Vinylogous Mannich Reactions. The Asymmetric Total Synthesis of (+)-Croomine

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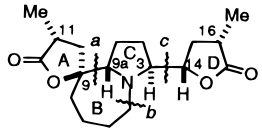
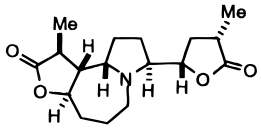
The alkaloid-rich extracts obtained from plants belonging to the *Stemonaceae* family (*Stemona* and *Croomia* species) have been used in traditional Chinese folk medicine to prepare herbal teas for treating numerous disorders, including pertussis, pulmonary tuberculosis, and bronchitis; several alkaloids also exhibit insecticidal activity.[1] Although this class of alkaloids is relatively small, there is an increasing interest in representative members of the family owing to their unique and complex structures coupled with the rich opportunities for developing new chemistry for their synthesis.[2] As illustrated by the prototypical examples croomine (**1**) and stemonine (**2**), these novel polycyclic alkaloids incorporate a butyrolactone ring that is appended or annelated to a 1-azabicyclo[5.3.0]decane nucleus.



1



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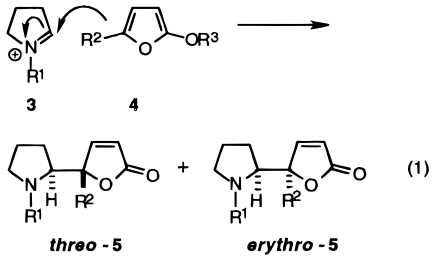
We have recently investigated the vinylogous Mannich reaction as a key construction for the synthesis of alkaloid natural products.[3] The general plan is illustrated by the nucleophilic addition of the 2-trialkylsilyloxy furan **4** to the cyclic iminium ion **3** to provide a mixture of the isomeric adducts *threo*-**5** and *erythro*-**5** in which the *threo*-**5** product typically dominates (eq 1).[3a,4] Since the stereochemistry at the

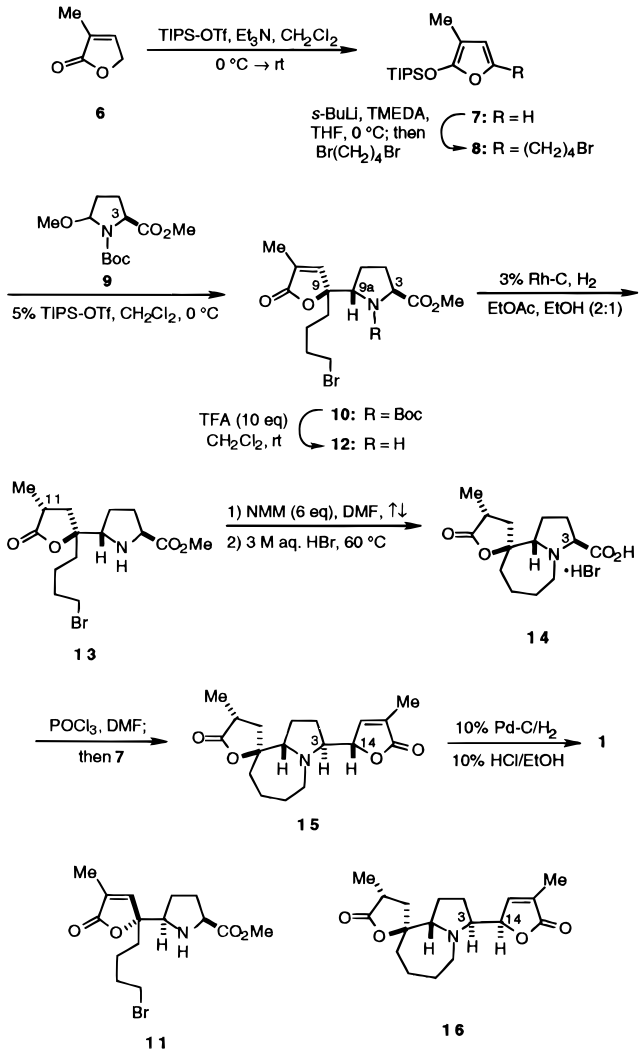


3 **4**

threo - **5** *erythro* - **5** (1)

newly created stereogenic centers in the *threo*-**5** adduct corresponds to the pairwise relationships at C(9)−C(9a) and C(3)−C(14) of croomine (**1**), it occurred to us that vinylogous Mannich reactions might be applied to the design of a highly convergent strategy for the synthesis of **1** and related alkaloids. In such an approach to **1**, both the A and D rings would be appended by sequential addition of substituted silyloxy furan subunits to the pyrrolidine core C, thereby forming bonds *a* and *c*. The seven-membered B ring would be constructed via intramolecular *N*-alkylation to make bond *b*. We now report the successful implementation of this strategy in an extraordinarily concise, asymmetric synthesis of (+)-croomine (**1**).

Scheme 1



The synthesis commenced with the reaction of commercially available 3-methyl-2-(5*H*)-furanone (**6**) (Scheme 1) with triisopropylsilyl triflate (TIPS-OTf) in the presence of triethylamine to give the (trialkylsilyl)oxy furan **7** in 99% yield.[5,6] The furan **7** is destined to be incorporated as both the A and D rings of the target **1**. Metallation of **7** followed by alkylation with 1,4-

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(3) (a) Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, 55. (b) Martin, S. F.; Liras, S. *J. Am. Chem. Soc.* **1993**, *115*, 10450. (c) Martin, S. F.; Clark, C. W.; Corbett, J. W. *J. Org. Chem.* **1995**, *60*, 3236.

