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# Vinylogous Mannich reactions: selectivity and synthetic utility

Scott K. Bur[†] and Stephen F. Martin[*]

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

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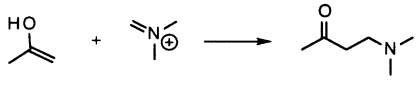
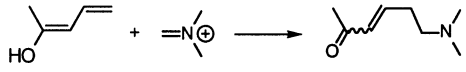
## 1. Introduction

The Mannich reaction, which is typified by the addition of enols to iminium salts (Eq. (1)), has become one of the more important carbon–carbon bond forming reactions in organic synthesis. The resulting β-aminocarbonyl compounds, termed Mannich bases, are versatile synthons that can be converted into a variety of useful derivatives including Michael acceptors, amino alcohols, and further functionalized carbonyl compounds.[1] These aminoalkylation reactions have recently been reviewed.[2]



(1)

The vinylog of the Mannich reaction, in which the addition of a dienol (or equivalent) to an iminium ion to produce a δ-aminocarbonyl compound (Eq. (2)), has recently garnered the interest of a number of researchers. Not only is the δ-aminocarbonyl structural array seen in a number of natural products, but also it is a useful and versatile functional unit in its own right.



(2)

There have been several reviews in which selected accounts

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* Corresponding author. Tel.: +1-512-471-3815; fax: +1-512-471-4180; e-mail: sfmartin@mail.utexas.edu

† Present address: Department of Chemistry, Emory University, Atlanta, GA 30322, USA.


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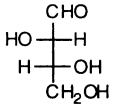
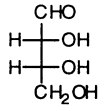
of the more interesting applications of the vinylogous variant of the Mannich reaction are presented.[2–5] A much larger body of literature from which to extract insight exists, however, and the goal of this review is to compile that body of the literature into a singular source while highlighting some of the insights into the stereoselectivities observed in this carbon–carbon bond forming process.

In the interest of clarity, a few comments should be made regarding the language used to describe the reactants and products. Though most of the terminology is straightforward, a few subtleties are potentially confusing. With regard to the iminium ion reaction partner, several types of ions have been reported to undergo reactions with dienol nucleophiles. The general term 'iminium ion' will be used to encompass the array of *N*-acyl, *N*-alkoxy, and *N*-alkyl iminium ions as well as Lewis acid (LA) complexed imines. With respect to the nucleophilic reactant, the general term 'dienol' will be used rather loosely to encompass the range of reaction partners from silyldienol ethers to vinyl ketene acetals.

When describing the products that arise from additions of dienols to iminium ions, issues of nomenclature are often encountered. More specifically, language that allows a clear understanding of the stereochemical relationship between, for example, two diastereomeric adducts without the burden of assigning *R* and *S* to the stereogenic centers is desirable. Many of the compounds produced in the vinylogous Mannich reaction contain vicinal heteroatoms about the newly formed carbon–carbon bond. For these adducts, the threo–erythro system of nomenclature that is derived from the sugars threose and erythrose is the most widely used, although it is at times problematic.




D-(+)-threose

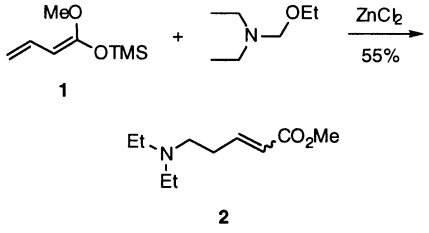



D-(-)-erythrose

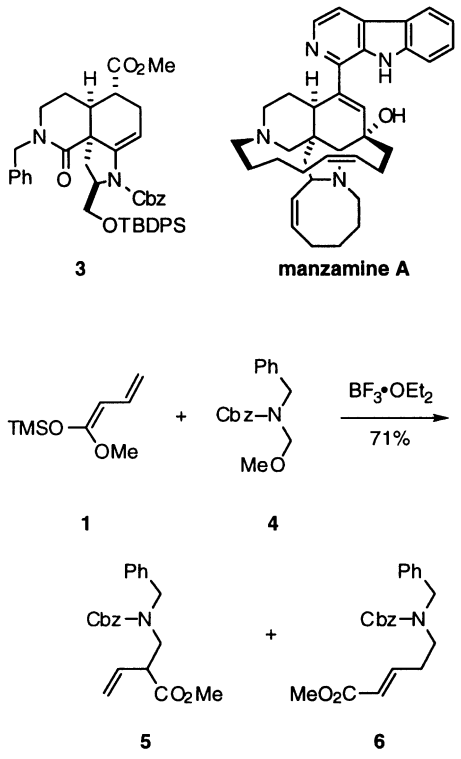
## 2. Acyclic iminium ions reacting with acyclic dienols

### 2.1. *N*-Acyl and trialkyl iminium ions

Oida and Tanimoto reported that the $ZnCl_2$ catalyzed reaction of vinyl ketene acetal **1** with *N*,*N*-diethylethoxymethylamine generated the amino ester **2** in modest yield with only the γ-aminoalkylation product being observed (Eq. (3)).[6] An *E* configuration of the olefin was assumed based on the literature precedent,[7,8] but this was not rigorously established.




1 2 (3)

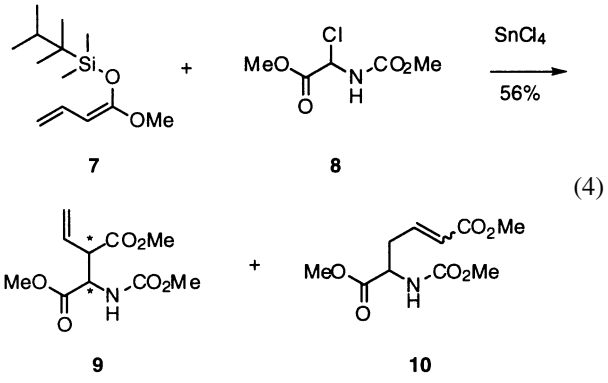



3 manzamine A 1 4 5 6

**Scheme 1.**

Pandit examined the Lewis acid mediated reaction of **4** with **1** in a first generation approach to the tricyclic core **3** of the marine alkaloid manzamine A.[9,10] However, in sharp contrast with the high regioselectivity observed in the Oida study (Eq. (3)), this reaction was not regioselective, and a mixture (1:1) of the α- and γ-adducts **5** and **6**, respectively, was obtained in 71% yield (Scheme 1).

Speckamp has also reported poor regioselectivity in the $SnCl_4$ mediated reaction of the dimethylthexylsilyl ketene acetal **7** with **8** to give a mixture (67:33) of **9** (as a 1:1 ratio of diastereomers) and **10** (as a 72:28 ratio of *E*/*Z* isomers) (Eq. (4)).[11]

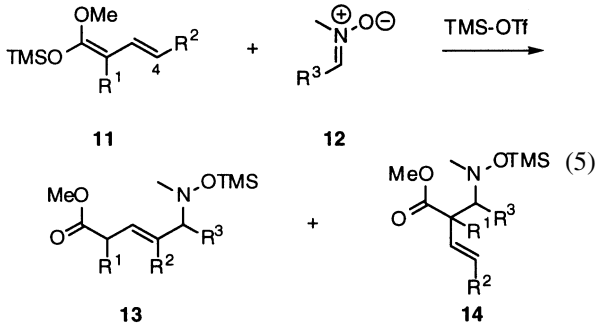



7 8 9 10 (4)

### 2.2. *O*-Silylated nitrones

Other researchers have reported high levels of regioselectivity in the reaction of acyclic dienols with acyclic iminium

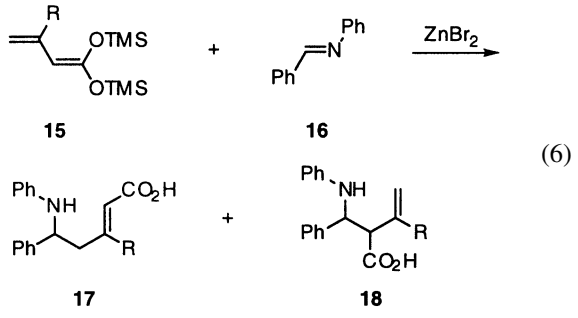
ions. For example, Trombini has investigated an interesting variant of the vinylogous Mannich reaction that uses *O*-silylated nitrones as iminium ion reaction partners in an addition-cyclization route to isoxazolidines.[12] When variously substituted dienol ethers **11** were added to aldonitrones **12** in the presence of trimethylsilyl triflate (TMS-OTf), adducts **13** and **14** were isolated in yields ranging from 60 to 96% (Eq. (5)).[13] In a majority of the examples presented, reaction at the γ-carbon of the dienol ether to give **13** predominated (36–48:1). Substitution at C(4) of the dienol ($R^2$=Et) effected a reversal of regioselectivity (1:9, **13**:**14**), with **13** being obtained as a mixture (1:1) of diastereomers (10% yield) and **14** being produced as a 2:1 ratio of diastereomers (87% yield). The relative stereochemistry of the major adduct **14** was not reported.




(5)

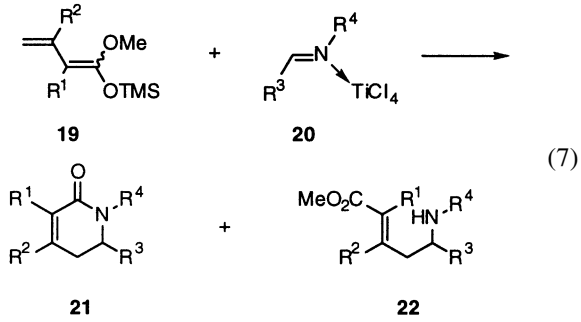
### 2.3. Imine–Lewis acid complexes

Several researchers have investigated the addition of dienol ethers to imine–Lewis acid complexes. While some have observed hetero Diels–Alder products from such reactions,[14–18] others have isolated 1,2-addition products from these reactions. Mladenova and Bellassoued, for example, have reported that the zinc bromide mediated addition of vinyl ketene bis(trimethylsilyl) acetals **15** to the aryl imine **16** produced **17** and **18** with a high degree of regio- and stereoselectivity.[19] 1,2-Addition at the γ-carbon was favored producing **17** (85:15) with dominant *E*-olefin geometry (80:20, Eq. (6)). In a subsequent publication, Bellassoued presented a study in which Lewis acid, solvent, and temperature were independently varied and concluded that the regioselectivity was not significantly affected by any of these parameters.[20] The combination of $ZnBr_2$ in THF at 20°C was optimal with respect to overall yield. Imines derived from alkyl amines failed to react under the examined conditions.




(6)

Ojima studied the addition of dienols to imines in the presence of $TiCl_4$.[21] Reactions of dienols **19** with imine complexes **20** were selective for either the cyclic products **21** or the acyclic products **22** depending on the substitution of the ketene acetal (Eq. (7)). When $R^1$=Me, the reaction was either unselective (38:42 when $R^3$=$^i$Pr and $R^4$=Bn) or **22** was the exclusive product (when $R^3$=Ph). When $R^2$=Me, the cyclic product was produced almost exclusively. When aniline derived imines were employed (e.g. $R^4$=Ph), the product distribution shifted in favor of **22**. These results are in accord with those reported by Mladenova and Bellassoued, who found that diarylimines ($R^3$ and $R^4$=aryl) gave acyclic products (cf. Eq. (6)).

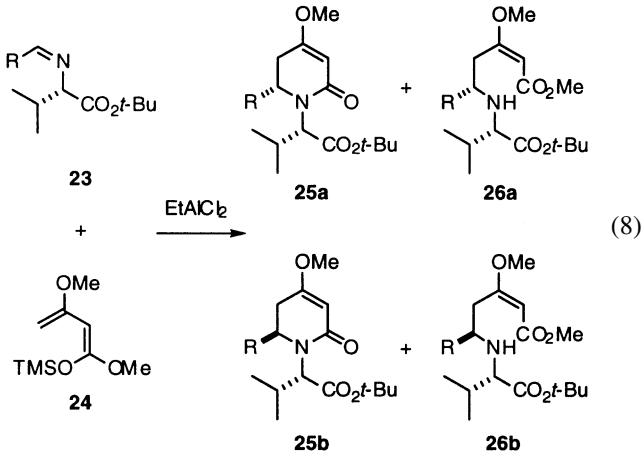



(7)

When the reactions were quenched below −50°C, the acyclic adduct **22** was observed as the only product. However, **22** slowly cyclized to **21** at higher temperatures. From these data, it was postulated that **22** was a common intermediate in all of these reactions. Midland, however, has isolated Diels–Alder adducts in similar experiments, and he reported that these adducts can decompose to either the acyclic or the cyclic products depending on the way in which the reactions were quenched.[22] Owing to the pericyclic nature of the reaction mechanism, the acyclic products isolated by Midland had a *Z*-olefin geometry. Determination of the olefin geometry in **22** was not discussed, though it was drawn in the *E* configuration as shown. This structural assignment, which is in accord with several reports,[11,19] is consistent with an addition rather than a cycloaddition mechanism. However, the observed ease of *O*- to *N*-transacylation (e.g. **22**→**21**) is consistent with the formation of acyclic products having the *Z* configuration about the olefin via cycloaddition as suggested by Midland. It is unclear, therefore, whether the reactions reported by Ojima are truly vinylogous Mannich reactions, hetero-Diels–Alder reactions, or reactions in which these two pathways are competitive. Careful analysis of the olefin geometry of the kinetic products in these reactions could help define the reaction mechanism.

