwent an

Scheme 6

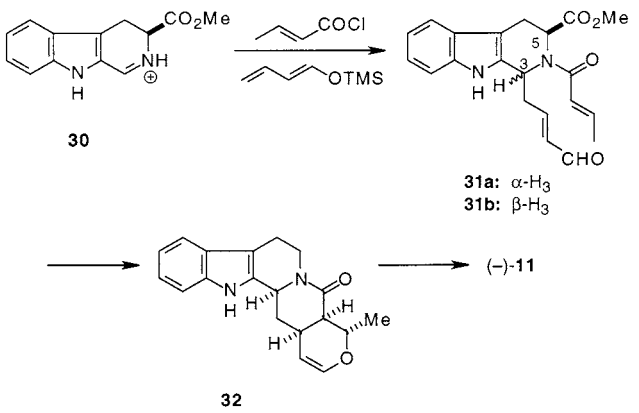


intramolecular hetero Diels–Alder reaction to give **26**, refunctionalization of which led to the requisite corynantheoid intermediate **27**. Following the same oxidation–rearrangement protocol we had developed for the synthesis of akuammicine, **27** was transformed into **28**. Because **28** had been previously converted in four steps to strychnine by Overman,[18] its preparation in only 13 reactions from tryptamine constituted a short formal synthesis of this complex alkaloid.

Developing an Enantioselective VMR. The discovery that VMRs could be exploited for the rapid preparation of key intermediates in the synthesis of a number of complex indole alkaloids led naturally to the question of whether an enantioselective variant could be developed. Indeed, we discovered that **30**, which was prepared in two steps from L-tryptophan methyl ester, underwent a VMR with 1-trimethylsilyloxybutadiene in the presence of crotonyl chloride, albeit with surprisingly low diastereoselectivity, to furnish a mixture (1.5:1) of **31a** and **31b** (Scheme

7).[19] The major product **31a** was then converted via an

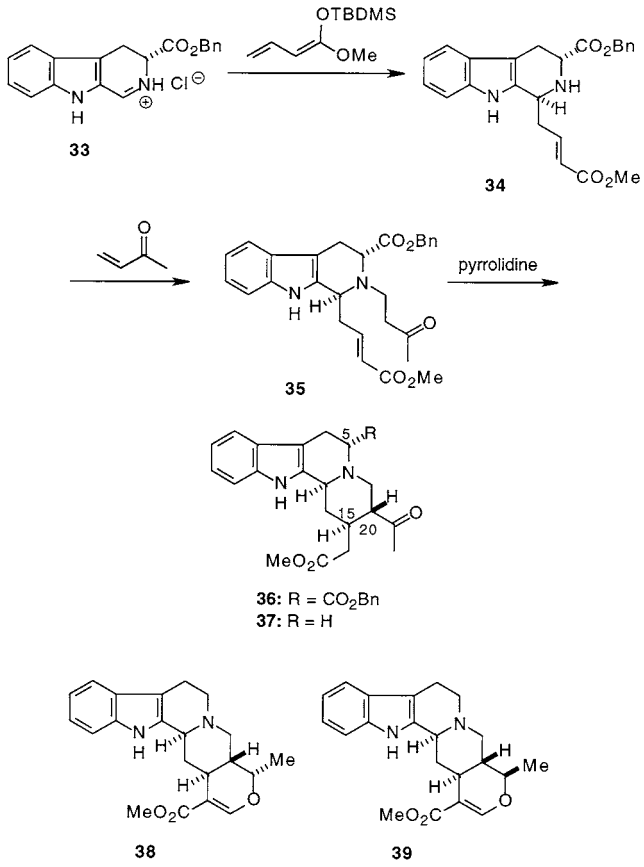
Scheme 7



intramolecular Diels–Alder reaction and removal of the ester function at C(5) to give enantiomerically pure **32**, which was transformed into (−)-tetrahydroalstonine (**11**).

The modest stereoselectivity in the VMR of **30** with a 1-alkoxydiene (Scheme 7) was obviously a disappointment, so we explored related constructions in a quest for a more diastereoselective process. We subsequently found that more nucleophilic vinyl ketene acetals added directly to the iminium salt **33**, which was prepared in two chemical operations from D-tryptophan, in a highly stereoselective fashion to produce the trans adduct **34** as the only isolable product (Scheme 8). This discovery paved

