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General strategies for the stereoselective synthesis of alkaloid natural products

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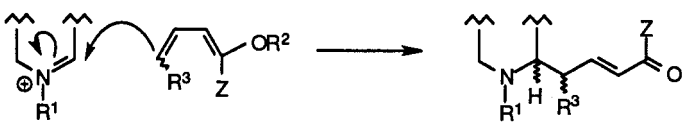
Abstract. We have recently discovered that vinylogous Mannich reactions are powerful strategy-level reactions for the construction of skeletal subunits common to a variety of alkaloids. Such reactions have been implemented in tandem with hetero Diels-Alder reactions for the synthesis of the representative heteroyohimboid alkaloid tetrahydroalstonine (**4**). One of the intermediates in the synthesis of **4** was then converted into **6**, which was subjected to a novel, biogenetically-patterned oxidative reorganization to give the *Strychnos* alkaloid akuammacine (**10**). Both bimolecular and intramolecular vinylogous Mannich reactions have been applied to the syntheses of the *Ergot* alkaloids rugulovasines A and B (**21** and **22**, respectively), and two consecutive bimolecular vinylogous Mannich reactions of furans have been implemented for the rapid assembly of a tetracyclic intermediate in an asymmetric total synthesis of croomine (**40**).

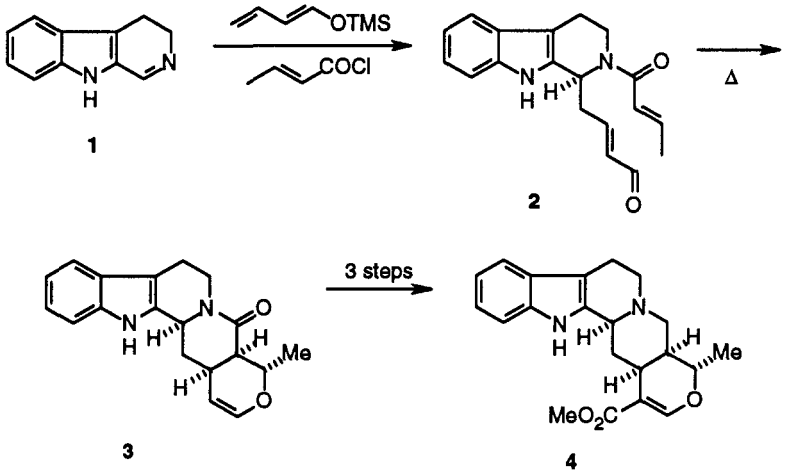
One of the major challenges in contemporary synthetic organic chemistry is the design and execution of concise approaches to complex natural products. Strategies that utilize reactions that rapidly assemble the skeletal framework of such natural targets are thus especially attractive. In the context of developing new and general strategies for the facile synthesis of complex alkaloid natural products possessing diverse structural features, we have recently explored constructions involving novel variants of inter- and intramolecular vinylogous Mannich reactions in tandem with selected biomimetic transformations. In this context, we discovered that a vinylogous Mannich reaction could be used for the facile preparation of δ-amino-α,β-unsaturated carbonyl compounds, which are versatile intermediates in alkaloid synthesis (eq 1). Having identified the potential for such processes, we began a general study of vinylogous Mannich reactions to establish their efficiency, stereochemistry, scope, and limitations. The use of such constructions in contemporary alkaloid synthesis constitutes the substance of the present report.



(1)

Synthesis of Heteroyohimboid Alkaloids via Tandem Vinylogous Mannich and Diels-Alder Reactions. One of the first examples in our laboratory of a vinylogous Mannich reaction involved the addition of 1-trimethylsilyloxy butadiene to the *N*-acyliminium ion derived from the reaction of **1** with crotonyl chloride to give **2** (Scheme 1).[1] Cyclization of **2** via an intramolecular hetero Diels-Alder reaction gave **3**, which was then elaborated into racemic tetrahydroalstonine (**4**) in a total of eight steps from commercially available starting materials. We subsequently extended this technology to the asymmetric syntheses of several important heteroyohimboid alkaloids (**4**) from L-tryptophan.[2] These syntheses are among the shortest entries to complex alkaloids of the indole family, and they illustrate the potential of applying vinylogous Mannich reactions in the design of new strategies for alkaloid synthesis.