In reactions similar to those performed by Ojima, Waldmann has reported that the reaction of **23** with **24** in the presence of a variety of Lewis acids produced mixtures of **25a**,**b** and **26a**,**b** in modest to good yields (Eq. (8)).[23,24] When R=Ph, a mixture (97:3) of cyclic diastereomers **25a** and **25b** (84% yield) was observed to the virtual exclusion of **26a**,**b**. When R=alkyl, however, mixtures (18:82) of both cyclic **25a**,**b** and acyclic **26a**,**b** were isolated; the diastereoselectivity did not change significantly (93:7, **25a**+**26a**:**25b**+**26b**). The geometry of the carbon–carbon double bonds of **26a** and **26b** were drawn in the *E* configuration, but no evidence was presented to support this assignment. Unlike the acyclic products reported by both Ojima and

Midland, compounds **26a**,**b** did not readily cyclize to **25a**,**b** under either the Lewis acidic reaction conditions or upon heating in chloroform; however, they did cyclize upon heating with one equivalent of acetic acid in toluene. It is possible that two mechanistic pathways are operative in this reaction: The acyclic products were formed by a vinylogous Mannich reaction mechanism, in which case the *E*-olefin geometry should predominate. The cyclic products were produced by a pericyclic mechanism, producing the *Z*-olefin geometry. In the conversion of **26a**,**b** to **25a**,**b**, the acid may have isomerized the olefin from the *E* to the *Z*-geometry before transacylation could occur. Again, a careful study of the olefin geometry in the acyclic adducts **26a**,**b** would, perhaps, offer insight into the reaction mechanisms that afford the observed products in these reactions.



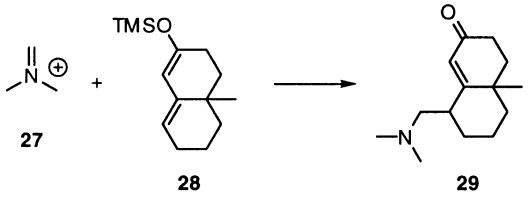
(8)

Although the line between a cycloaddition mechanism and an addition-cyclization mechanism is unclear, a cycloaddition mechanism should have consequences on the observed olefin geometry in the products. More basic research is needed to probe the mechanisms through which acyclic dienols add to imines. A deeper understanding of the reaction parameters that favor cycloaddition-like products or addition-like products could then be exploited in applications where the olefin geometry is important or where the cyclic products are desired. Understanding the factors that control the regiochemical course of these reactions is also an essential prerequisite for the rational application of this methodology to synthesis.

## 3. Acyclic iminium ions reacting with cyclic dienols

### 3.1. *N*-Acyl and trialkyl iminium ions

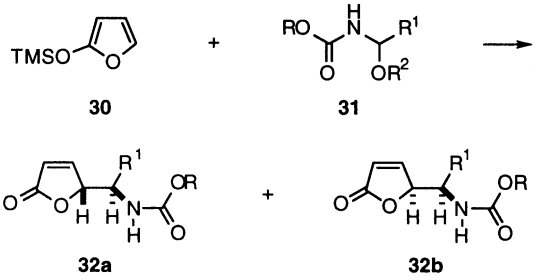
In the context of addressing the regiochemical shortcomings of the classical Mannich reaction, Danishefsky examined the reaction of regiochemically defined silyl enol ethers and the Eschenmoser salt **27** with the expectation of introducing carbon functionality at the γ-position of an enone (Eq. (9)).[25,26] Accordingly, reacting the *s-trans* constrained dienol ether **28** with **27** produced the δ-amino enone **29** as a single diastereomer; the relative stereochemistry of the newly formed stereogenic center was not determined.



(9)

Although the dienol moiety in **28** is constrained within a cyclic array, the reactivity may not be different from acyclic dienols. A number of studies have examined the stereochemical outcome of vinylogous Mannich reactions employing 2-trialkylsilyloxyfurans. This methodology has been developed in concert with other additions, such as the vinylogous aldol reaction, which also employs silyloxyfurans as nucleophilic partners. Many of the stereochemical preferences found in these other reactions are similar to those observed in the vinylogous Mannich reaction.[3,4,27–33]

Harding, for example, has studied the Lewis acid-catalyzed reaction of 2-trimethylsilyloxyfuran (**30**) with *N*-acyliminium ions derived from compounds having the general structure **31** (Eq. (10)).[34] Generally, mixtures of adducts **32a** (threo) and **32b** (erythro) were produced in modest yields (41–56%) wherein **32a** predominated (1.6–3.3:1). No α-alkylated products were detected, and modest diastereoselectivities were realized for all but $R^1$=$CCl_3$ or Ph, in which cases the diastereoselectivity increased substantially (9:1). Neither the amount of $BF_3{\cdot}OEt_2$ nor the temperature affected the diastereoselectivities.



(10)

The origins of the observed diastereoselectivity are not clear. Analysis of limiting transition states is complicated by the acyclic nature of the iminium ion, because it can be formed with either *E* or *Z*-olefin geometry and can react from either the *s-cis* or *s-trans* conformation with respect to the *N*-acyl group (Fig. 1). Drawing an analogy to the vinylogous aldol reactions reported by Jefford,[35] the major product was suggested to come from an endo-Diels–Alder like transition state involving the *s-cis*/*E* iminium ion.

A novel and concise entry into the Ergot family of alkaloids using a vinylogous Mannich reaction as a key step was reported by our laboratory.[36] Thus, the intermolecular addition of silyloxyfuran **33** to the iminium ion generated upon protonation of enamine **34** with camphorsulfonic acid (CSA) produced a mixture (1:2) of butenolides **35** (Scheme 2). A photostimulated $S_{RN}1$ reaction furnished the spirolactone **36**, and removal of the *N*-benzyl protecting group delivered a mixture (1:2) of rugulovasines A (threo) and B (erythro) **37**.

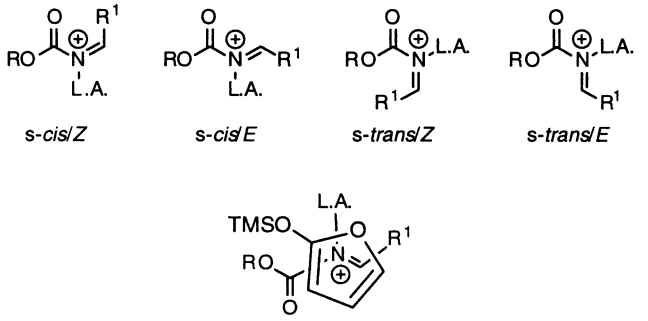
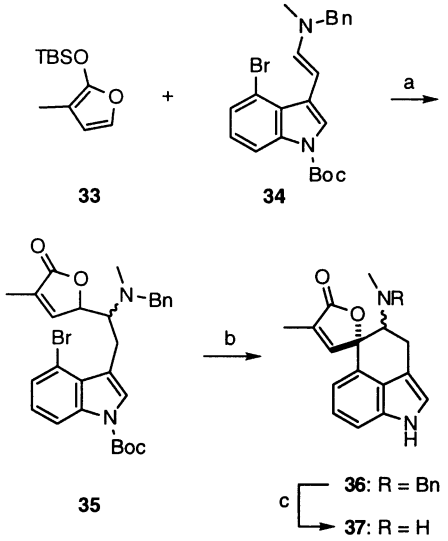



**Fig. 1.** Conformations of the iminium ion and proposed transition state leading to **32a**.

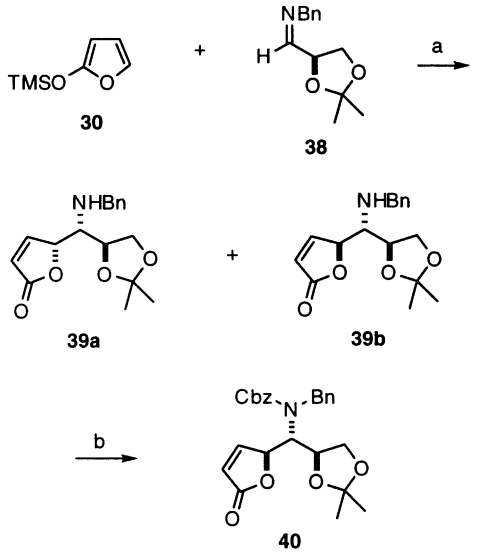
### 3.2. Imine–Lewis acid complexes

Casiraghi has reported that the $BF_3{\cdot}OEt_2$ promoted addition of silyloxyfuran **30** to the *N*-benzylimine **38** derived from D-glyceraldehyde produced a mixture (1:1) of diastereomeric adducts **39a** (threo) and **39b** (erythro) in 66% yield (Scheme 3).[37] In the context of future discussions, it is important to note that this reaction was quenched at −85°C with saturated aqueous $NaHCO_3$ and then allowed to warm to room temperature.

This mixture was subjected to the mildly basic Schotten–Baumann conditions (aq. $NaHCO_3$, Cbz-Cl, dioxane, rt), and only the benzyloxycarbonyl (Cbz) protected erythro product **40** was isolated. The erythro isomer **40** appears to be thermodynamically preferred. Because **39** was isolated as a mixture (1:1) of diastereomers and **40** was the only stereoisomer isolated from the *N*-acylation reaction, it was suggested that the observed product ratio from the vinylogous Mannich reaction was, perhaps, the result of a partial equilibrium rather than a kinetic distribution. In a more recent publication, Casiraghi and Rassu reported that the addition of **30**–**38** under the same conditions produced **39a** (threo) with >92% diastereomeric excess.[38] When subjected to Schotten–Baumann conditions, **40** was again




**Scheme 2.** (a) CSA, then **33**, 80°C. (b) *t*-BuOK, $NH_3$, reflux, $h\nu$. (c) HCl, EtOH, $H_2$, $Pd(OH)_2/C$.




**Scheme 3.** (a) $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, −85°C, 66%. (b) Cbz-Cl, 7% aq. $NaHCO_3$, dioxane, rt, 68%.

the only reported stereoisomer produced. It is believed that the erythro isomer is the kinetically favored, but the butenolide is readily epimerized in either the workup or during isolation.[39]

In support of this belief, Casiraghi and associates published a synthesis of the potential HIV protease inhibitor **41** in which the erythro diastereomer was selectively produced in a vinylogous Mannich reaction very similar to that described in Scheme 3.[40] Compound **41** is a derivative of the pseudo-$C_2$-symmetric compounds **42** and **43** that are micromolar and nanomolar inhibitors, respectively, of HIV protease (Fig. 2). In the key reaction, 2-*tert*-butyldimethylsilyloxyfuran (**44**) was reported to add to imine **38** to produce the butenolide **39a**,**b** (83% yield) as a mixture (1:9) of adducts predominating in the erythro diastereomer shown (Scheme 4).

The sense of stereoselection was proposed to arise from a transition state resembling **46** in which a Felkin–Anh approach of the furan is preferred, giving addition to the *si*-face of the imine.[41] Aside from the requirement that the major adduct arise from addition of the *re*-face of the dienol ether to the imine, no rationale was offered for the synclinal

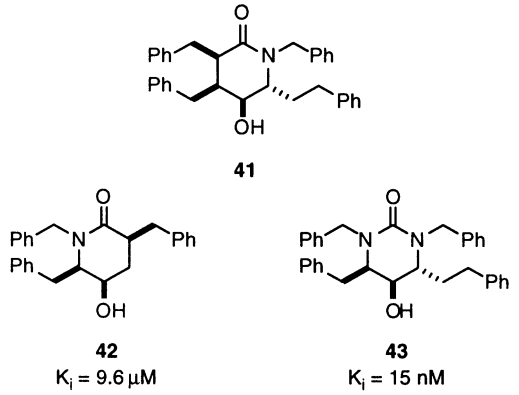
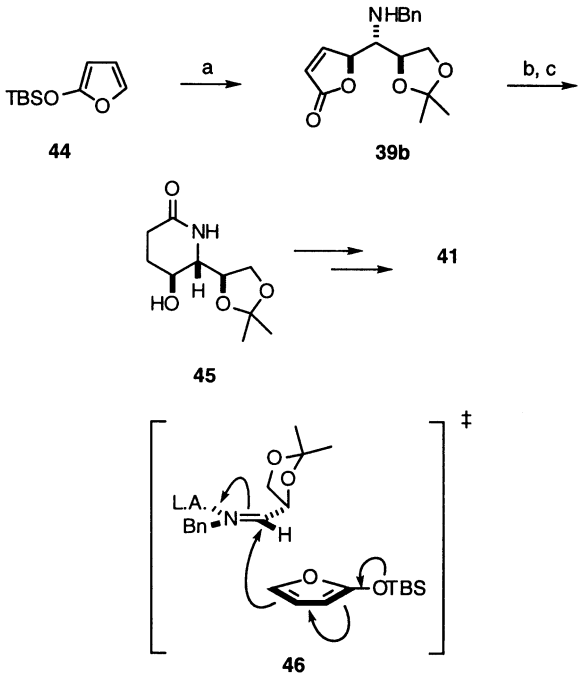



**Fig. 2.** HIV protease inhibitors.



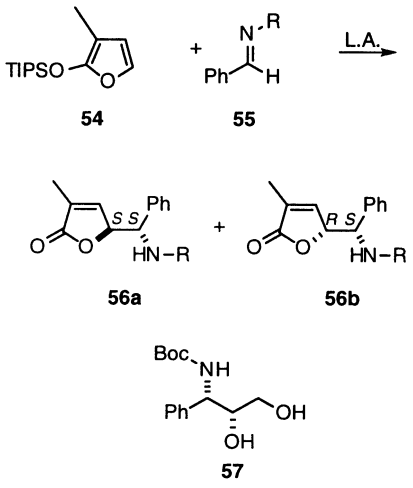

**Scheme 4.** (a) *tert*-Butyldimethylsilyl trifluoromethanesulfonate, **38**, −80°C, 83% (1:9; **39a**:**39b**). (b) $H_2$, Pd–C. (c) DBU, 80°C, 62% from **39a**.