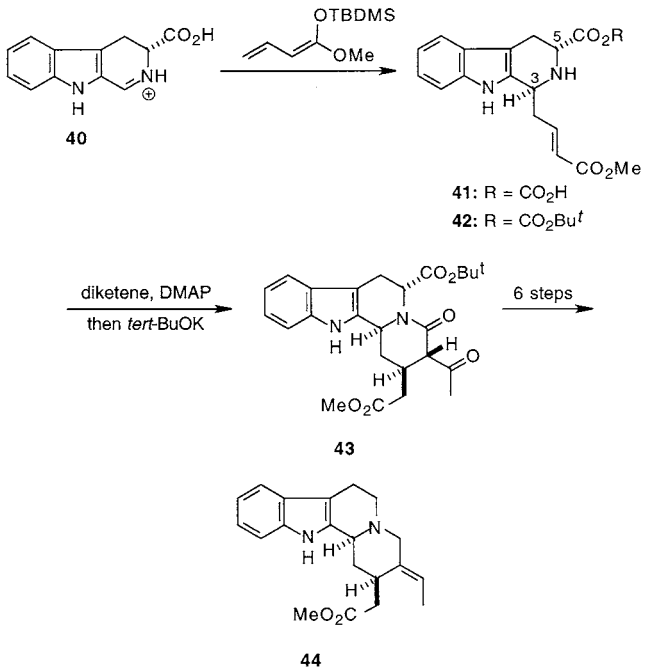
Scheme 8



the way for enantioselective syntheses of (−)-ajmalicine (**38**) and (+)-19-*epi*-ajmalicine (**39**).[19] In the event, *N*-alkylation of **34** with methyl vinyl ketone gave **35** that cyclized upon treatment with pyrrolidine to give **36**, which possesses the desired trans relationship between the side chains at C(15) and C(20). Removal of the C(5) ester from **36** according to the Barton protocol gave **37**,[20] which was transformed into (−)-ajmalicine (**38**) in three steps following the procedures set forth some years ago by van Tamelen.[21] A slightly modified sequence of reactions was applied to an enantioselective synthesis of (+)-19-*epi*-ajmalicine **(39)**.

Our previous synthesis of geissoschizine (**17**) (Scheme 3) was not readily adaptable to an enantioselective synthesis of **17**, so we developed a variation of the tactics depicted in Scheme 8 that provided an expeditious solution to this problem (Scheme 9).[22] Thus, **40** underwent

Scheme 9

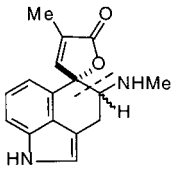


a facile VMR to give **41**, which was converted into the ester **42**. *N*-Acylation of **42** with diketene followed by a base-catalyzed intramolecular Michael reaction gave **43**, which was transformed in six steps involving sequential reductions and decarboxylation into **44**, the immediate precursor of (+)-geissoschizine.

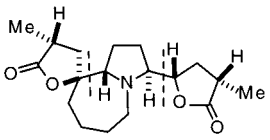
The VMR of acyclic dienol derivatives with cyclic iminium ions has clearly played a strategic role in the design of concise entries to a variety of indole alkaloids, both in racemic and enantiomerically pure forms. In particular, VMRs have allowed the rapid construction of intermediates that are subsequently transformed via intramolecular Diels–Alder reactions, biomimetic reorganizations, and Michael reactions to elaborate more complex intermediates or the natural targets themselves. However, an equally fertile field has been in the area of

VMRs in which 2-trialkylsilyloxyfurans serve as the dienol partners to furnish adducts having butenolide rings (see Scheme 1).

Expanding the Scope of the VMR. Our initial interest in VMRs involving furans was stimulated by recognizing that a number of natural products, including the *Ergot* alkaloids rugulovasines A (**45**) and B **(46)** and the *Stemona* alkaloid croomine (**47**), contain a butenolide ring as a



45: β–H
46: α–H

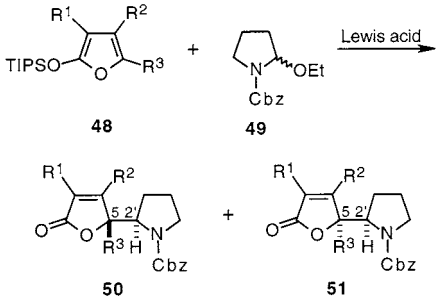


47

structural subunit. Indeed, we envisioned that two VMRs might be implemented in a synthesis of **47**. Because VMRs in which furans add to iminium ions create two new stereocenters, it was necessary to establish the stereochemical outcome of such processes before we could entertain the prospect of using such constructions in alkaloid synthesis.

Preliminary studies of the stereochemistry of the addition of **48** ($R^1-R^3 = H$) to the acyl iminium ion generated in situ from **49** using Lewis acids revealed that the reaction proceeded with good stereoselectivity to give a mixture (5:1) of the *threo* and *erythro* adducts **50** ($R^1-R^3 = H$) and **51** ($R^1-R^3 = H$), respectively (Scheme 10).[23] Similar

Scheme 10



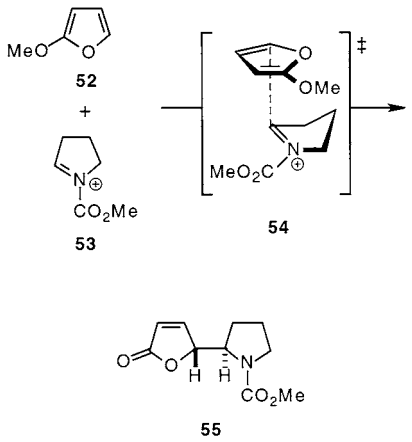
48 **49** **50** **51**

R^1-R^3 = H, Me H

observations were subsequently made by Morimoto.[24] The stereoselectivity of this reaction was later optimized to about 15:1 in investigations in which we also probed the effects of varying alkyl substitution on the furan ring upon the stereochemistry of the addition; in all cases the *threo* adducts were the major products.[25] Significantly, the relative stereochemistry at the newly created contiguous centers in **50** corresponds to the same pairwise relationships found in croomine, thereby lending early support to our hypothesis that VMRs of furans might be exploited in the design of a concise synthesis of **47** (vide infra, Schemes 19 and 20).