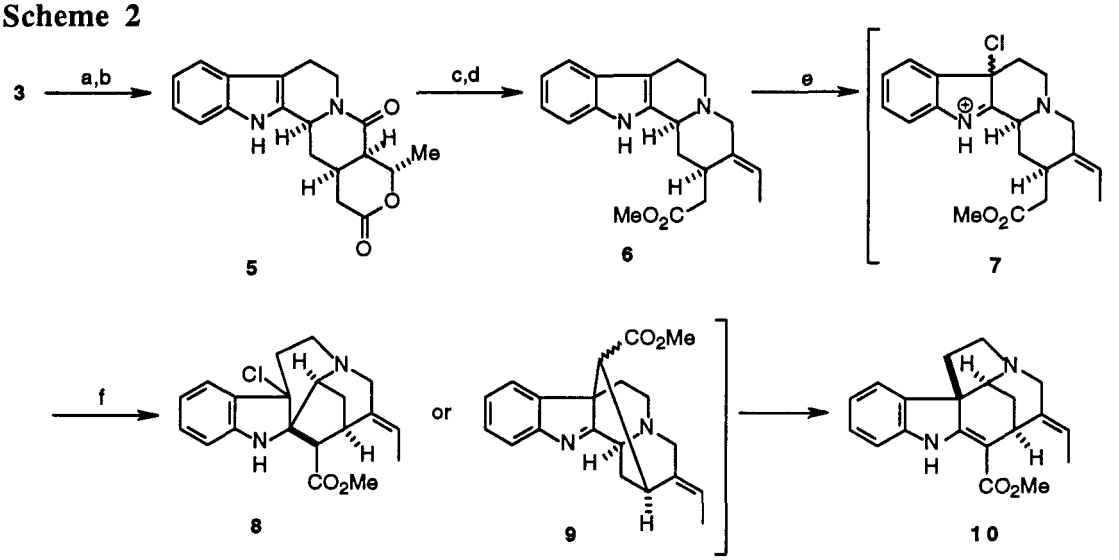
Scheme 1



1 2 3 4

A Biogenetic Approach to the *Strychnos* Alkaloids. Total Synthesis of Akuammacine (10). The structurally-complex alkaloids of the *Strychnos* family have inspired numerous synthetic investigations. Although strychnine (**11**) has recently been a focal point of such studies,[3] there have also been total syntheses of akuammacine (**10**).[4] In order to explore a novel biomimetic entry to these alkaloids,[5] we converted the pentacyclic intermediate **3**, which had been accessed in only four steps from tryptamine via consecutive vinylogous Mannich and Diels-Alder reactions (Scheme 1), into deformyl geissoschizine (**6**), a well known intermediate in the syntheses of corynantheoid alkaloids (Scheme 2).[6] Subsequent reaction of **6** with *tert*-butylhypochlorite in the presence of $SnCl_4$ followed by treatment of the intermediate

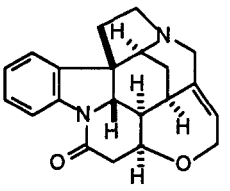
Scheme 2



5 6 7 8 9 10

(a) *p*-TsOH, aq. THF. (b) $(Ph_3P)_3RuCl_2$, Et_3N, $PhCH{=}CHCOCH_3$. (c) NaOMe, MeOH; $(COCl)_2$, 0 °C. (d) Me_3OBF_4, 2,6-(*t*-Bu)$_2$-Py; $NaBH_4$. (e)$SnCl_4$, toluene; *tert*-BuOCl, -20 °C. (f) LiHMDS, -40 °C → rt.

chloroindolinine **7** with lithium hexamethyldisilazide gave (±)-akuammacine (**10**). The mechanism of this biogenetically-patterned transformation has not been established; however, it seems likely that intermediates related to **8** or **9** are involved subsequent to the initial oxidation of the indole ring with electropositive halogen to give **7**. The applications of this and related biomimetic transformations to the facile syntheses of other indole alkaloids including strychnine (**11**) are currently being investigated.