'aldol-like' orientation of the furan in **46**. Hydrogenation and base-catalyzed *O*→*N* acyl transfer furnished lactam **45** in 62% yield from **39b**. Lactam **45** was then converted to **41** by a series of chemical manipulations.

In other applications of the vinylogous Mannich reaction, Casiraghi and coworkers have synthesized two stereoisomers of (−)-swainsonine by independent but parallel routes.[42] In one such approach, silyloxyfuran **30** was added to imine **47** to give the erythro adduct **48** as the only reported product (Scheme 5). Hydrogenation of **48** followed by exposure of the resulting amine to base produced the lactam **49**, which was then reduced and deprotected to provide amine **50**. Cyclization of **50** afforded **51** in 56% overall yield from imine **47**. By substituting imine **52** for **47** in the same series of reactions outlined in Scheme 5, **53** was synthesized in 61% overall yield from **52**.

In the vinylogous Mannich reactions of both **47** and **52** with **30**, the erythro isomer was the only reported adduct, and no regioisomeric products were observed. Facial selectivity with regard to the iminium ion is again consistent with a Felkin–Anh approach of the nucleophilic furan.

While Casiraghi and coworkers have controlled the absolute configurations of the newly formed stereocenters in the vinylogous Mannich reaction by employing chiral imines, our laboratory has examined the use of chiral Lewis acid promoters in the reaction of silyloxyfurans with aldimines.[43] In the presence of $Ti(O^iPr)_4$, silyloxyfuran **54** added to imine **55** (R=2-$HOC_6H_5$) to furnish a mixture (2:1) of adducts **56a** (threo) and **56b** (erythro) in 80% yield (Eq. (11)). When the reaction was conducted in the presence of the chiral Lewis acid complex formed by mixing (*S*)-BINOL with $Ti(O^iPr)_4$ (2:1, 20 mol%), the additions proceeded with good diastereoselectivity (91:9) and modest enantioselectivity (48%). The absolute stereochemistry of **56a** was determined by conversion into the known amino diol **57** and comparing the specific rotation to that reported for enantiomerically pure material. Other chiral ligand–Lewis acid complexes promoted the addition of **54** to **55** with higher diastereoselectivity, but racemic adducts were produced. A hydroxyl group in the imine (R=2-$HOC_6H_6$) was found to be crucial as substrates lacking this coordinating functionality (i.e. R=4-$MeOC_6H_5$) participated in the reaction to give products **56a** and **56b** in both good yields and diastereoselectivities, albeit with no enantioselectivity.

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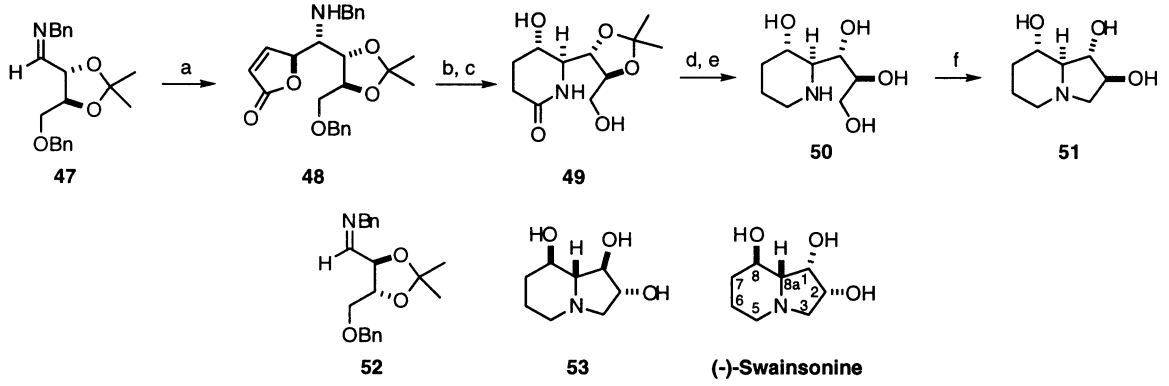
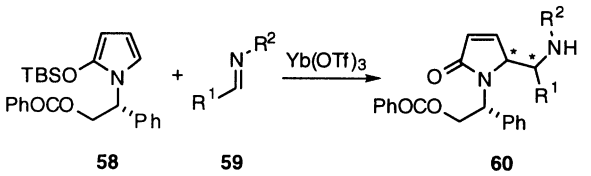



**Scheme 5.** (a) **30**, $BF_3{\cdot}OEt_2$, −85°C, 77%. (b) $H_2$, Pd–C, NaOAc, 90%. (c) DBU, $C_6H_6$, reflux, 95%. (d) $BH_3{\cdot}$DMS. (e) aqueous TFA (60%), then Dowex$^-$OH, 93% from **49**. (f) $Ph_3P$, $CCl_4$, TEA, 92%.

Royer has recently reported that the ytterbium triflate-catalyzed addition of 2-silyloxypyrrole **58** to imines **59** derived from aromatic aldehydes produced mixtures of diastereomers in which erythro products predominated (Eq. (12)).[44] For example, the reaction of **58** with **59** ($R^1$, $R^2$=Ph) produced **60** as a mixture (53:23:18:6; 76:24 erythro/threo) of diastereomers in 70% yield. The erythro stereochemistry of the major adduct was confirmed by its transformation to **61**. In this study, the presence of a coordinating hydroxyl group in the imine ($R^2$=2-HO–$C_6H_4$) increased the erythro selectivity (95:5) with little loss in yield (67%). Reactions involving aliphatic aldehyde derived imines or $BF_3{\cdot}OEt_2$ as a promoter failed. The erythro selectivity in reactions employing the *N*-alkylpyrrole **58** as compared with the threo selectivity that we have observed using silyloxyfurans is curious, and the basis for this reversal of selectivity is presently unknown.

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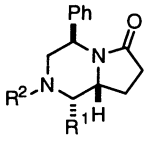
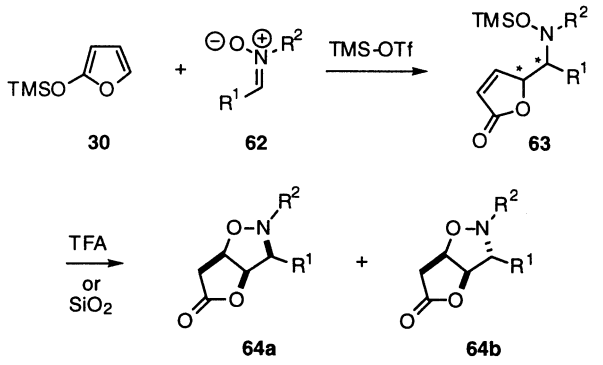



61

### 3.3. *O*-Silylated nitrones

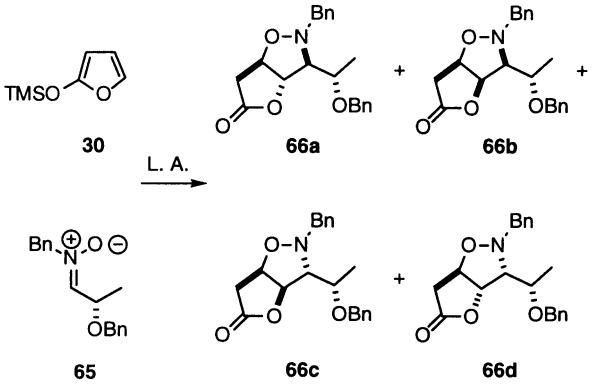
In an extension of earlier work (cf. Eq. (5)), Trombini has shown that silyloxyfuran **30** adds to *O*-silylated nitrones with modest to good stereoselectivity.[45] When achiral nitrones of the general structure **62** were allowed to react with **30** in the presence of catalytic amounts of TMS-OTf, the adducts **63** were produced. Subsequent treatment of **63** with trifluoroacetic acid and/or silica gel chromatography afforded mixtures of bicyclic isoxazolidines **64a** (threo) and **64b** (erythro) (Scheme 6). Because the intermediate adducts **63** were treated with acid, rather than base, the equilibration noted by Casiraghi (Scheme 3) is probably not an issue. Some of the substituent effects that contribute to the stereoselectivity were noted: When $R^1$=alkyl and $R^2$=methyl, no selectivity was observed. In each example where $R^1$=aryl, the selectivity favors **64a** (threo, 3.3–24:1); when $R^2$= benzyl, **64b** (erythro) was preferred (2.4–7.3:1) except when $R^1$=aryl. These observations were used to formulate the limiting transition states through which the reactants must pass (vide infra).

The use of chiral nitrone **65** as a substrate provided more insight into the stereochemical course of the addition (Eq. (13)).[46] When the reaction was conducted in the presence of catalytic TMS-OTf, a mixture (49:3:42:6) of four diastereomers **66a–d**, respectively, was produced in 97% combined yield. In an effort to enhance the stereoselectivity through double stereodifferentiation, chiral Lewis acids were employed in catalytic amounts; however, no change




**Scheme 6.**

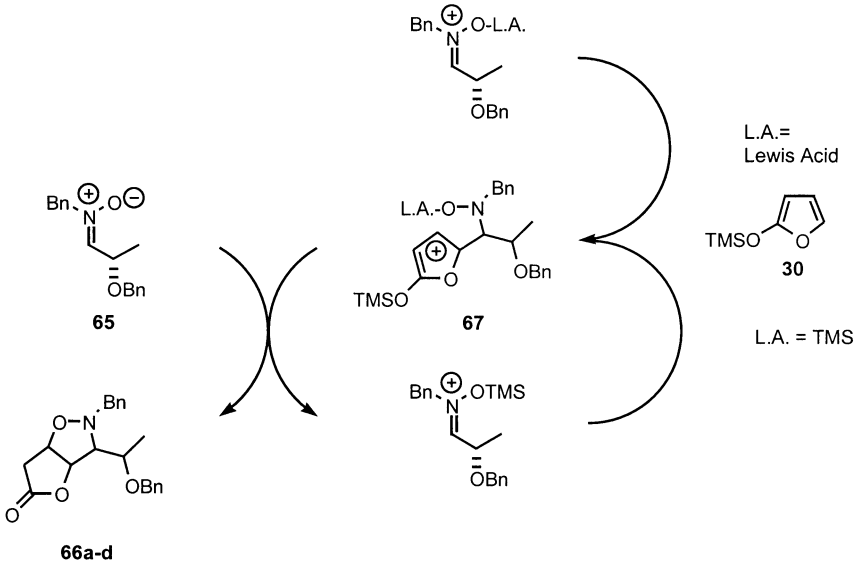
in product distribution was observed.




(13)

A catalytic cycle wherein the trimethylsilyl group from the oxonium ion **67** acts as an efficient Lewis acid promoter may be proposed to account for the product ratios that were similar to the TMS-OTf promoted reaction (Scheme 7). The use of stoichiometric amounts of Lewis acid promoters was therefore examined with the hope that this silyl transfer pathway would be prevented. Whilst the stoichiometric use of a chiral Lewis acid promoter did change the stereoselectivity, no double stereodifferentiation was observed; both enantiomers of $Ipc_2BOTf$ returned the same mixture (93:0:2:5) in roughly the same yield (85–88%). The chirality of the boron ligand was presumably too far removed from the reacting centers in the transition state to induce stereoselection. Similar observations regarding chiral induction were made in this laboratory (cf. Eq. (11)).[43] Although the use of achiral Lewis acids in stoichiometric quantities generally returned mixtures similar to those obtained using stoichiometric amounts of the chiral promoters, it is interesting to note that $ZrCl_4$ furnished **66a** as the only detectable stereoisomer.

From these studies, Trombini developed a transition state model that accounts for the experimentally observed stereoselectivities.[45] First, with respect to the facial selectivity of the iminium ion, the additions follow the Felkin–Anh model. Diastereofacial selectivity with respect to the furan, however, is less well defined. The four limiting transition states **68a–d** represented by Newman projections relative to the incipient carbon–carbon bond were proposed to account for the observed selectivities (Fig. 3). For the addition to iminium ions derived from dialkyl substituted




**Scheme 7.**

nitrones ($R^1$=alkyl, $R^2$=methyl), transition states **68b** and **68d** were selected based solely on steric demand, but neither of these two transition states should be preferred. When the carbon substituent is aromatic ($R^1$=aryl), the enhanced selectivity was attributed to the secondary orbital interactions that are possible in either transition state **68a** or **68c**.[47–50] The $A^{1,3}$-interaction between the nitrone oxygen and the aromatic group when $R^1$=Ph or 1-naphthyl precludes coplanarity of the aromatic ring and the nitrone moiety, and may interfere with an approach of the furan as depicted in **68a** and **68c** (vide infra). However, slightly skewed conformations in which the nitrone moiety and the aromatic ring retain some π-delocalization could still allow for the orientations **68a** and **68c**. As a further stabilizing factor, Trombini suggested that transition state **68a** maximizes an electrostatic interaction between the nitrone oxygen and the developing cationic character on C(4) of the furan ring. However, the selective formation of threo products in additions to imines derived from aromatic aldehydes lacking functionality that is capable of participating in such an electrostatic interaction (cf. Eq. (11))[43] renders the importance of this stabilizing effect unclear.