We conducted calculations at the RHF/3-21G* level and determined that the Diels–Alder-like transition state **54**, which leads to the *threo* adduct **55** (Scheme 11), was about

Scheme 11

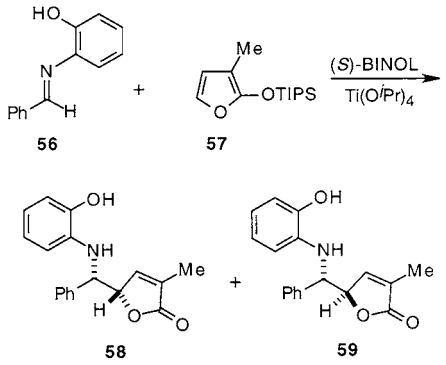


52 **53** **54** **55**

0.9 kcal/mol lower in energy than other competing transition states.[26] Consistent with a hypothesis advanced by Woerpel,[27] we also found that the furan approached from inside the fold of the five-membered iminium ion. Further computational studies are in progress to explore the stereochemistry of other VMRs.

In the context of deploying VMRs for the enantioselective syntheses of alkaloids, we explored the additions of furans to aryl imines promoted by chiral Lewis acids. In the first example of a catalytic, enantioselective version of this process, we discovered that the addition of **57** to **56** in the presence of (*S*)-BINOL and $Ti(O^iPr)_4$ occurred with good diastereoselectivity (91:9) to afford the major diastereomer **58** in 48% enantiomeric excess; the enantiomeric excess of the minor product **59** was not determined (Scheme 12).[28] The phenolic hydroxyl group on the

Scheme 12



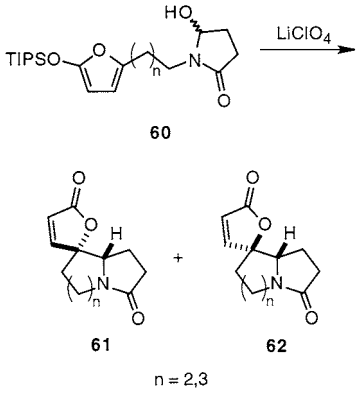
56 **57** **58** **59**

imine reactant was critical to observing significant enantioselectivity in the addition. We examined a variety of other chiral ligands and Lewis acids to induce this transformation but have not yet been able to improve upon this catalytic system. Hence, this is an area that demands further experimentation and optimization.

Finally, in the methodological arena, we explored the stereochemistry of intramolecular VMRs of silyloxyfurans

with *N*-acyl iminium ions (Scheme 13). For example, when

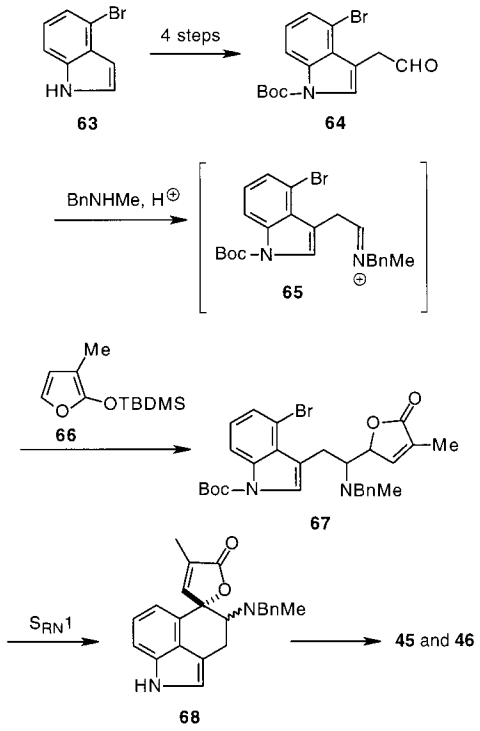
Scheme 13



60 ($n = 2$) was exposed to 3 M $LiClO_4$ in diethyl ether, a mixture (11:1) of **61** ($n = 2$) and **62** ($n = 2$) was obtained.[29] Other Lewis acids such as $ZnCl_2$, Et_2AlCl, and $BF_3{\cdot}OEt_2$ were also effective in promoting the cyclization, although these gave lower diastereoselectivities. Increasing the length of the tether led to an erosion in stereoselectivity as the $LiClO_4$-promoted cyclization of **60** ($n = 3$) gave a mixture (2:1) of **61** ($n = 3$) and **62** ($n = 3$). Interestingly, the major products of all of these intramolecular VMRs were the *erythro* isomers **61**. The stereochemical course of the intramolecular process thus appears to be *opposite* that observed in the intermolecular additions (see Scheme 10), although the generality of this trend remains to be rigorously established.