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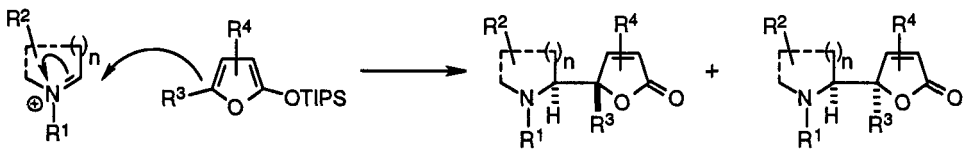
Furans as Reaction Partners in Vinylogous Mannich Reactions. It is apparent that vinylogous Mannich reactions of acyclic, electron-rich dienes allow rapid access to skeletal arrays that may be quickly elaborated into complex alkaloids, and it occurred to us that such additions deserved more extensive examination as a general construction for the synthesis of selected alkaloid natural products. One general strategy may be exemplified by the nucleophilic addition of a substituted 2-trialkylsilyloxy furan **13** to a cyclic iminium ion **12** to provide a mixture of the isomeric adducts ***threo*-14** and ***erythro*-14** in which the ***threo*-14** product typically dominates (Scheme 3).[7,8] Although we are currently examining the structural features that influence the stereochemical outcome of these additions, the underlying viability of vinylogous Mannich reactions of furans to elaborate structural subunits found in alkaloids had been established. It remained to apply these reactions to problems in alkaloid synthesis.

Scheme 3

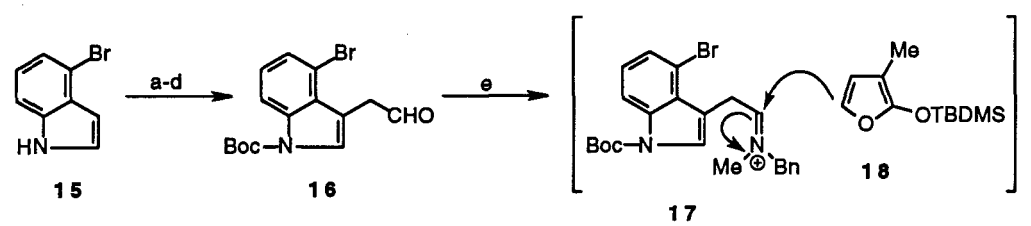


12 13 *threo*-14 *erythro*-14

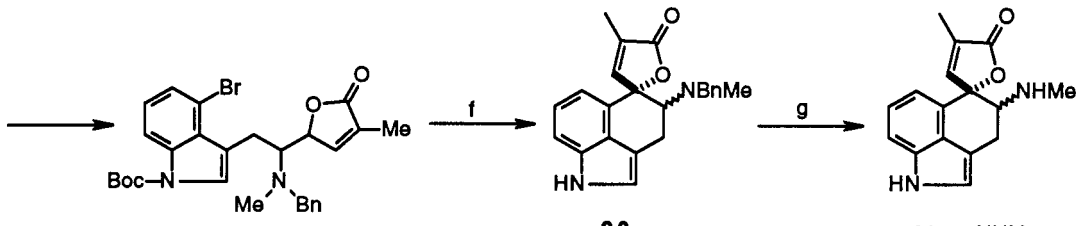
n = 1, 2

Total Synthesis of Ergot Alkaloids. Owing to their biological activity the *Ergot* alkaloids have long been the focus of attention,[9] and several members of this class have piqued our own interest. We envisioned that a general strategy for the synthesis of a number of *Ergot* alkaloids could be developed in which vinylogous Mannich reactions played a pivotal role. Such a construction was first applied to the design of a concise syntheses of rugulovasines A and B (**21** and **22**, respectively)[10] according to the plan outlined in Scheme 4.[11] Condensation of the aldehyde **16**, which was prepared in four steps from commercially available 4-bromoindole (**15**), with *N*-benzyl-*N*-methylamine followed by reaction of the iminium salt **17** thus produced *in situ* with the furan **18** gave **19** as a mixture of diastereomers. Cyclization of **19** via an $S_{RN}1$ reaction then provided **20**, which was then deprotected to give a mixture (1:2) of rugulovasines A and B in a total of only seven chemical operations.