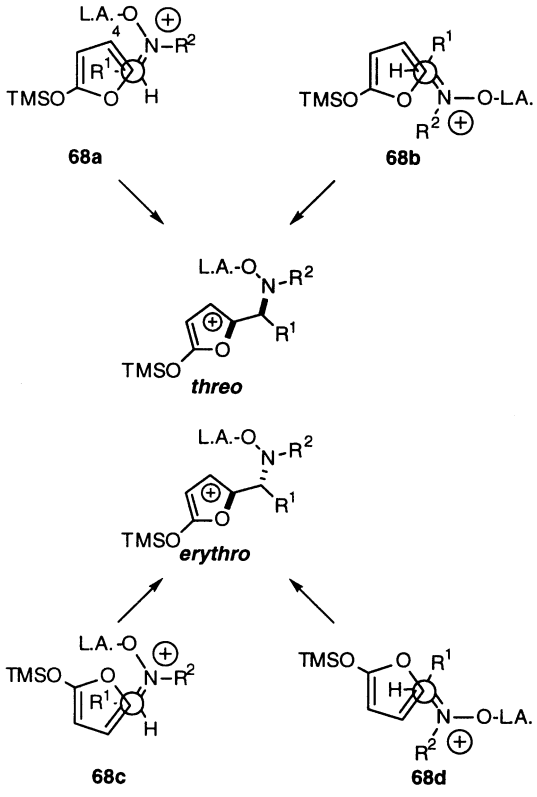



**Fig. 3.** Proposed transition states for the Lewis acid promoted addition of **30** to nitrones.

Trombini did not appear to consider Diels–Alder-like transition states similar to that shown in Fig. 1. An alternative explanation that does not rely on subtle stereoelectronic effects can be offered based upon the Diels–Alder-like approach of the furan to the iminium ion. The $A^{1,3}$-interaction between the nitrone oxygen and the aromatic group forces the aromatic group out of the iminium ion plane and may preclude transition state conformations such as those depicted in **68a** or **68c**. A Diels–Alder-like orientation of the furan would account for the observed stereoselectivity (Fig. 4).

When the nitrogen substituent is benzyl ($R^2$=Bn), Trombini postulated that conformers **68b** and **68d** were preferred for steric reasons and that **68d** would be favored by secondary orbital interactions between the aromatic π-systems of the furan and the benzyl group (Fig. 5).[46] The erythro selectivity obtained when Casiraghi and coworkers[37,38] employed *N*-benzyl imines in vinylogous Mannich reactions (Schemes 3 and 5) is consistent with Trombini's observations. The interactions when $R^1$=aryl appear to over-ride the stabilizing effect of $R^2$=benzyl.

Having probed some of the parameters that guide the stereoselectivities, Trombini applied the nitrone variant of the vinylogous Mannich reaction to the synthesis of polyhydroxylated piperidines and lactams such as the azasugar precursors **69a–d** (Scheme 7).[51,52]

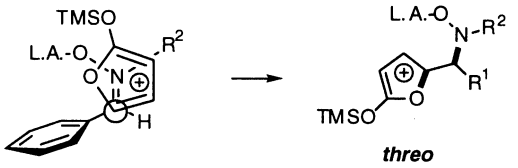



**Fig. 4.** Alternative transition state for threo selective Lewis acid promoted addition of **30** to nitrones.

Based on the examples presented in this section, silyloxyfurans may participate as nucleophilic reaction partners in vinylogous Mannich reactions to give adducts, sometimes with a high degree of stereoselectivity. Several interesting applications to the stereoselective synthesis of some important natural and unnatural compounds of both biological importance (Schemes 2, 4, and 5) and synthetic interest (Eqs. (10), (13) and (9), and Scheme 8) have been recorded. However, the origins of the diastereoselectivity observed in these reactions are not well defined, although several transition state models, such as the Diels–Alder-like (Figs. 1 and 4) and the extended transition states (Fig. 3), have been proposed. The present lack of compelling evidence for the preference of one transition state over another makes it difficult to draw meaningful conclusions. Moreover, the general sense of stereoselection in the reactions of silyloxyfurans with acyclic iminium ions may be due to the aromatic nature of the furan itself and may not be observed in the reactions of other *s-cis* constrained dienol ethers with iminium ions.

## 4. Cyclic iminium ions reacting with acyclic dienols

### 4.1. Natural products synthesis

Stevens reported one of the most ingenious applications of the reaction of cyclic iminium ions with acyclic dienols. He discovered that dienol **70** added to the common alkaloid berberine (**71**) to give the intermediate enamino enone **72** (Scheme 9).[53] Spontaneous intramolecular Michael addition of **72** generated the zwitterionic intermediate **73a** that isomerized to **73b** and subsequently cyclized to give karachine (**74**) in 66% yield.

Our laboratory has also exploited the synthetic utility of additions of dienols to cyclic iminium ions. In developing a unified strategy for the synthesis of indole alkaloids, we found that a vinylogous Mannich reaction followed by an intramolecular Diels–Alder reaction allowed rapid entry into a number of natural products in this class. For example, acylation of 3,4-didehydro-β-carboline (**75**) with the pyrone derivative **76** generated an acyliminium ion to which dienol **77** added to provide the substituted β-carboline **78** in 86% yield (Scheme 10).[54] In contrast to the reports of Pandit[9] and

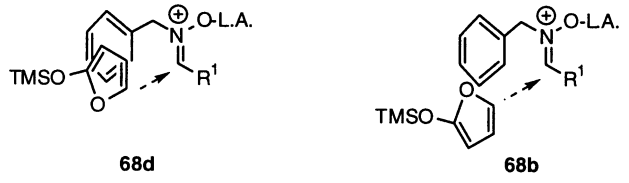
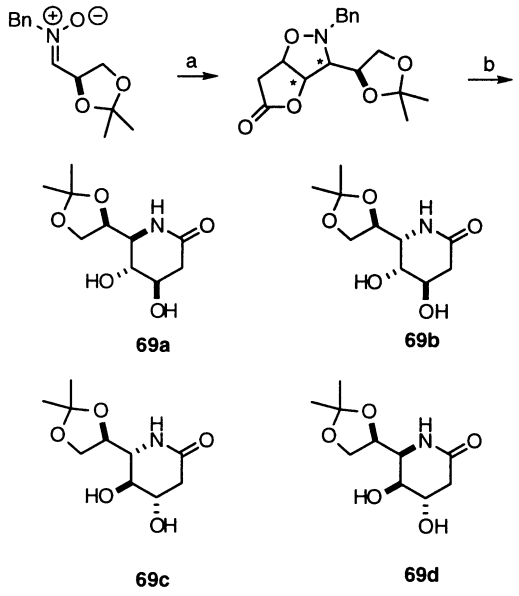


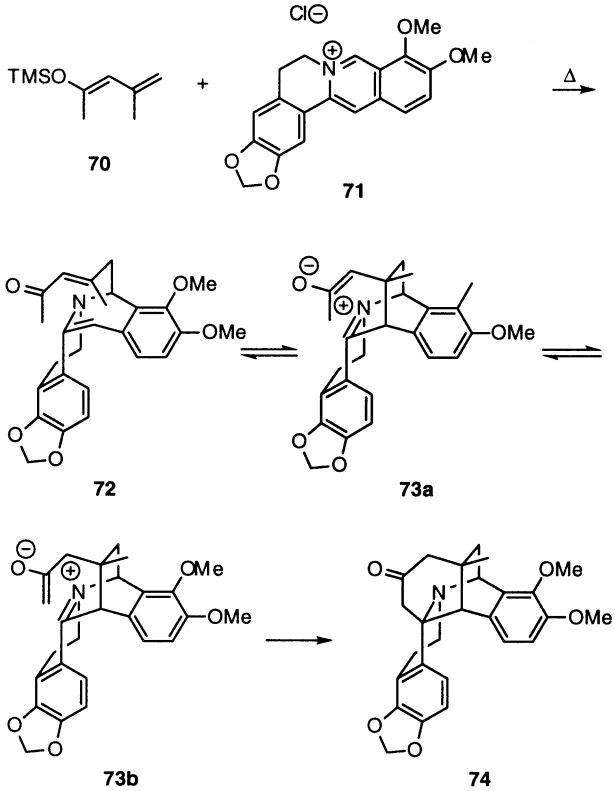

**Fig. 5.** Transition state conformations showing potential π-stacking in **68d** and no interaction in **68b**.



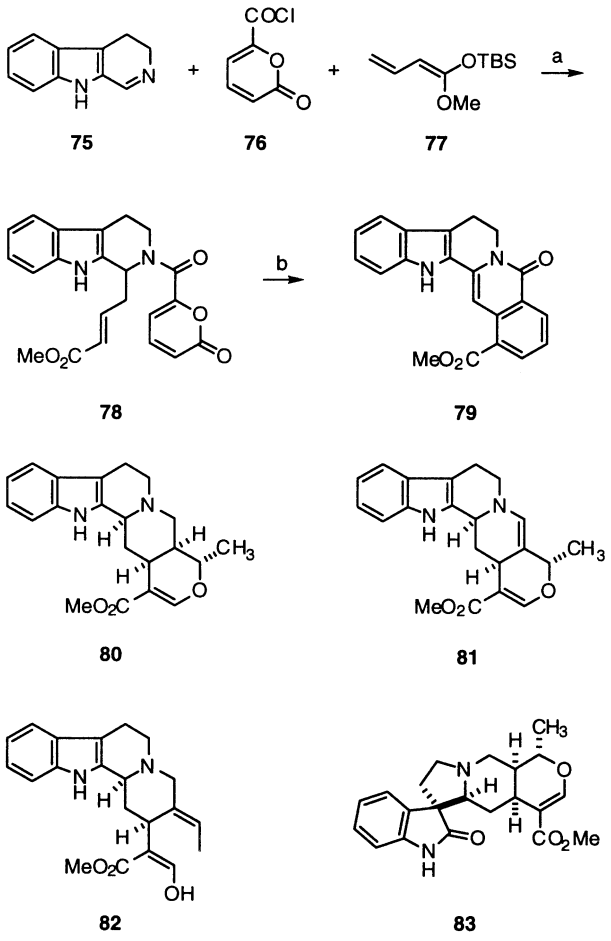

**Scheme 8.** (a) Lewis acid, **30**. (b) $H_2$ (45 psi), $Pd(OH)_2$, 65–87%.

Speckamp[11] (see Scheme 1 and Eq. (4)), no regioisomers arising from addition of the α-carbon of the dienol were detected. Heating **78** with benzoquinone in mesitylene produced gambirtannine (**79**) in 91% yield.

A similar strategy was applied to the syntheses of the heteroyohimboid alkaloids (±)-tetrahydroalstonine (**80**) and (±)-cathenamine (**81**), the corynantheoid alkaloid (±)-geissoschizine (**82**), and the 2-oxindole alkaloid (±)-isopteropodine (**83**).[54]




**Scheme 9.**




**Scheme 10.** (a) THF, −78→rt, 86%. (b) Δ, mesitylene, benzoquinone, 180°C, 91%.

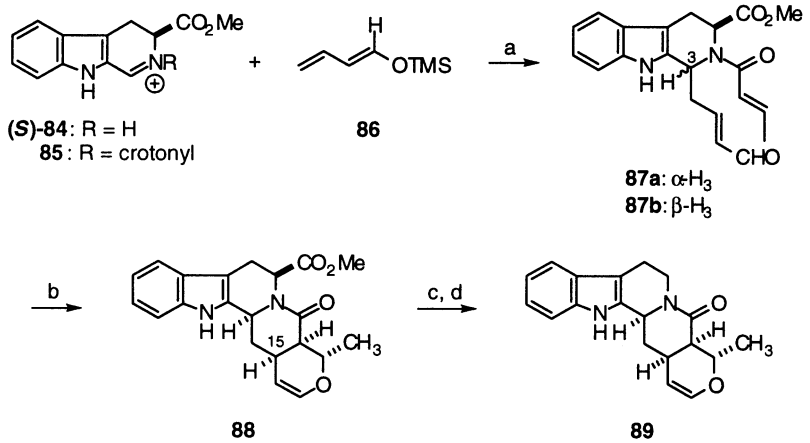
In each of the aforementioned cases, the vinylogous Mannich reaction was performed with achiral reaction partners. However, we found that use of a chiral β-carboline derivative as the electrophile led to the preparation of several indole alkaloids in enantiomerically pure form. The synthesis of (−)-tetrahydroalstonine (**80**) illustrates this approach (Scheme 11).[55] The iminium salt (*S*)-**84** was treated with the silyloxydiene **86** in the presence of crotonyl chloride to deliver a mixture (8:1, 53% combined yield) of the C(3)-epimeric diastereomeric adducts **87a** and **87b**. There was no detectable reaction between **86** and (*S*)-**84** in the absence of crotonyl chloride, suggesting that the *N*-acyl iminium ion **85** was formed in situ as a requisite intermediate in this process. Heating the major adduct **87a**, which possesses the absolute stereochemistry at C(3) corresponding to the natural product, induced a hetero Diels–Alder cycloaddition to provide a mixture (5:1) of pentacyclic adduct **88** together with a small amount of the corresponding C(15) epimer. Hydrolysis of the ester followed by a Barton radical decarboxylation sequence[56] furnished the pentacycle **89**, which intersects the previous racemic synthesis of tetrahydroalstonine (**80**).[54]

Although the silyloxydiene **86** did not react with (*S*)-**84** in the absence of crotonyl chloride, the more electron rich diene **77** added readily to this iminium ion. This important observation led to the development of a plan for the concise synthesis of (−)-ajmalicine (**92**) that is outlined in Scheme 12. Addition of diene **77** to (*R*)-**84** proceeded with virtually complete diastereoselectivity to give the *trans*-product **90** in 69% yield. Subsequent *N*-alkylation of **90** with methyl vinyl ketone (MVK) and exposure of the resulting aminoketone to base provided the tetracyclic product **91** in 92% yield from **90**. Compound **91** was then converted to (−)-ajmalicine (**92**). (+)-Geissoschizine (**82**) was also synthesized by a related sequence.[57]

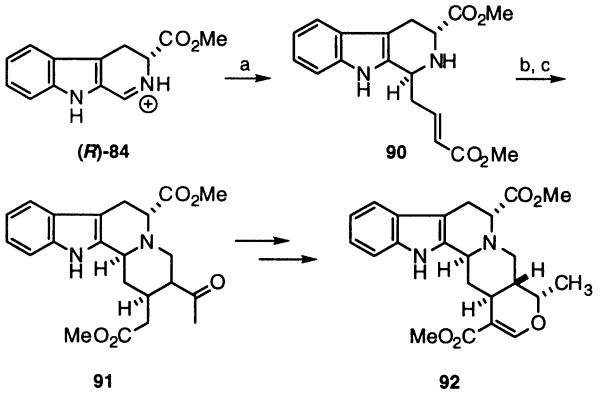
### 4.2. Stereoelectronic and steric effects in additions to six-membered ring iminium ions

The differing stereoselectivities in the additions of dienols to the *N*-acyl iminium ion **85** and the protonated imine (*R*)-**84** is noteworthy. Although it is perhaps not immediately obvious why a reversal of facial selectivity should occur, the balance between the steric and stereoelectronic effects that dictate the stereochemical course in the additions of nucleophiles to six membered-ring iminium ions has been analyzed in several systems. The discussion that follows will provide some general insights relevant to this issue.