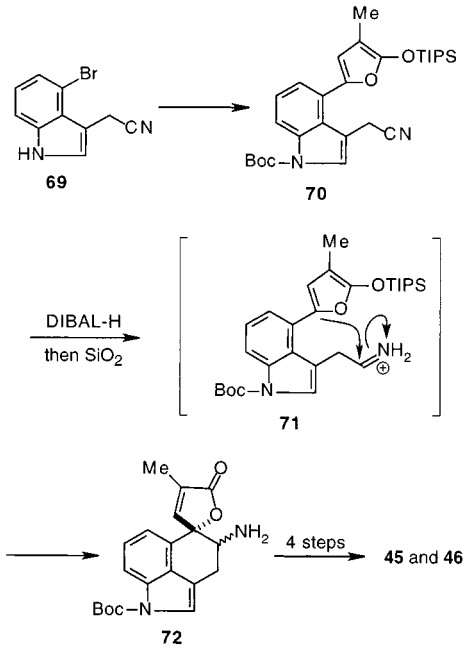
Applications of VMRs Involving Furans. That two new stereocenters are formed by vinylogous Mannich additions involving 2-silyloxyfurans as the dienol component might be an issue in some cases; however, both of the diastereomeric rugulovasines A (**45**) and B (**46**) are natural products that are known to interconvert readily.[30] Hence, **45** and **46** emerged as ideal targets for our initial explorations. Our first synthesis of this pair of alkaloids commenced with readily available 4-bromoindole (**63**), which was converted in four steps to the aldehyde **64** (Scheme 14).[31] Reaction of **64** with *N*-benzyl-*N*-methylamine generated the intermediate iminium ion **65** that underwent a facile VMR with **66** to deliver an inseparable diastereomeric mixture (1:2) of adducts **67**. Initial attempts using methylamine as the amine reactant in this three-component condensation process were unsuccessful. The next step in the sequence was an intramolecular $S_{RN}1$ reaction that created the sterically congested spirocyclic lactone moiety, thereby completing the assembly of the rugulovasine skeleton. $S_{RN}1$ reactions have not enjoyed wide application in the synthesis of natural products, and we were delighted to find that irradiation of **67** in refluxing ammonia in the presence of freshly sublimed potassium *tert*-butoxide furnished a mixture (1:2) of the *N*-benzylrugulovasines **68**. Selective hydrogenolysis of the *N*-benzyl group provided a separable mixture (1:2) of **45** and **46**.

Scheme 14



Although we had completed the syntheses of rugulovasines A and B using an intermolecular VMR as a key step, we were intrigued by exploiting an intramolecular variant, especially since this transform would correspond to the presumed mechanism for interconverting these alkaloids. The stage for this inquiry was quickly set by preparing **70** from **69** in a one-pot process involving a Stille reaction followed by acylation of the indole nitrogen atom (Scheme 15).[32] Hydride reduction of the nitrile

Scheme 15

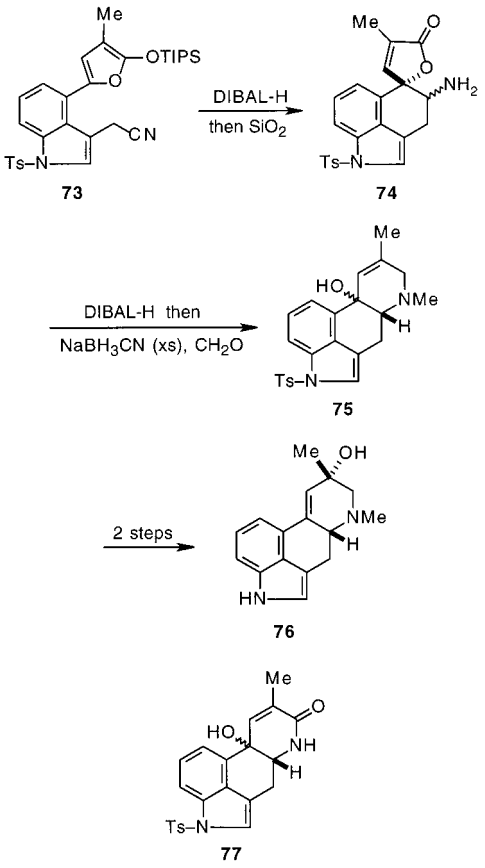


function in **70** generated **71**, which underwent spontaneous vinylogous

Mannich cyclization to give a mixture (2:1) of epimeric amines **72** that was in turn converted to **45** and **46** in only four steps. It is perhaps of interest to note that each of the routes summarized in Schemes 14 and 15 gives a different rugulovasine epimer as the major product.

The fact that inter- and intramolecular VMRs could be exploited for the rapid construction of the tetracyclic ring system of the rugulovasines A and B led us to query whether the spirobicyclic butyrolactone subunit might be reorganized to generate the fused tetracyclic system found in setoclavine (**76**) and other *Ergot* alkaloids (cf Scheme 1). Indeed, a lactone−lactam rearrangement of a dihydroindole analogue of **72** was known.[33] The spirocyclic lactone **74** was thus first prepared from **73** via an intramolecular VMR (Scheme 16).[32] The *N*-tosyl group was

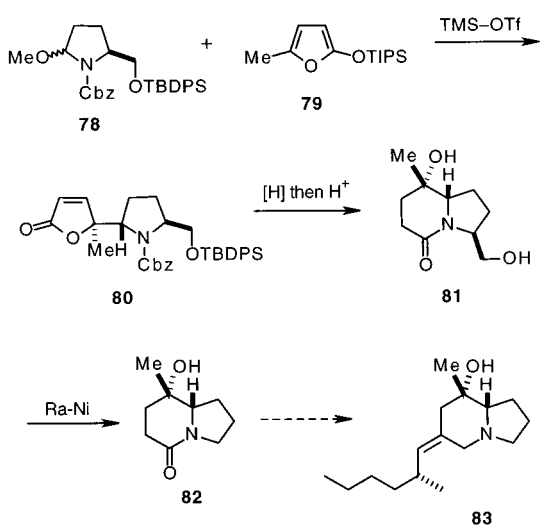
Scheme 16



employed in this sequence, as we had observed some loss of the *N*-Boc protecting group under the conditions required to transform **70** into **72**. Although we have been able to effect the lactone−lactam rearrangements of several aminoalkyl butenolides **6** to give unsaturated lactams of general type **7** (vide infra), we have also found that these transformations are sometimes problematic, and we were unable to identify conditions that efficiently promoted the conversion of **74** to the hydroquinolone **77**. It was thus necessary to develop another tactic for transforming **74** into **76**. Hence, hydride reduction of **74** followed by spontaneous rearrangement and dehydration of the intermediate amino lactols led to a mixture of epimeric dihydropyridines that was treated with $NaBH_3CN$ and formaldehyde to furnish a mixture of diastereomeric amino alcohols **75**. Deprotection of **75** and solvolysis of the resulting allylic alcohols gave setoclavine (**76**).