Scheme 4



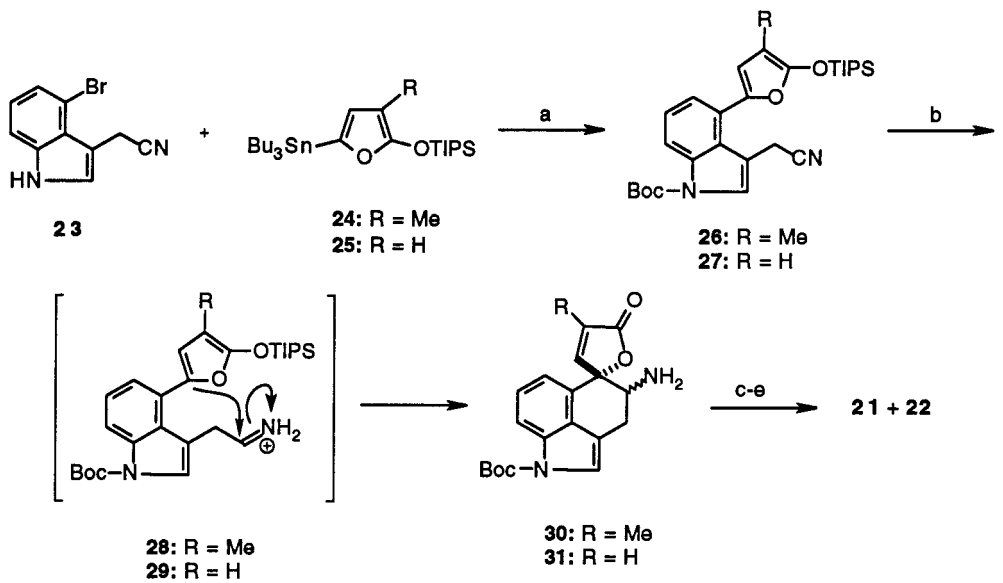
15 16 17 18



(a) $HNMe_2$, CH_2O. (b) KCN, aq. DMF (1:1). (c) $(Boc)_2O$, DMAP, Et_3N. (d) DIBAL-H. (e) BnNHMe, $H^{\oplus}$. (f) *tert*-BuOK, NH_3 (liq), hv. (g) HCl; H_2, 20% $Pd(OH)_2$, EtOH, rt.

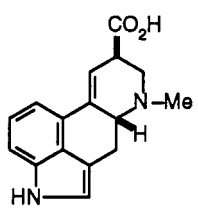
An intramolecular variant of this reaction was then examined as a potential general route to the *Ergot* alkaloids.[12] The key intermediate **26** was prepared by the Stille coupling of the bromo indole **23**, which was prepared in two steps from **15**, with the substituted furan **24** (Scheme 5). Hydride reduction of the nitrile group in **26** then gave the iminium salt **28** *in situ* that underwent facile cyclization by a vinylogous Mannich reaction to give **30** as mixture (ca. 2:1) of diastereomers. *N*-Methylation of **30** was achieved via a derived

Scheme 5



(a) $Pd(Ph_3P)_4$, PhMe, K_2CO_3, Δ; $(Boc)_2O$, DMAP, Et_3N. (b) DIBAL-H; SiO_2. (c) Cbz-OSuc, Et_3N. (d) NaH, MeI. (e) 30% HBr, HOAc.

carbamate, and subsequent global deprotection then gave rugulovasines A and B (**21** and **22**). Similarly, **23** was converted into **31**, and tactics for converting this substance into lysergic acid (**32**) are being studied.