Analysis of the conformational preferences that are




**Scheme 11.** (a) Crotonyl chloride, $CH_2Cl_2$, 53%. (b) Mesitylene, 170°C, 81% (5:1). (c) TMSOK, 60%. (d) *i*-BuOCOCl, NMM; $C_5H_4NaNOS$, $Et_3N$; *t*-BuSH, *hν*, 63%.




**Scheme 12.** (a) **77**, $CH_2Cl_2$, 0°C→rt, 69%. (b) MVK, 60°C, 94%. (c) 4 Å molecular sieves, pyrrolidine, 72 h, 98%.

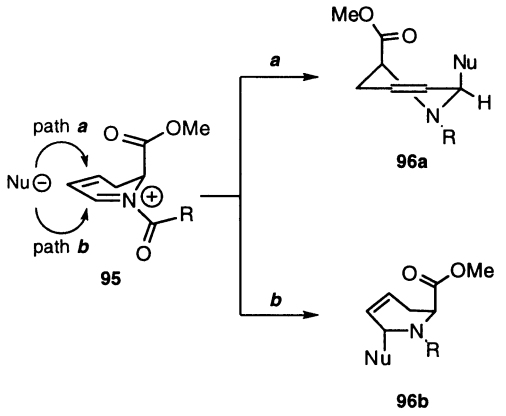



**Fig. 7.** Stereochemical course in the addition to dihydropyridinium salts.

enforced by steric interactions suggests two dominant conformations, **93a** and **93b**, for a monosubstituted six-membered ring iminium ion (Fig. 6). The reactive conformation of the iminium ion is dominated, in this instance, by the $A^{1,2}$-interaction between the alkoxycarbonyl group and the nitrogen substituent R.[58,59] When R=H, the interaction is minimal, and the alkoxycarbonyl prefers the pseudo-equatorial position (e.g. **93a**); when R≠H, the alkoxycarbonyl substituent prefers the pseudoaxial position (e.g. **93b**) in order to minimize $A^{1,2}$-strain.

On the basis of stereoelectronic principles, the nucleophile attacks via a trajectory that allows a *trans* diaxial alignment between the incoming nucleophile and the developing lone pair on nitrogen because this geometry allows for maximum orbital overlap in the transition state (path a or path b).[60–65] Eclipsing interactions develop when the reaction progresses through a boat-like transition state (path a) to give products **94a** and **94d**. This pathway is kinetically disfavored relative to the staggered conformation that develops if the complex progresses through a chair-like transition state (path b) to give products **94b** and **94c**.[66–68] Thus, the preferred trajectory gives a *trans*-disubstituted product if R=H (e.g. **94b**) but a *cis*-disubstituted product if R≠H (e.g. **94c**).

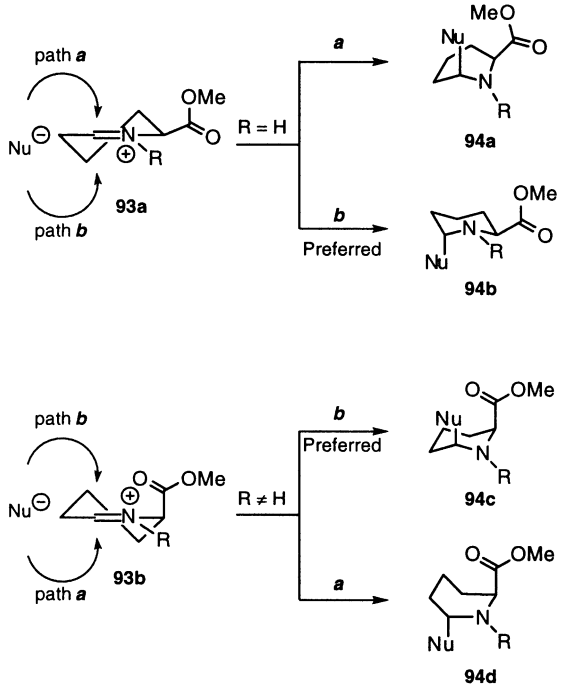


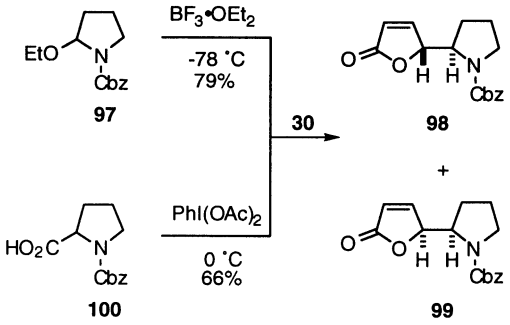

**Fig. 6.** Stereoelectronic and steric interactions in nucleophilic addition to six-membered ring iminium ions.

This generalized overview describes the factors associated with mono-unsaturated six-membered rings, but a similar analysis may be applied to nucleophilic additions to the *N*-acyl iminium ion **85** and the protonated imine (*R*)-**84**. In these cases, however, the electrophilic dihydropyridinium ring would be expected to be puckered as shown in **95** (Fig. 7) to alleviate the $A^{1,2}$-strain that would arise from a coplanar orientation of the *N*-acyl group and the adjacent carbomethoxy group.[69–71] Furthermore, the products from these additions should reside in half-chair-like or boat-like cyclohexene conformations. The boat conformation of cyclohexene is approximately 2.7 kcal/mol higher in energy than the half-chair,[72,73] whereas the boat conformation of cyclohexane is approximately 6 kcal/mol higher in energy than the chair conformation.[74] The difference in energies between the boat and half-chair conformation of cyclohexene is thus approximately 3.3 kcal/mol lower in energy than the difference in energies between the boat and chair conformations of cyclohexane. It then follows that the energy difference between paths ***a*** and ***b*** in nucleophilic additions to dihydropyridinium salts such as **95** will be lower than that between the corresponding paths for additions to iminium salts such as **93b**. Because nucleophilic additions to unsaturated *N*-acyl iminium ions **95** would thus be expected to proceed with lower stereoselectivity than additions to their saturated counterparts **93**, the low diastereoselectivity in the addition to **85** (Scheme 11) is not surprising. On the other hand, nucleophilic additions to the iminium ion **89** occur via axial attack on the more stable conformer in which the carbomethoxy group is equatorial (cf. **93a→94b**).

## 5. Cyclic iminium ions reacting with cyclic dienols

### 5.1. Silyloxyfurans reacting with *N*-acyliminium ions

The addition of silyloxyfurans to cyclic iminium ions has been examined by a number of investigators. However, the first report of such a reaction was from this laboratory and




**Scheme 13.**

involved the addition of **30** to the iminium ion derived from **97** to produce a mixture (8.5:1) of **98** (threo) and **99** (erythro) (Scheme 13).[75] The ratio was determined by $^1$H NMR analysis of the crude reaction mixtures because it was found that a sample of **98**, which was homogeneous by $^1$H NMR, equilibrated during capillary gas chromatographic analysis, giving a 1.9:1 ratio of **98** and **99**. When **98** and **99** were independently resubjected to the conditions of the vinylogous Mannich reaction, no equilibration occurred; however, exposure of **98** and **99** to triethylamine and 4-dimethylaminopyridine did induce equilibration. Hernández recently reported that *N*-benzyloxycarbonylpyroglutamate (**100**) could be oxidatively decarboxylated using iodosobenzene diacetate to produce the same iminium ion intermediate as that derived from **97**.[76] Addition of **30** to the iminium ion thus generated afforded a mixture (6:1) of **98** and **99**.

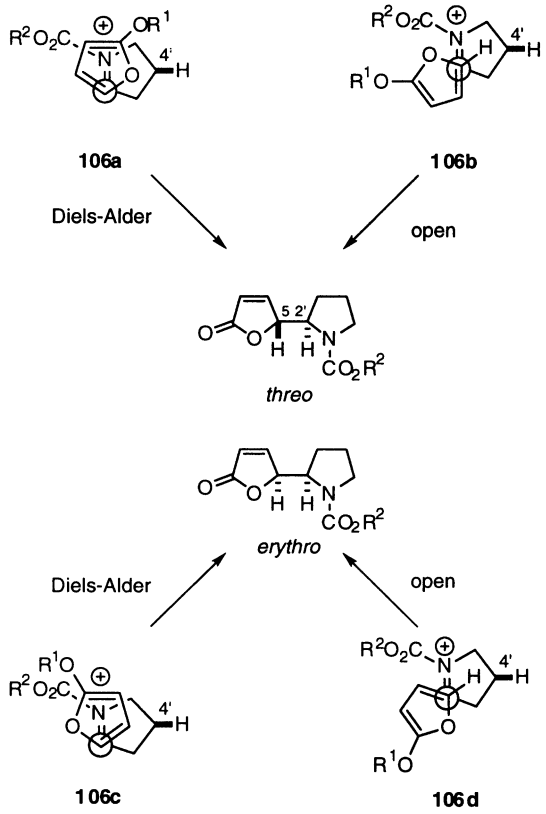
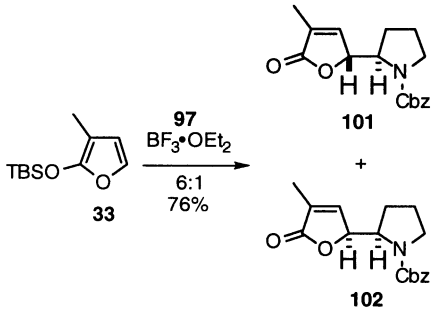


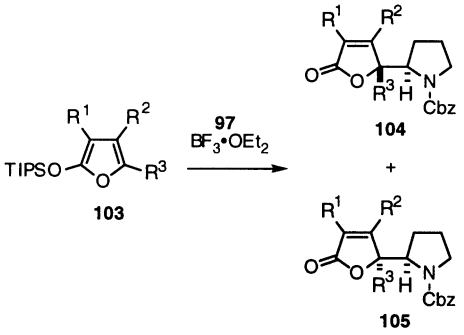

**Fig. 8.** Limiting transition states for the addition of **103** to iminium ions derived from **97**.

In that original report, we found that the silyloxyfuran **33** underwent a vinylogous Mannich reaction with the iminium ion derived from **97** to furnish a mixture (6:1) of **101** and **102** in 76% yield (Eq. (14)).[75] In a more recent study of this same reaction, Morimoto probed the effects of solvent and Lewis acid promoter on the stereoselectivity of the addition and found that the combination of TMS-OTf and $Et_2O$ was optimal although variations were small.[77]




(14)

In order to determine some of the structural features that affect the stereochemical outcome of these vinylogous Mannich reactions, we have recently studied the addition of substituted silyloxyfurans **103** to iminium ions generated from **97** to produce adducts **104** and **105** (Eq. (15)).[78] In each case, the threo adduct **104** was the major stereoisomer formed (3–15:1), though substitution at any carbon of the furan ring was found to be detrimental to the stereoselectivity. Of the singly substituted silyloxyfurans, substitution at C(5) ($R^3$=Me) elicited the largest decrease (3.5:1), whereas substitution at C(4) ($R^2$=Me) was the least damaging to diastereomeric ratios (9:1). Perhaps the most noteworthy fact from this study, though, is that quaternary carbon centers, which are difficult to form,[79–81] were stereoselectively generated (3–5:1) in good to excellent yields (70–96%).




(15)

Based upon transitions states invoked for the additions of nucleophiles to carbonyl groups,[35,82–85] a set of limiting transition states, generalized in Fig. 8, was proposed in which two Diels–Alder-like transition states **106a** and **106c** compete with two open transition states **106b** and **106d**.[75,78] The results of the substituent effect study were supportive of a Diels–Alder-like transition state such as **106a**.