Pumiliotoxin 251D (**83**) emerged as another interesting target to test the utility of the vinylogous Mannich/lactone−lactam rearrangement strategy for alkaloid synthesis. Because the indolizidine **82** had been previously converted to **83** by Gallagher,[34] we focused on its preparation as the primary objective. The *N*-acyl iminium ion precursor **78**, which was prepared in three steps from commercially available (*S*)-(−)-5-hydroxymethyl-2-pyrrolidinone, was allowed to react with the furan **79** to give a mixture (4.8:1) of adducts, the major diastereomer of which was **80** (Scheme 17).[35] The protected hydroxymethyl

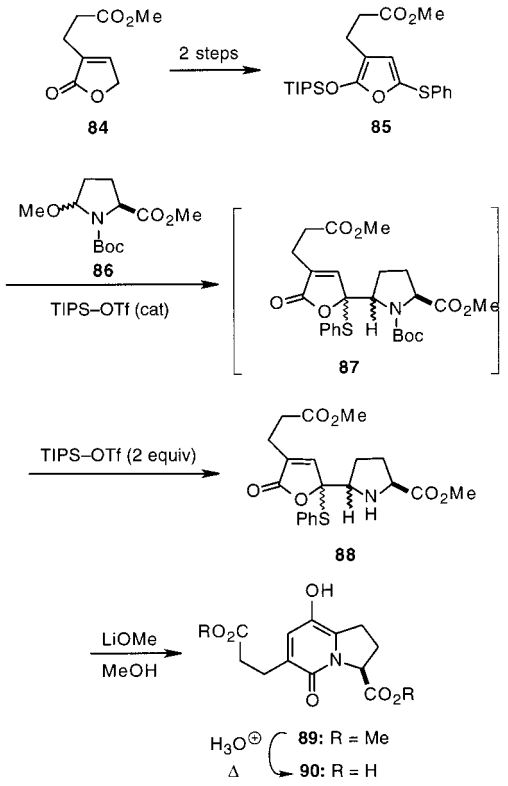
Scheme 17



group, which would later be removed, had thus nicely fulfilled its role in setting the absolute stereochemistry at the two stereocenters in the bicyclic core of **83**. Reduction of the double bond in **80** and removal of the *N*-Cbz protecting group proceeded with spontaneous lactone−lactam rearrangement leading, after acid-catalyzed *O*-desilylation, to **81** in a single operation. Excision of the superfluous hydroxymethyl group with Raney nickel gave (−)-**82**,[36] thereby completing a formal enantioselective synthesis of **83**.

We have recently completed an enantioselective synthesis of the angiotensin-converting enzyme inhibitor (−)-A58365A (**90**), another indolizidine target of considerable interest (Scheme 18).[37] The silyloxyfuran **85** was first prepared from the readily available butenolide **84** in a total of five operations from commercially available materials. The VMR of **85** with the *N*-acyl iminium ion derived from **86** gave a mixture of diastereomeric adducts **87**. In practice these were not isolated, but rather excess TMS−OTf was added to effect direct removal of the *N*-Boc protecting group, furnishing **88** as a mixture of four diastereomers (ca. 53:41:4:2). Inasmuch as this mixture

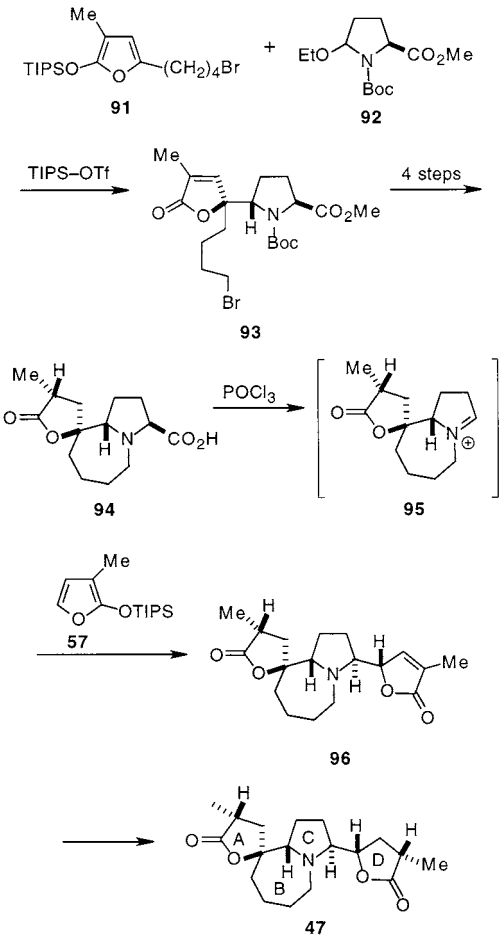
Scheme 18



would converge to a single compound in the subsequent-step, the diastereomers were not separated and individually characterized. Thus, treatment of **88** with methanolic lithium methoxide induced the desired lactone−lactam rearrangement to provide the dimethyl ester **89**. Because **89** had been previously converted into **90** in two steps by Danishefsky,[38] its preparation already constituted a formal synthesis. We found, however, that acid-catalyzed hydrolysis of the methyl esters of **89** directly afforded **90**, thereby completing an efficient total synthesis of the natural product.