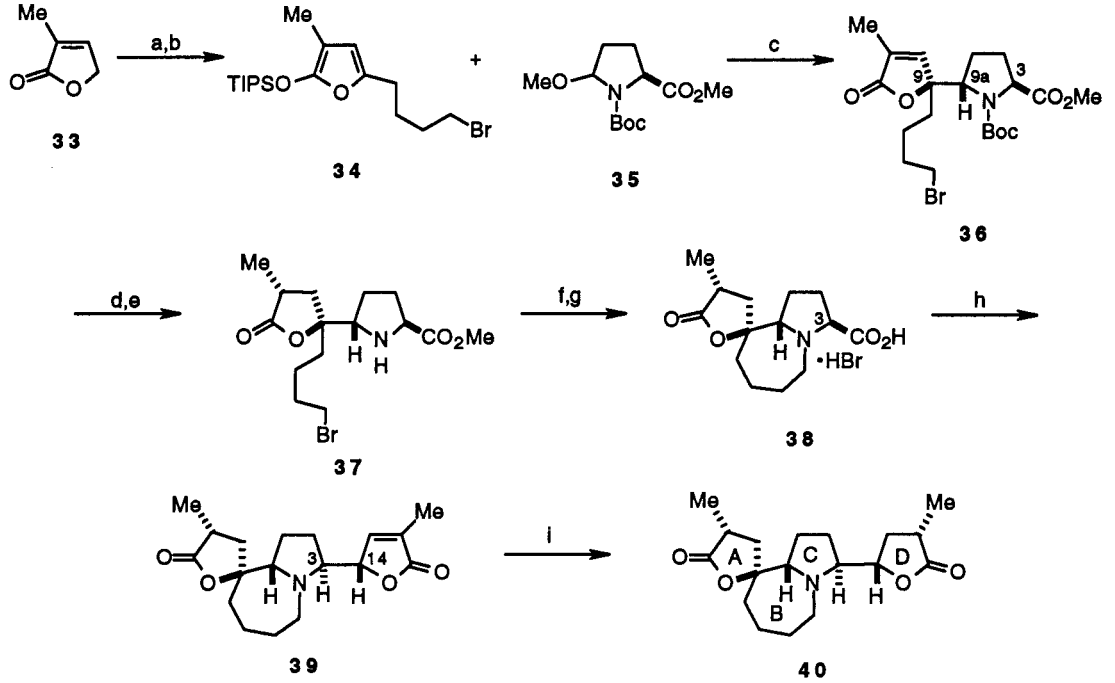


32

Total Synthesis of Croomine. There is an increasing interest in alkaloids found in the plants of the *Stemonaceae* family (*Stemona* and *Croomia* species) owing to their unique and complex structures coupled with the rich opportunities for developing new chemistry for their synthesis.[13] Since the pairwise relationships at C(9)-C(9a) and C(3)-C(14) of the archetypal alkaloid croomine (**40**) are *threo*, an appealing

strategy for the synthesis of **40** was envisioned in which the A and D rings would be appended by sequential vinylogous Mannich additions of substituted silyloxy furan subunits to the pyrrolidine core C (Scheme 6).[14] The requisite starting materials **34** and **35** were assembled from **33** and L-pyroglutamic acid by straightforward procedures. In the first vinylogous Mannich reaction, the furan **34** was allowed to react with the acyl iminium ion that was generated *in situ* by the triisopropylsilyl triflate-catalyzed ionization of **35** to afford a mixture from which the adduct **36** crystallized. This addition occurred preferentially via the *threo*

Scheme 6



(a) TIPS-OTf, Et_3N, CH_2Cl_2, 0 °C → rt. (b) *s*-BuLi, TMEDA,THF, 0 °C; $Br(CH_2)_4Br$. (c) TIPS-OTf, CH_2Cl_2, 0 °C. (d) CF_3CO_2H (10 eq), CH_2Cl_2, rt. (e) 5% Rh-C, H_2, EtOAc/EtOH (2:1). (f) NMM (6 eq), DMF, ↑↓. (g) 3 M aq. HBr, 60 °C. (h) $POCl_3$, DMF; 3-methyl-2-triisopropylsilyloxyfuran. (i) 10% Pd/C, H_2, 10% HCl/EtOH.

manifold, and the carboxyl function at C(3) fulfilled its predestined role in the synthesis by directing the diastereofacial selectivity in the addition. Elaboration of the B ring of croomine by a sequence involving highly stereoselective reduction of the butenolide moiety and cyclization led to the tricyclic **38**, thereby setting the stage for the second vinylogous Mannich reaction. The tertiary α-amino acid function in **38** underwent decarbonylation upon reaction with $POCl_3$ to give an intermediate iminium ion that was trapped *in situ* with 3-methyl-2-triisopropylsilyloxy furan to give a separable mixture (ca 2:1) of the desired *threo*-adduct **39** together with its *erythro*-isomer. Stereoselective hydrogenation from the less hindered face of **39** then delivered (+)-croomine (**40**).

Conclusions. It is apparent that the vinylogous Mannich reaction in conjunction with hetero Diels-Alder reactions and biomimetic transformations constitutes a powerful strategic element for the design and execution of concise syntheses of a variety of complex alkaloid natural products. Despite its demonstrated utility, further applications of vinylogous Mannich reactions to problems in alkaloid synthesis will be compromised until higher levels of stereochemical control may be realized. Studies directed toward elucidating the stereochemical control elements in these additions is under current investigation as are other novel applications of this construction.

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