Calculations at the RHF/3-21G* level were conducted in this laboratory to probe the energetics associated with the limiting transition states **106a–d**.[86] By modeling the addition of **107** to **108** (Fig. 9), transition state geometries were found that correspond to each of the four orientations

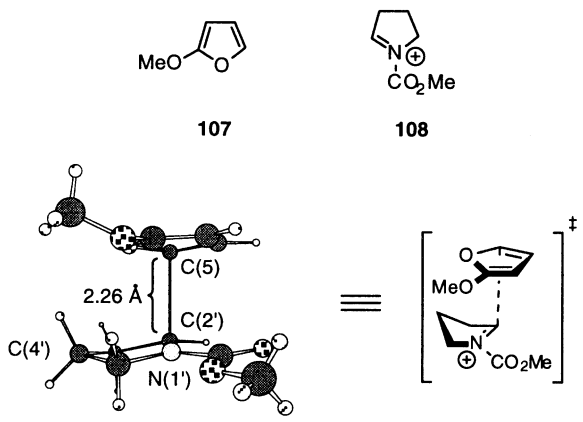
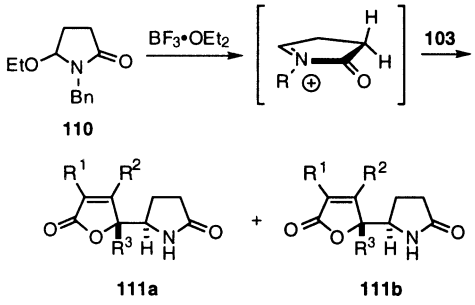



**Fig. 9.** Calculated transition state for configuration **106a**.

proposed in Fig. 8. The threo producing Diels–Alder-like array **106a** was found to be 0.9 kcal/mol lower in energy than the erythro open orientation **106d**, 1.3 kcal/mol lower than the erythro Diels–Alder-like transition state, and 1.8 kcal/mol lower than the threo open array. Examination of the transition state geometries for **106a–d** ($R^1$, $R^2$=Me) also revealed that the iminium ion adopted a shallow envelope conformation with the N(1′)-C(2′) double bond occupying the flattened portion of the envelope and the C(4′) carbon approximately 19–23° out of the N(1′)-C(2′)-C(3′) plane. The envelope was oriented such that the furan approached the iminium ion from inside the fold.

Woerpel has recently proposed such an inside attack to explain the origins of stereoselectivity in nucleophilic additions to five-membered ring oxonium ions,[87] and the transition state geometries calculated for **106a–d** suggest that five-membered ring iminium ions react in an analogous fashion. In general terms, the factors that influence the stereochemical course in the additions of nucleophiles to five-membered ring iminium ions appear to be similar to those discussed in the addition of nucleophiles to six-membered ring iminium ions. The nucleophile must follow a trajectory in which the nucleophile and the developing lone pair on the nitrogen are anti-periplanar (path ***a*** or path ***b***, Fig. 10). The five-membered ring adopts an envelope conformation in which the double bond lies within the flat portion of the envelope. If the nucleophile follows the trajectory of path ***a***, the reaction progresses towards the product conformation **109a**, wherein the substituents on the ring are staggered. If the nucleophile follows the trajectory of path ***b***, however, the transition state collapses to the product conformation **109b**, wherein several of the substituents on the ring are eclipsed. Approach of the nucleophile from inside the fold of the envelope (path ***a***) should therefore be kinetically preferred.

Additions to the iminium ion generated from **110** have also been studied in this laboratory, and the diastereoselectivities in these reactions were found to be low (1.1–2.8:1) (Eq. (16)).[75,78] A crystal structure obtained from the major product of the reaction of **103** ($R^2$=Me) with **110** confirmed that the major product was again the threo adduct **111a** ($R^1$, $R^3$=H; $R^2$=Me). One plausible explanation for the lack of selectivity in these reactions is that the introduction of an additional $sp^2$ center into the five-membered ring iminium ion derived from **110** makes the iminium ion more planar. This increased planarity would reduce the incipient steric interactions between the incoming furan and the iminium ion in transition states **106a–d** making them closer in energy.




(16)

In a further demonstration of the power inherent to this methodology, an asymmetric synthesis of (+)-croomine (**118**) was developed in this laboratory that capitalized on the fact that substitution around the silyloxyfuran ring did not change the predominating threo relationship between the newly formed stereocenters (Scheme 14).[78,88] Disubstituted silyloxyfuran **112** was added to the iminium ion produced in situ by the action of triisopropylsilyl trifluoromethansulfonate (TIPS-OTf) on the pyroglutamate derivative **113**. The crystalline adduct **114**, whose structure was confirmed by single crystal X-ray analysis, was isolated in 32% yield, while the only other isomer detected (<1%) was epimeric at C(**9a**) (croomine numbering). This transformation is remarkable for the degree of asymmetric induction in the formation of a quaternary carbon center.[80,81,89] Removal of the *tert*-butyloxycarbonyl group followed by hydrogenation afforded **115** as the only detectable isomer. Cyclization and ester hydrolysis furnished acid **116**. Generation of a second iminium ion from the amino acid **116** following the protocol of Rapoport[90] and subsequent addition of **103** ($R^1$=Me) gave a mixture (2:1) of **117** and

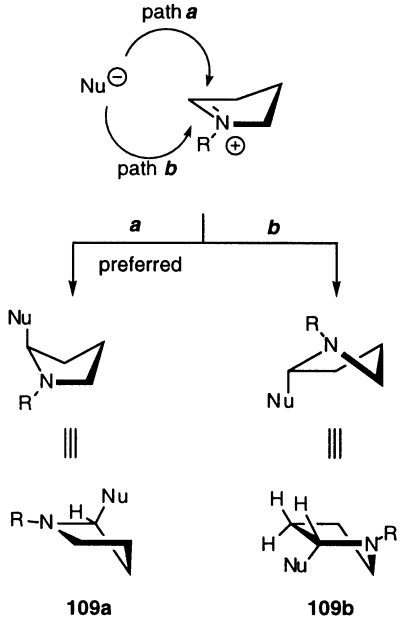
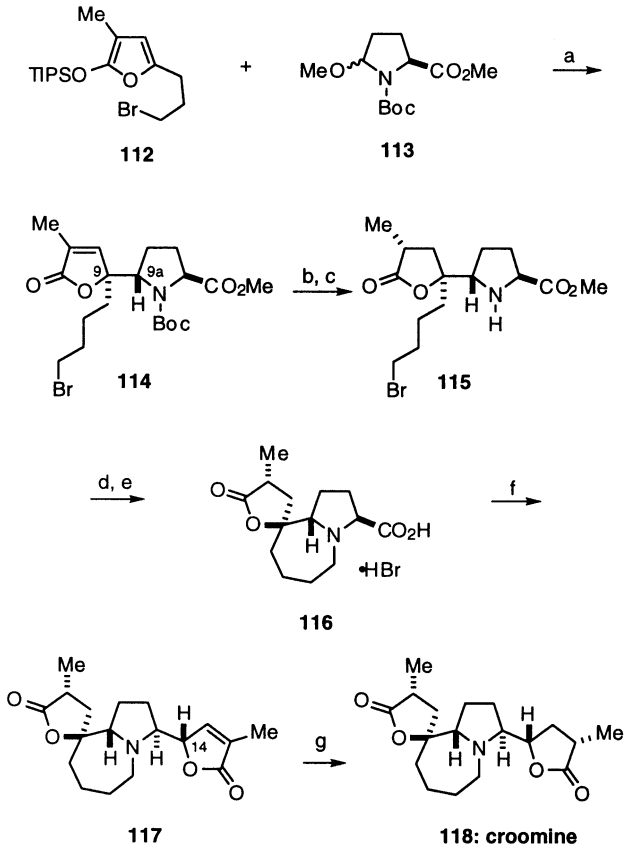



**Fig. 10.** Stereoelectronic and steric interactions in nucleophilic additions to five-membered ring iminium ions.

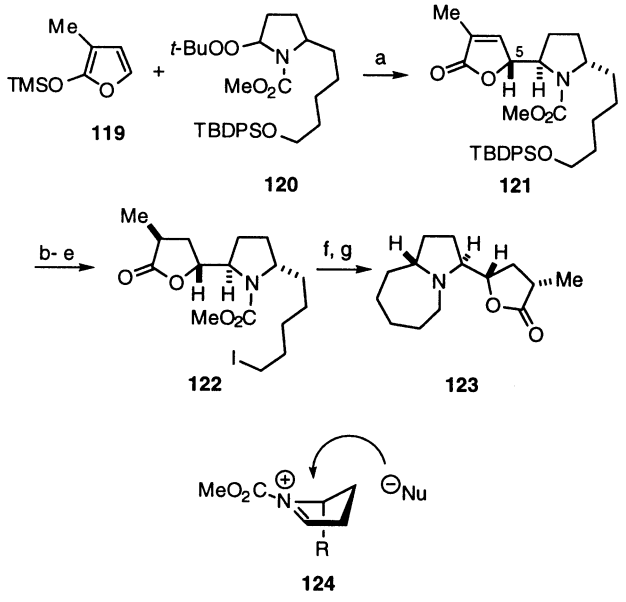



**Scheme 14.** (a) TIPS-OTf, 32%. (b) $CF_3CO_2H$, 100%. (c) 3% Rh/C, $H_2$, 98%. (d) NMM, DMF, reflux, 80%. (e) 3 M HBr, 93%. (f) $POCl_3$, DMF, then **103** ($R^1$=Me), 47%. (g) 10% Pd/C, $H_2$, 10% HCl, 85%.

the C(14) epimer in 47% yield. Finally, hydrogenation produced **118**. While the two key vinylogous Mannich reactions proceeded in only modest yields, the brevity of the synthesis is notable.

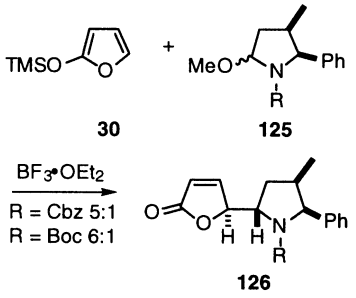
Morimoto and coworkers have published a similar route to the azabicyclic core common to croomine and related Stemona alkaloids (Scheme 15).[91] Addition of **119** to the iminium ion arising from racemic **120** produced a mixture (9:1) of **121** (threo) and its C(5) epimer in 91% yield. Hydride reduction and conversion of the protected hydroxy functional group to an iodide gave carbamate **122**. Deprotection of the nitrogen followed by cyclization gave the azabicyclic core **123** in 50% yield. The stereoselection in the addition of **119** to the iminium ion derived from **120** follows the model outlined in Fig. 10. In this case, the methoxycarbonyl group forces the iminium ion side-chain into an axial orientation as indicated in **124**. No comment was made on the facial selectivity with regard to the silyloxyfuran, but these results are consistent with the results observed in this laboratory (cf. Scheme 13).[75]

Hanessian demonstrated that changing the nitrogen-protecting group on the iminium precursor may not significantly change the stereoselectivity.[92] For example, addition of **30** to the iminium ion derived from **125** (R=Boc) produced a mixture (6:1) of diastereomers wherein the threo adduct **126** predominated (Eq. (17)); no addition syn to the phenyl group was observed. When the protecting



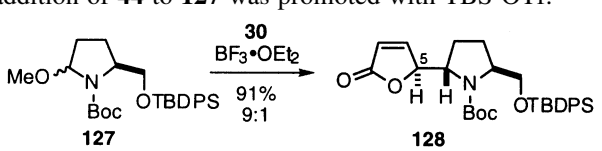

**Scheme 15.** (a) TMS-OTf, 91%. (b) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, 91%. (c) TBAF. (d) MsCl, TEA. (e) NaI, 87% for three steps. (f) TMSI. (g) Δ, $CH_3CN$, 50% for two steps.

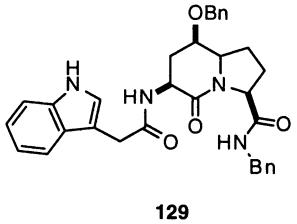
group was changed from *tert*-butoxycarbonyl (Boc) to Cbz, the selectivity remained nearly the same at 5:1.




(17)

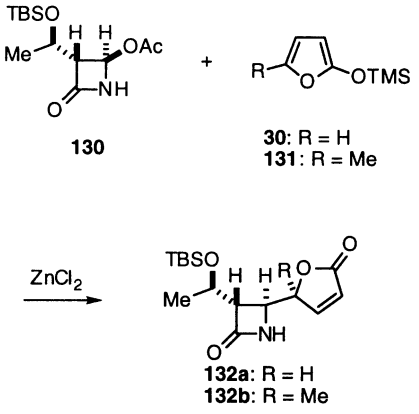
In another example, Hanessian has used the Lewis acid promoted reaction between **30** and the iminium ion derived from **127** to build β-turn peptidomimetic scaffolds such as **129**, which mimics tachykinin NK-2 receptor antagonists (Eq. (18)).[93] In this case, the vinylogous Mannich reaction proceeded to give a mixture (9:1) of adducts **128** and the corresponding C(5) epimer. Addition to the face of the iminium ion syn to the protected hydroxymethyl group was not observed in this case. Casiraghi has observed similar results when *tert*-butyldimethylsilyloxyfuran (**44**) was employed as the dienol reaction partner. Thus, **128** was reported as the only adduct (78% yield) when the addition of **44** to **127** was promoted with TBS-OTf.[94]



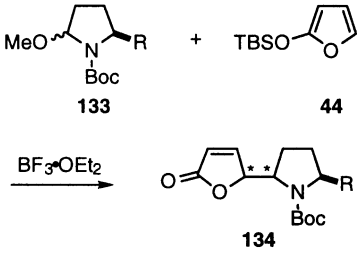

(18)

Hanessian has also reported that the additions of 2-silyloxyfurans to iminium ions derived from β-lactams are highly selective.[95] For example, the $ZnCl_2$ mediated reaction of **30** with **130** produced **132a** in 85% yield as a mixture (98:2) in which the threo product predominated (Eq. (19)). Similarly, the use of furan **131** selectively produced the threo diastereomer **132b** in 89–92% yield. Interestingly, when $BF_3{\cdot}OEt_2$ was employed as the promoter, the diastereoselection in the addition of **30** to **130** fell to 3:2, only slightly favoring the threo isomer.