(4) For a review of the reactions of trialkylsilyloxy furans with electrophiles, see: (a) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607. For related reactions, see: (b) Harding, K. E.; Coleman, M. T.; Liu, L. T. *Tetrahedron Lett.* **1991**, *31*, 3795. (c) Morimoto, Y.; Nishida, K.; Hayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 5773. (d) Pelter, A.; Ward, R. S.; Sirit, A. *Tetrahedron: Asymm.* **1994**, *5*, 1745. (e) Hanessian, S.; Raghavan, S. *Biorg. Med. Chem. Lett.* **1994**, *4*, 1697.

(5) The structure assigned to each compound is in full accord with its spectral (^{1}H and ^{13}C NMR, IR, mass) characteristics; molecular composition of new compounds was established by high resolution mass measurements of purified materials. All yields are based on isolated, purified material judged >95% pure by ^{1}H NMR spectroscopy; the structures of compounds **10**, **11**, **15**, and **16** were determined by X-ray crystallography.

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dibromobutane provided **8** in 83% yield.[7] The chiral methoxypyrrolidine **9** was then prepared in two steps from L-methyl pyroglutamate according to standard procedures,[8] thereby setting the stage for the first vinylogous Mannich reaction. In the event, reaction of **8** with the acyl iminium ion that was generated *in situ* by the triisopropylsilyl triflate-catalyzed ionization of **9** afforded a mixture from which the *threo* adduct **10** crystallized in 32% yield; the stereochemical relationships at C(3), C(9), and C(9a) in **10** were secured by X-ray crystallography.[5,9] Because the ^{1}H and ^{13}C NMR spectra of the crude reaction mixture were complex, it was not possible at this stage to determine whether other stereoisomeric adducts were present. However, repeated chromatography of the mixture led to the isolation of the *threo*-adduct **11**,[5] which arose from addition of the furan **7** to the *more* hindered face of the intermediate acyl iminium ion, in less than 1% yield; neither of the two possible *erythro* isomers was isolated. Thus, the vinylogous Mannich reaction had occurred preferentially via the *threo* manifold as expected, and the carboxyl function at C(3) had fulfilled its first role in the synthesis by directing the diastereofacial selectivity in the addition.

Acid-catalyzed removal of the *tert*-butyloxycarbonyl protecting group from **10** gave the amine **12**, which underwent highly stereoselective reduction, likely directed by the basic nitrogen of the pyrrolidine ring,[10] to give **13** in >96% overall yield. Cyclization of **13** to elaborate the B ring of croomine was readily achieved by heating **13** in refluxing dimethylformamide (DMF) in the presence of *N*-methylmorpholine (NMM); use of stronger bases such as triethylamine in this reaction led to significant epimerization at C(11). Subsequent hydrolysis of the intermediate methyl ester in refluxing aqueous 3 M HBr furnished **14** in 74% overall yield from **13**.

The stage was now set for the carboxyl group at C(3) to play its second role in the synthesis. Rapoport has reported that the acid chlorides of tertiary α-amino acids are thermally unstable and decarbonylate to give iminium salts that may be trapped by suitable nucleophiles.[11] The application of this protocol to **14** would then enable the regioselective generation of an iminium function that would undergo a vinylogous Mannich reaction to form the C(3)−C(14) bond and introduce the butyrolactone D ring of croomine. In the event, treatment of **14** with $POCl_3$ in DMF at room temperature followed by reaction of the intermediate iminium salt formed *in situ* with the furan **7** gave a separable mixture (ca. 2:1) of the desired *threo*-adduct **15** and the *erythro*-product **16** in 47% combined yield.[5,12] The synthesis was then completed by the stereoselective hydrogenation from the less hindered face of the hydrochloride salt of **15** to deliver (+)-croomine (**1**) (85% yield). The spectral characteristics (^{1}H and ^{13}C NMR) of the synthetic **1** thus obtained were identical to those reported.[1e,2a]

This asymmetric synthesis of the complex alkaloid (+)-croomine (**1**) is remarkably concise and requires only 9 steps in the longest linear sequence with a total of 11 steps from commercially available starting materials. All of the chirality in the product is derived from L-pyroglutamic acid. Although the key vinylogous Mannich reactions proceeded with modest efficiencies in the present instance, this useful methodology allows for the rapid assembly of the skeletal framework of alkaloids of the *Stemonaceae* family. Investigations directed toward identifying the stereochemical control elements in vinylogous Mannich reactions together with the applications of such additions to the total syntheses of other alkaloid natural products are in progress, and these results will be reported in due course.

Acknowledgment. We thank the National Institutes of Health and the Robert A. Welch Foundation for supporting this research. We are grateful to Professor David R. Williams (Indiana University) for providing ^{1}H and ^{13}C NMR spectra of croomine for comparison. We also thank Mr. Terrance L. Clayton for conducting several unreported model studies related to the preparation of **10** and Dr. Vincent M. Lynch for performing the X-ray crystallographic analyses of compounds **10**, **11**, **15**, and **16**.

Supporting Information Available: Spectral data for all new compounds and croomine and X-ray crystallographic data for compounds **10**, **11**, **15**, and **16** (60 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions..

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(9) All numbering of intermediates corresponds to the numbering scheme shown for croomine (**1**).

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(12) Approximately 5% of an isomer that has not yet been identified was also isolated.