The example that perhaps best illustrates the power of the VMR as a strategy for alkaloid synthesis is our enantioselective synthesis of (+)-croomine (**47**). Examination of the structure of **47** reveals that both the A and D rings might be appended by sequential additions of silyloxyfuran units to the central pyrrolidine ring C. The requisite silyloxyfuran **91** and *N*-acyl iminium ion precursor **92** were each prepared in two steps from commercially available starting materials.[25,39] The first VMR involving **91** and **92** was promoted by ionization of **92** with catalytic amounts of triisopropylsilyl triflate to give a relatively complex mixture from which **93** fortunately crystallized (Scheme 19). The structure of **93** was unequivocally established by X-ray crystallography, indicating, as expected, that the addition had occurred predominantly via the requisite *threo* manifold from the face of the iminium ion opposite the methyl ester group. Small quantities (<1%) of the other *threo* isomer, which resulted from addition from the face syn to the ester group, were also

Scheme 19



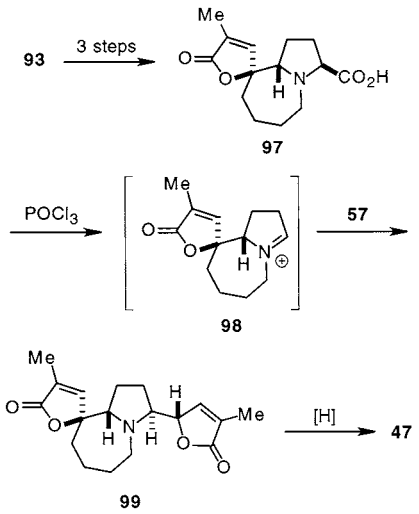
isolated from the reaction mixture. Despite some effort, we were unable to isolate either of the corresponding *erythro* adducts, although we certainly cannot exclude their formation.

The conversion of **93** into **94** proceeded smoothly, setting the stage for the second VMR. The requisite iminium ion **95** was generated in situ by a slight modification of the original Rapoport protocol and allowed to react with the silyloxyfuran **57** to deliver **96**, together with lesser quantities (*threo/erythro* = 2:1) of the corresponding *erythro* adduct as a separable mixture.[40,41] Stereoselective hydrogenation of **96** then furnished (+)-croomine (**47**) in a total of only 11 chemical operations from commercially available starting materials.

Despite the brevity of this enantioselective synthesis of **47**, we were intrigued by the challenge of devising an even more concise route. We reasoned that one step could be trimmed from the synthesis if both butenolide rings could be stereoselectively reduced in the same step. This tactic was not without risk, as there was no prior assurance that high selectivity could be achieved, and a preliminary examination of molecular models was by no means encouraging. To test this hypothesis, the adduct **93** was converted into **97**, and the second VMR was performed on the unsaturated iminium ion **98** to give a separable mixture (2:1) of **99** and its *erythro* isomer reduction

(Scheme 20). We were then delighted to discover that of

Scheme 20



99 by catalytic hydrogenation delivered (+)-croomine as the only isolable product.

Conclusions

It is rapidly becoming apparent that the VMR may be exploited for the rapid construction of polycyclic nitrogen heterocycles that are commonly found in important natural and unnatural products. The ability to induce a lactone−lactam or related reorganization on the initial adducts or their derivatives endows the strategy with further diversity and greatly broadens the scope of the process. Indeed, others have already implemented these reactions for the syntheses of peptide mimics[42] and alkaloids.[43,44] The VMR is applicable to a wide variety of cyclic and acyclic reaction partners, and it often proceeds with high levels of stereoselectivity. The utility of this powerful strategy for heterocycle and alkaloid synthesis will undoubtedly be expanded by future investigations from these and other laboratories.

I am especially grateful to have had the incredibly good fortune to work with an outstanding group of undergraduate and graduate students and postdoctoral associates over the years I have been at the University of Texas. The names of those who have specifically contributed to the present work are found in the numerous papers cited herein. I also wish to thank the National Institutes of Health, the Robert A. Welch Foundation, Pfizer, Inc., and Merck Research Laboratories for their generous ongoing support of our research in alkaloid synthesis.