(19)

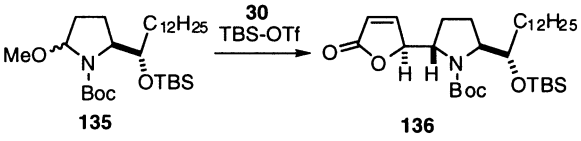
Figadère and coworkers have studied the addition of **44** to the iminium ions derived from a variety of pyroglutamate esters **133**, but the reactions were reported to be unselective (Eq. (20)).[96] For example, the $BF_3{\cdot}OEt_2$ promoted addition of **44** to **133** (R=$CO_2$Et) was reported to produce a mixture (15:7:22:56) of all four diastereomers of **134**. The stereochemical relationships were determined by analysis of NMR data, but details of these NMR experiments were not disclosed. Which products were *cis* and which were *trans* to the carboxylate was also not discussed, but the previous examples would suggest a 22:78 *cis*/*trans* ratio. These ratios did not change significantly when other Lewis acids such as $TrClO_4$, $Sc(ClO_4)_3$, $TiCl_4$, and $SnCl_4$ were employed. In addition to the poor stereoselectivities, the yields were universally poor (28–49%).




(20)

The lack of selectivity in these reactions was proposed to arise from a specific chelation event that changes the reactive conformation of the iminium ion (Fig. 11).[97] Three conformations of the intermediate iminium ion were suggested: **A**, where the C(5) substituent is pseudoaxial; **B**, where the C(5) substituent is pseudoequatorial; and **C**, where a Lewis acid chelates both carbonyl groups and forces the C(5) substituent into a pseudoequatorial position. The proposed trajectory of the nucleophile was consistent with the inside attack model (Fig. 10), and conformation **C** was invoked to explain addition to the same face of the iminium ion as the carbomethoxy group (*cis* addition). However, the observation that the product distribution for the addition of **44**–**133** did not change when a potentially bis-chelating Lewis acid such as $TiCl_4$ was used vis-à-vis a non-bis-chelating Lewis acid such as $BF_3{\cdot}OEt_2$ or $TrClO_4$ renders this explanation somewhat problematic.

In the context of developing methods for acetogenin synthesis, Figadère reported the more selective reaction of **30** with the pyrrolidine **135** in the presence of TMS-OTf (Eq. (21)).[97] This reaction was reported to produce a mixture (3:1) of **136** and the corresponding erythro diastereomer in 73% yield.




(21)

Because C(5) substituted silyloxyfurans could be successfully used in vinylogous Mannich reactions (see Eq. (14) and Scheme 14), investigations were initiated in this laboratory to apply such constructions to the synthesis of a representative member of the indolizidine family of alkaloid natural products. Pumiliotoxin 251D (**143**) was selected as a target, and the synthesis was initiated by the Lewis acid-mediated reaction of silyloxyfuran **138** with the pyroglutamate derivative **137** to give a mixture (1.4:1) of isomeric adducts **139** and the C(5) epimer **140** in 48% yield (Scheme 16).[98] In contrast to Figadère's reported selectivity in the additions of silyloxyfurans to pyroglutamate ester derived iminium ions,[96] no products arising from addition *cis* to the carbomethoxy group were detected. Determining the ratio of the diastereomers in the crude reaction mixture was initially complicated by the presence of four sets of signals (1.0:1.4:4.0:5.8) when the $^1$H NMR spectrum was obtained at ambient temperature. However, when the $^1$H NMR was measured at 100°C, these four signals coalesced into two sets of signals in a 1.4:1 ratio. This result indicates that there are two preferred rotational isomers for each of the two diastereomers at lower temperature. The structures of these diastereomers were confirmed by single crystal X-ray analyses of the bicyclic lactams **141** and **142** generated from **139** and **140** by hydrogenolysis followed by exposure to NaOMe.

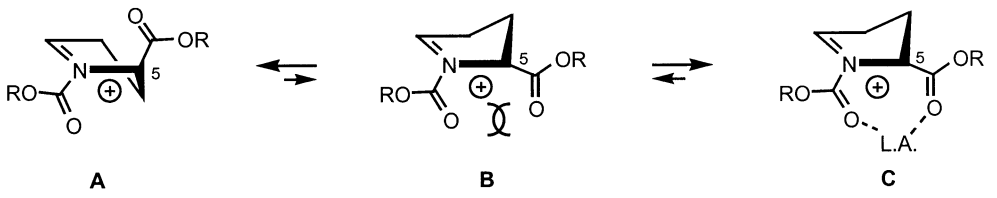
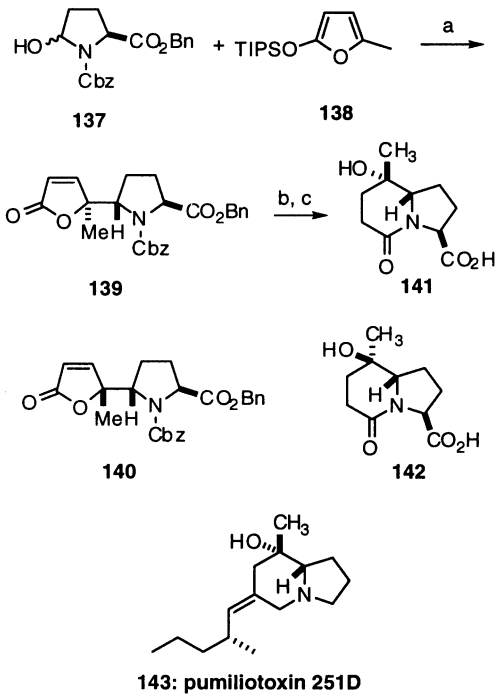



**Fig. 11.** Proposed conformational bias in the nucleophilic addition to pyroglutamate derived iminium ions.

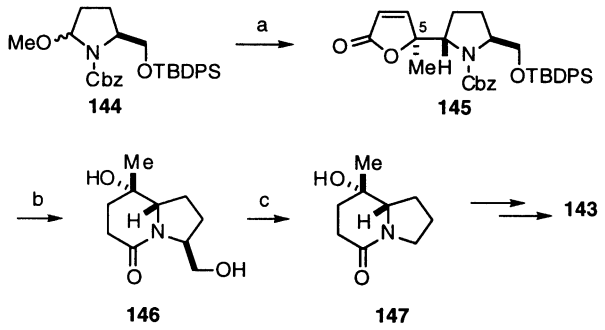



**Scheme 16.** (a) $Et_2AlCl$, 48% (1.4:1). (b) Pd/C, $H_2$. (c) NaOMe, 92% for two steps.

The poor selectivity and modest yield observed in the reaction between **137** and **138** prompted examination of another iminium ion precursor. When **144** was used in the vinylogous Mannich reaction, a mixture (4.8:1) favoring **145** was produced in 58% yield (Scheme 17). Again, addition only to the face anti to the hydroxymethyl group was observed, and the presence of rotational isomers complicated the $^1H$ NMR spectrum obtained at ambient temperature. Hydrogenation of the butenolide followed by the addition of acid resulted in the global deprotection and *O*⟶*N* acyl transfer to furnish **146** in 66% yield and in one pot. Removal of the extraneous hydroxymethyl group was accomplished with Raney nickel to produce **147**,[99] an advanced intermediate in several previous syntheses of **143**.

## 5.2. Silyloxyfurans reacting with *O*-silylated nitrones

Trombini and Lombardi have reported that the addition of 2-trimethylsilyloxyfuran (**30**) to the iminium ion derived from the cyclic nitrone **148** gave a mixture (4.5:1) of butenolides **149** (erythro) and the corresponding C(5) epimer (Scheme 18).[100] Selective deprotection of the trimethylsilyl ether afforded the tricycle **150** in 92% yield. Reduction of the lactone to a lactol using Dibal-H followed by catalytic hydrogenation afforded **151** in 66% yield. It is noteworthy that this vinylogous Mannich reaction, which produces erythro adducts selectively, is stereochemically complimentary to the threo selective addition of silyloxyfuran to *N*-acyliminium ions.

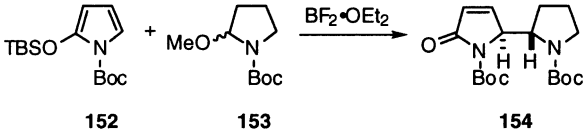



**Scheme 17.** (a) TMS-OTf, **138**, 57% (4.8:1). (b) Pd/C, $H_2$; then HCl, 66%. (c) Ra–Ni (W-2), PhMe, reflux, 71%.

The observed stereoselectivity was explained by invoking an aldol-like transition state that was stabilized by an electrostatic interaction of the nitrone oxygen with the cationic charge developing on C(4) of the furan as shown in **A** (Fig. 12, see also Fig. 3). The alternative aldol-like transition state **B** was suggested to be disfavored by an oxygen–oxygen lone pair repulsion as shown.

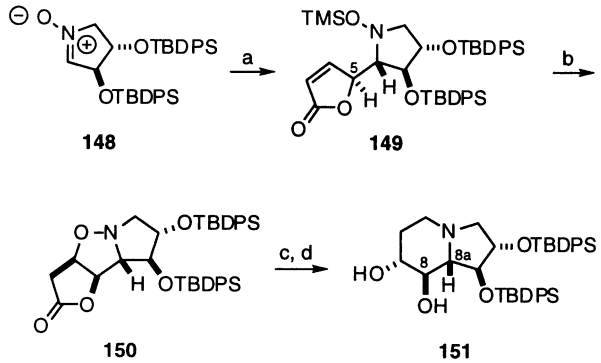
## 5.3. Silyloxypyrroles and thiophenes reacting with *N*-acyliminium ions

Figadère was the first to report the $BF_3{\cdot}OEt_2$ mediated addition of silyloxypyrrole **152** to the unsubstituted pyrrolidine **153** to furnish a mixture (7.1:1) of adducts in 40% yield favoring the threo adduct **154** (Eq. (22)).[96] The basis for this structural assignment was not discussed.



(22)

In developing a modular approach to the construction of acetogenin analogs, Casiraghi and Zanardi have studied the reactions of the 2-silyoxythiophene **155** and the 2-silyloxypyrrole **152** with **156**.[101] They found that **155** added to the iminium ion generated by the action of TBS-OTf on **156** to produce the threo adduct **157** as the only observed diastereomer in 47% yield (Scheme 19). On the other hand, **152** reacted with **156** under identical conditions to afford a mixture (3:2) of the erythro adducts **158** and **159** in 60% yield. Interestingly, the major product in this latter reaction arose from addition of the furan to the *more* hindered face of the iminium ion *cis* to the protected hydroxymethyl group. In a preliminary communication, **158** was incorrectly designated as having a C(5)-C(2′) threo relationship and arising from addition to the face opposite the protected hydroxymethyl group.[102]




**Scheme 18.** (a) TMS-OTf, **30**, 71% (4.5:1). (b) TFA, then $SiO_2$, 92%. (c) Dibal-H, −78°C, 67%. (d) $Pd(OH)_2/C$, $H_2$, 66%.

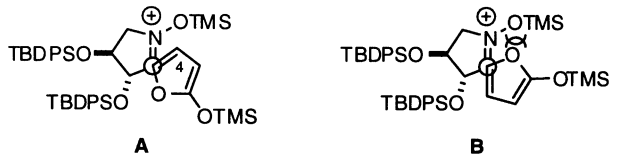
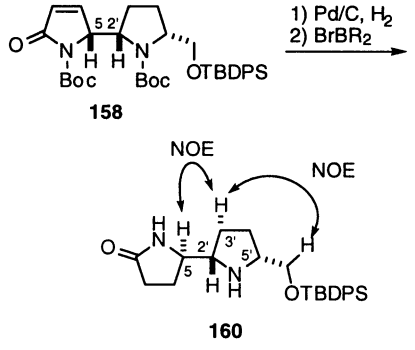



**Fig. 12.** Proposed transition states for the addition of **30** to the iminium ion derived from **148**.

These results contradict the stereochemical assignments made by Figadère for compound **154** (Eq. (22)). Casiraghi reported that the reaction mixtures arising from the addition of **152** to the iminium ion derived from **156** were complicated by rotational isomers, so the products were reduced, and the Boc groups were removed (Eq. (23)).[101] An extensive battery of $^1$H NMR experiments were then performed on the amino lactams. The relative stereochemical relationships were determined by NOE experiments wherein irradiation of the proton on the hydroxymethyl group of **160** enhanced the resonance of the C(3′) on the alpha face of the amine as shown in Eq. (23). Irradiation of the C(5) proton also enhanced the α-C(3′) proton. The conformation of **160** depicted in Eq. (23) was selected from a set of low energy conformations calculated by molecular mechanics using the TRIPOS force field.

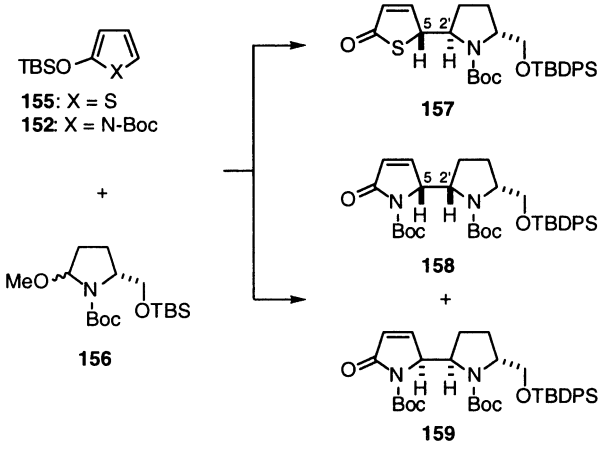



(23)

## 6. Intramolecular vinylogous Mannich reactions

### 6.1. Rugulovasines A and B

One of the first examples of an intramolecular vinylogous Mannich reaction was proposed by Weinreb and colleagues in the context of rationalizing the natural occurrence of the two diastereomeric Ergot alkaloids rugulovasines A and B (**37a**,**b**), which were isolated in racemic form.[103] They suggested that the interconversion of these four stereoisomers might proceed via a retro-vinylogous Mannich/vinylogous Mannich pathway involving the common achiral intermediate **161** (Fig. 13). Rebek later reported mechanistic studies that supported this hypothesis.[104]




**Scheme 19.**

Inspired by these observations, a second-generation, biomimetic strategy for the preparation of **37a** and **37b** (cf. Scheme 2) was developed in this laboratory.[105] The key element of the synthetic plan was to prepare an intermediate like **161** that could cyclize by an intramolecular vinylogous Mannich reaction (Scheme 20). This goal was realized when nitrile **162** was reduced by Dibal-H to give the imine **163** that, when protonated, underwent spontaneous cyclization as predicted to furnish **164** as a mixture (2:1) of diastereomers. Sequential *N*-acylation and methylation provided **165**, and stepwise deprotection then furnished a mixture (2:1) of the natural products **37a**,**b**.

### 6.2. Yohimbone

While exploring iminium ion initiated cyclizations of indole derivatives, Winterfeldt and Benson discovered an interesting process whereby treatment of the enol ether **166** with acetic acid and formaldehyde produced yohimbone **170**

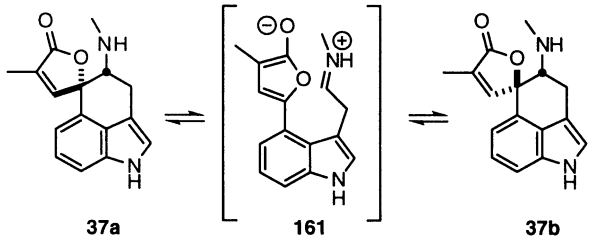
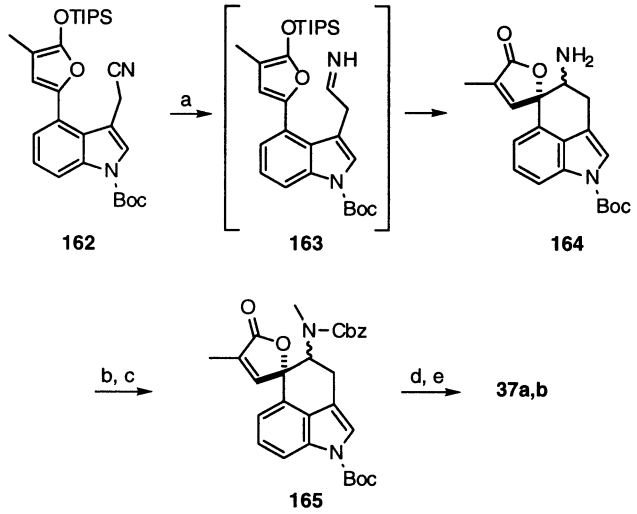
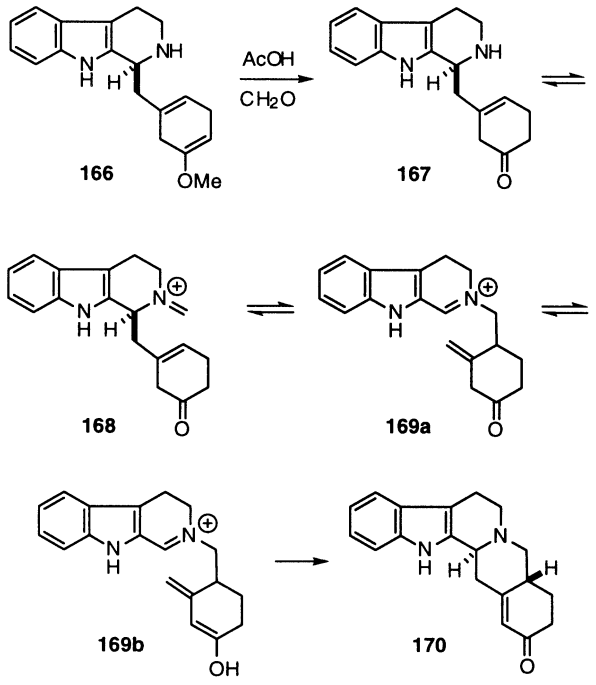



**Fig. 13.** The interconversion of rugulovasines A and B.




**Scheme 20.** (a) Dibal-H, −78°C→rt; then $SiO_2$, 71%. (b) Cbz-OSuc, TEA, DMF, 95%. (c) NaH, MeI, DMF, 0°C, 89%. (d) $Cs_2CO_3$, MeOH. (e) $H_2$, Pd/C, 75% for two steps.

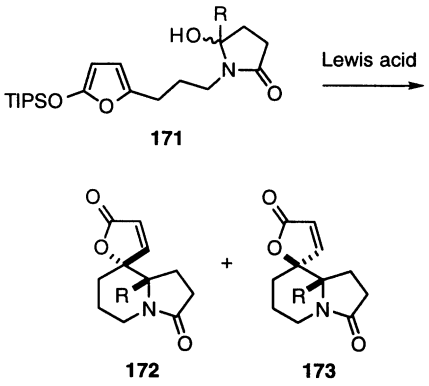



**Scheme 21.**

(Scheme 21).[106] Spectral evidence suggested that a rapid series of equilibrations occurred beginning when amino ketone **167** condensed with formaldehyde to produce the iminium ion **168**. This iminium ion underwent a facile aza-Cope rearrangement to furnish **169a**. Subsequent keto-enol tautomerism gave the dienol **169b** that cyclized to give the final product **170**. Some years later, Meyers studied the nature of the rapid sigmatropic rearrangement by subjecting (*S*)-**166** to Winterfeldt's conditions and determined that the system's stereochemical integrity was lost upon equilibration of **168** and **169a**.[107] Yohimbone (**170**) was isolated as a single, though racemic, diastereomer in 75% yield from **166**.

### 6.3. Spirocyclic lactone formation

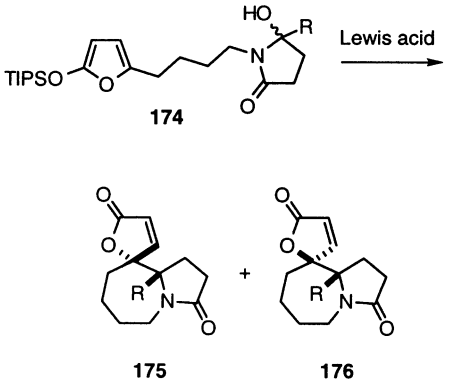
The cyclizations of silyloxyfurans tethered to *N*-acyl iminium ion precursors have also been studied in this laboratory.[108] In contrast to the related intermolecular reactions presented in Sections 5.1 and 5.2, the stereochemical relationship between the newly formed centers in the major product from these cyclizations was erythro. For example, when **171** (R=H) was exposed to Lewis acids, a mixture (6:1) of the erythro adduct **172** and the threo adduct **173** was produced in 83% yield (Eq. (24)). When R=H, the cyclization could also be effected by activating the hydroxyl group with trifluoroacetic anhydride to give similar mixtures of diastereomeric adducts. Varying the Lewis acid was found to have little effect, but lower temperatures increased the selectivity. When R=Me, activation of the hydroxyl group with trifluoroacetic anhydride failed to induce cyclization as did a variety of Lewis acids. Ethereal solutions of $LiClO_4$ alone produced the desired tricycles as a mixture (20:1) of diastereomers. Ethereal $LiClO_4$ solutions triggered the cyclization of **171** (R=H) to afford a mixture (11:1) of diastereomers.




(24)

The increase in selectivity when cyclizations were effected by $LiClO_4/Et_2O$ solutions as compared to reactions promoted by other Lewis acids is interesting. Although it is premature to propose a specific rationale for this phenomenon, other studies designed to elucidate the origins of the increase in diastereoselectivity obtained with the Diels–Alder and other reactions conducted in $LiClO_4/Et_2O$ solutions have led to the suggestion that chelation effects might be involved.[109–112]

The formation of seven-membered rings by intramolecular vinylogous Mannich reactions was much less erythro selective. For example, exposure of **174** (R=H) to Lewis acid produced a mixture (1.3:1) of **175** and **176** in 58% yield (Eq. (25)). When R=Me, it was necessary to use $LiClO_4/Et_2O$ to promote the cyclization, and a mixture (2:1) of **175** and **176** was obtained in 32% yield. Similarly, cyclization of **174** (R=H) in the presence of $LiClO_4$ gave a mixture (2:1) of **175** and **176** in 47% yield.




(25)

## 7. Conclusions

While considerable progress has been made in refining the vinylogous Mannich reaction, a number of areas still require attention if this method is to be exploited more extensively in synthesis. First, a careful study of reactions involving acyclic dienols and Lewis acid activated imines may help further the understanding of the reaction mechanism in terms of cycloaddition vs. addition-cyclization pathways. Second, the use of cyclic dienols other than silyloxyfurans warrants further examination. Closer scrutiny of the effects that quenching reactions with basic solutions have on product distribution may lead to a clearer understanding

of the kinetic vs. thermodynamic product distributions that arise from these reactions. In this context, care should be exercised in interpreting stereochemical results of vinylogous Mannich reactions unless it has been demonstrated that the products do not equilibrate during the reaction or quenching. The intramolecular reactions, in particular, have received little attention. The known examples of intramolecular vinylogous Mannich reactions have not adequately probed the origins of stereoselectivity, and no predictive models have been offered. If this were an easily predictable process, a variety of complex heterocyclic compounds could be accessed via relatively short synthetic routes.

Although some investigations have helped define the nature of the possible transition state geometries, this remains an area requiring closer scrutiny. Several transition state models have been proposed, but the paucity of studies designed to directly probe the transition states of vinylogous Mannich reactions has made drawing meaningful conclusions difficult. The construction of a general transition state model that explains the reactivity of more than one specific subset of vinylogous Mannich reactions (e.g. silyloxyfurans reacting with nitrones or silyloxyfurans reacting with cyclic *N*-acyliminium ions) would allow for a better understanding of the forces that influence the stereochemical course of the vinylogous Mannich reaction. Such a reliable model would undoubtedly make this reaction a more predictable and versatile tool for synthetic chemists.

The development of the vinylogous Mannich reaction has provided a powerful, often stereoselective, carbon–carbon bond forming tool that allows for the facile synthesis of a number of complex natural and unnatural products. Notably, the predictability of the stereochemical outcome in intermolecular reactions has allowed for the asymmetric construction of quaternary centers in the synthesis of natural products, a highly coveted process in synthetic organic chemistry. Future investigations will undoubtedly continue to demonstrate the power and utility of this important carbon–carbon bond forming process.

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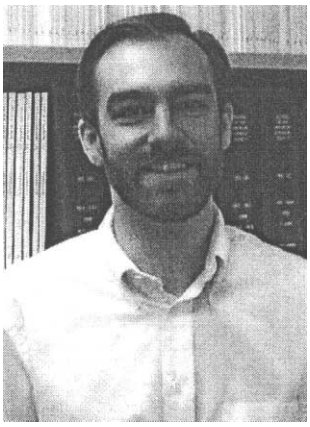
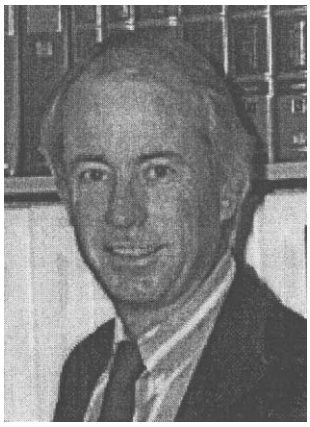
**Biographical sketch**



**Scott K. Bur** received his B.S. from the University of Michigan in 1994. After an externship with Parke-Davis pharmaceuticals in Ann Arbor, he attended the University of Texas at Austin to work with Professor Stephen Martin, earning a Ph.D. in August 2000. He is currently an NIH postdoctoral fellow in the laboratories of Professor Albert Padwa at Emory University. His research interests include heterocyclic methodology, natural product synthesis, and the application of computational methods to synthetic organic problems.



**Stephen Martin**, a native of New Mexico, received his B.S. degree in chemistry from the University of New Mexico in 1968 and his Ph.D. degree from Princeton University in 1972. After a postdoctoral year at the University of Munich and another at Massachusetts Institute of Technology, 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 the concise syntheses of complex natural products that exhibit useful biological activity, whereas in the latter he has been involved in the design and synthesis of novel peptide mimics and the study of the mechanism, structure and function of enzymes that hydrolyze phospholipids. He has been honored for his outstanding accomplishments by receiving a number of awards, including the Arthur C. Cope Scholar Award in 1996 and a Alexander von Humboldt Senior Scientist Award for the period 1995–1997. He has served on numerous editorial boards, and he is presently the regional editor of *Tetrahedron* for the Americas.