References

(1) Arend, M.; Westermann, B.; Risch, N. Modern Variants of the Mannich Reaction. *Angew. Chemie, Int. Ed.* **1998**, *37*, 1044−1070.
(2) Bur, S. K.; Martin, S. F. Vinylogous Mannich Reactions: Selectivity and Synthetic Utility. *Tetrahedron* **2001**, *57*, 3221−3242.
(3) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. The Vinylogous Aldol Reaction: A Valuable, Yet Understated Carbon−Carbon Bond-Forming Maneuver. *Chem. Rev.* **2000**, *100*, 1929−1972.
(4) Martin, S. F.; Benage, B.; Williamson, S. A.; Brown, S. P. Applications of the Intramolecular Diels−Alder Reaction of Heterodienes to the Syntheses of Indole Alkaloids. *Tetrahedron* **1986**, *42*, 2903−2910.
(5) Gutzwiller, J.; Pizzolato, G.; Uskokovic, M. A Novel Synthesis of Racemic Ajmalicine, 19-Epiajmalicine, Tetrahydroalstonine, and Akuammigine. *J. Am. Chem. Soc.* **1971**, *93*, 5907−5908.
(6) Martin, S. F.; Rüeger, H.; Williamson, S. A.; Grzejszczak, S. General Strategies for the Synthesis of Indole Alkaloids. Total Synthesis of (±)-Reserpine and (±)-α-Yohimbine. *J. Am. Chem. Soc.* **1987**, *109*, 6124−6134.
(7) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. Unified Strategy for the Synthesis of Indole and 2-Oxindole Alkaloids. *J. Am. Chem. Soc.* **1991**, *113*, 6161−6171.
(8) Brands, K. M. J.; Pandit, U. K. Synthesis of the 'Tricyclic Heart' of Manzamines. *Tetrahedron Lett.* **1989**, *30*, 1423−1426.
(9) Mooiweer, H. H.; Ettema, K. W. A.; Hiemstra, H.; Speckamp, W. N. Preparation of γ-Oxo-α-amino Acids from Silyl Enol Ethers and Glycine Cation Equivalent; a Facile Synthesis of (±)-5-Hydroxy-4-oxonorvaline (HON). *Tetrahedron* **1990**, *46*, 2991−2998.
(10) Martin, S. F.; Benage, B.; Hunter, J. E. A Concise Strategy for the Total Syntheses of the Indole Alkaloids (±)-Tetrahydroalstonine, (±)-Geissoschizine and (±)-Cathenamine. *J. Am. Chem. Soc.* **1988**, *110*, 5925−5927.
(11) Martin, S. F.; Mortimore, M. New Methods for the Synthesis of Oxindole Alkaloids. Total Syntheses of Isopteropodine and Pteropodine. *Tetrahedron Lett.* **1990**, *31*, 4557−4560.
(12) Martin, S. F.; Geraci, L. S. A Concise Approach to the Aromatic Yohimboid and Protoberberine Alkaloids via Intramolecular Diels−Alder Reactions. *Tetrahedron Lett.* **1988**, *29*, 6725−6728.
(13) Battersby, A. R.; Hall, E. S. The Intermediacy of Geissoschizine in Indole Alkaloid Biosynthesis: Rearrangement to the *Strychnos* Skeleton. *J. Chem. Soc., Chem. Commun.* **1969**, 793−794.
(14) Scott, A. I.; Cherry, P. C.; Qureshi, A. A. Mechanisms of Indole Alkaloid Biosynthesis: The *Corynanthe*−*Strychnos* Relationship. *J. Am. Chem. Soc.* **1969**, *91*, 4932−4933.
(15) Heimberger, S. I.; Scott, A. I. Biosynthesis of Strychnine. *J. Chem. Soc., Chem. Commun.* **1973**, 217−218.
(16) Martin, S. F.; Clark, C. C.; Ito, M.; Mortimore, M. A Biomimetic Approach to the Strychnos Alkaloids. A Novel, Concise Synthesis of (±)-Akuammicine and a Route to (±)-Strychnine. *J. Am. Chem. Soc.* **1996**, *118*, 9804−9805.
(17) Ito, M.; Clark, C. C.; Mortimore, M.; Goh, J. B.; Martin, S. F. Biogenetically Inspired Approach to the Strychnos Alkaloids. Concise Syntheses of (±)-Akuammicine and (±)-Strychnine. *J. Am. Chem. Soc.* **2001**, *123*, 8003−8010.
(18) Knight, S. D.; Overman, L. E.; Pairaudeau, G. Asymmetric Total Syntheses of (−)- and (+)-Strychnine and the Wieland-Gumlich Aldehyde. *J. Am. Chem. Soc.* **1995**, *117*, 5776−5788.
(19) Martin, S. F.; Clark, C. C.; Corbett, J. W. Applications of Vinylogous Mannich Reactions. Asymmetric Synthesis of the Heteroyohimboid Alkaloids (−)-Ajmalicine, (+)-19-*epi*-Ajmalicine, and (−)-Tetrahydroalstonine. *J. Org. Chem.* **1995**, *60*, 3236−3242.
(20) Barton, D. H. R.; Crich, D.; Motherwell, W. B. The Invention of New Radical Chain Reactions. Part VIII. Radical Chemistry of Thiohydroxamic Esters: A New Method for the Generation of Carbon Radicals from Carboxylic Acids. *Tetrahedron* **1985**, *41*, 3901−3924.
(21) van Tamelen, E. E.; Placeway, C.; Schiemenz, G. P.; Wright, I. G. Total Syntheses of *dl*-Ajmalicine and Emetine. *J. Am. Chem. Soc.* **1969**, *91*, 7359−7371.
(22) Martin, S. F.; Chen, K. X.; Eary, C. T. An Enantioselective Total Synthesis of (+)-Geissoschizine. *Org. Lett.* **1999**, *1*, 79−81.
(23) Martin, S. F.; Corbett, J. W. The Stereochemical Course of Nucleophilic Additions of 2-Trialkylsiloxyfurans to Cyclic *N*-Acyliminium Ions. *Synthesis* **1992**, 55−57.
(24) Morimoto, Y.; Nishida, K.; Hayashi, Y. An Efficient Approach toward Pyrrolidinyllactone System Characteristic of the *Stemona* Alkaloids. Lewis Acid-Catalyzed Stereoselective Reaction of *N*-Benzyloxycarbonyl-2-methoxypyrrolidine with 3-methyl-2-trimethylsiloxyfuran. *Tetrahedron Lett.* **1993**, *34*, 5773−5776.
(25) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. Applications of Vinylogous Mannich Reactions. Concise Asymmetric Total Syntheses of (+)-Croomine. *J. Am. Chem. Soc.* **1999**, *121*, 6990−6997.
(26) Bur, S. K.; Martin, S. F. Vinylogous Mannich Reactions: Some Theoretical Studies on the Origins of Diastereoselectivity. *Org. Lett.* **2000**, *2*, 3445−3447.
(27) Larsen, C. H.; Ridgeway, B. H.; Shaw, J. T.; Woerpel, K. A. A Stereoelectronic Model to Explain the Highly Stereoselective Reactions of Nucleophiles with Five-Membered-Ring Oxocarbenium Ions. *J. Am. Chem. Soc.* **1999**, *121*, 12208−12209.
(28) Martin, S. F.; Lopez, O. D. Vinylogous Mannich Reactions. Catalytic, Asymmetric Additions of Triisopropylsilyloxyfurans to Aldimines. *Tetrahedron Lett.* **1999**, *40*, 8949−8953.
(29) Martin, S. F.; Bur, S. K. The Stereochemical Course of Intramolecular Vinylogous Mannich Reactions. *Tetrahedron Lett.* **1997**, *38*, 7641−7644.

(30) Rebek, J.; Shue, Y.-K.; Tai, D. F. The Rugulovasines: Synthesis, Structure, and Interconversions. *J. Org. Chem.* **1984**, *49*, 3540−3545.
(31) Martin, S. F.; Liras, S. Novel Applications of Vinylogous Mannich Reactions. Total Synthesis of Rugulovasines A and B. *J. Am. Chem. Soc.* **1993**, *115*, 10450−10451.
(32) Liras, S.; Lynch, C. L.; Fryer, A. M.; Vu, B. T.; Martin, S. F. Applications of Vinylogous Mannich Reactions. Total Syntheses of the *Ergot* Alkaloids Rugulovasines A and B and Setoclavine. *J. Am. Chem. Soc.* **2001**, *123*, 5918−5924.
(33) Rebek, J. J.; Tai, D. F.; Shue, Y.-K. Synthesis of Ergot Alkaloids from Tryptophan. *J. Am. Chem. Soc.* **1984**, *106*, 1813−1819.
(34) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. Enantioselective Synthesis of Pumiliotoxin 251D. A Strategy Employing an Allene-Based Electrophile-Mediated Cyclization. *J. Am. Chem. Soc.* **1991**, *113*, 2652−2656.
(35) Martin, S. F.; Bur, S. K. Vinylogous Mannich Reactions. Stereoselective Formal Synthesis of Pumiliotoxin 251D. *Tetrahedron* **1999**, *55*, 8905−8914.
(36) Krafft, M. E.; Crooks, W. J. I.; Zorc, B.; Milczanowski, S. E. Reaction of Raney Nickel with Alcohols. *J. Org. Chem.* **1988**, *53*, 3158−3163.
(37) Reichelt, A.; Bur, S. K.; Martin, S. F. Applications of Vinylogous Mannich Reactions. Enantioselective Synthesis of the Angiotensin Converting Enzyme Inhibitor (−)-A58365A. *Tetrahedron*, in press.
(38) Fang, F. G.; Danishefsky, S. J. Total Synthesis of the Angiotensin-Converting Enzyme Inhibitor A58365A: On the Use of Pyroglutamate as a Chiral Educt. *Tetrahedron Lett.* **1989**, *30*, 3621−3624.
(39) Martin, S. F.; Barr, K. J. Vinylogous Mannich Reactions. The Asymmetric Total Synthesis of (+)-Croomine. *J. Am. Chem. Soc.* **1996**, *118*, 3299−3300.
(40) Dean, R. T.; Padgett, H. C.; Rapoport, H. A High Yield Regiospecific Preparation of Iminium Ion Salts. *J. Am. Chem. Soc.* **1976**, *98*, 7448−7449.
(41) Csendes, I. G.; Lee, Y. Y.; Padgett, H. C.; Rapoport, H. Iminium Salts from α-Amino Acid Decarboxylation. Application to the Synthesis of Some 1-Azabicyclo[*x.y.*0] Systems. *J. Org. Chem.* **1979**, *44*, 4173−4178.
(42) Hanessian, S.; McNaughton-Smith, G. A Versatile Synthesis of a β-Turn Peptidomimetic Scaffold: An Approach Towards a Designed Model Antagonist of the Tachykinin NK-2 Receptor. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1567−1572.
(43) Casiraghi, G.; Rassu, G. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science Publishers: Amsterdam, 1992; Vol. 11, pp 429−480.
(44) Kende, A. S.; Hernando, J. I.; Milbank, J. B. J. First Total Synthesis of (±)-Stemonamide and (±)-Isostemonamide. *Org. Lett.* **2001**, *3*, 2505−2508.

AR950230W