Applications of Vinylogous Mannich Reactions. Concise Enantiospecific Total Syntheses of (+)-Croomine

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Received January 8, 1999

Abstract: Because the vinylogous Mannich reaction of substituted furans with iminium ions is a useful construction in alkaloid synthesis, it is important to know what effects substituents on the two reacting partners have upon the stereoselectivity of the reaction. Toward this end, the additions of the methylated furans **9a**−**h** to the iminium ion generated in situ from the ethoxy carbamate **10** were examined. Generally, mixtures (3−24:1) of the *threo* and *erythro* adducts **11a**−**h** and **12a**−**h** were obtained in 50−96% combined yields, with the *threo* isomers being the major products. Two extraordinarily concise asymmetric syntheses of (+)-croomine (**1**) have been completed using a novel strategy, highlighted by two vinylogous Mannich reactions as key constructions. The first such reaction involved the addition of 5-(4-bromobut-1-yl)-3-methyl-2-(triisopropylsilyloxy)furan to the *N*-acyliminium salt derived from the L-pyroglutamic acid derivative **17** to give the adduct [5(*S*),2′(*S*),5′(*S*)]-5-(4″-bromobut-1″yl)-5-[*N*-(*tert*-butoxycarbonyl)-2′-(methoxycarbonyl)-pyrrolidin-5′-yl]-3-methyl-2(5*H*)-furanone (**18**) as the major product. Refunctionalization of **18** led to the tricyclic intermediate [3′*S*-[3′α,9′α(*S**),9′aα]]-decahydro-4-methyl-5-oxospiro[furan-2(3*H*),9′-[9*H*]pyrrolo[1,2-*a*]azepin]-3′-carboxylic acid, hydrobromide salt, which was, in turn, converted to an iminium salt that underwent a second vinylogous Mannich reaction to give [3′*S*-[3′α(*R**),9′α(*S**),9′aα]]-3′-(2,5-dihydro-4-methyl-5-oxo-2-furanyl)decahydro-4-methylspiro[furan-2(5*H*),9′-[9*H*]pyrrolo[1,2-*a*]azepin-5-one (**24**) as the major adduct. Stereoselective reduction of the unsaturated lactone **24** gave **1**, completing a synthesis that required a total of only 11 chemical steps from commercially available starting materials. In a second approach, the initial Mannich adduct [5(*S*),2′(*S*),5′(*S*)]-5-(4″-bromobut-1″-yl)-5-[2′-(methoxycarbonyl)pyrrolidin-5′-yl]-3-methyl-2(5*H*)-furanone was transformed into the unsaturated tricyclic intermediate [3′*S*-[3′α(*R**),9′α(*S**),9′aα]]-3′-(2,5-dihydro-4-methyl-5-oxo-2-furanyl)-1′,2′,3′,5′,6′,7′,8′-octahydro-4-methylspiro[furan-2(5*H*),9′-[9*H*]-pyrrolo[1,2-*a*]azepin]-5-one, which underwent hydrogenation to give **1** as the only isolable product, thereby completing a synthesis that required only 10 steps.

Extracts from plants used for medicinal purposes have long been the source of natural products with interesting biological properties. Indeed, plants belonging to the *Stemonaceae* family (*Stemona* and *Croomia* species) were used historically in Chinese and Japanese medicine to treat respiratory disorders, including pertussis, pulmonary tuberculosis, and bronchitis, and several alkaloids exhibit insecticidal and neuromuscular activity.[1,2] The extracts of these plants were found to be rich in alkaloids having novel structures, as is illustrated by the representative members of this class croomine (**1**), stemonine (**2**), and tuberostemonine (**3**). Each of these alkaloids incorporates a butyrolactone ring that is either appended or annelated to a 1-azabicyclo[5.3.0]decane nucleus. This unusual molecular architecture has served as a stimulus for the development of new chemistry and strategies for the construction of the skeleton, and the successful total syntheses of a number of the natural alkaloids as well as simpler model structures have been recorded.[3,4]

Our interest in alkaloids of the *Stemona* family arose from more general investigations of the vinylogous Mannich reaction as a key construction for the synthesis of alkaloid natural products.[5−7] In the context of rapidly assembling the molecular framework of croomine (**1**), we envisioned that two substituted silyloxyfuran subunits, which would be the progenitors of the

(1) Goetz, M.; Edwards, O. E. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1976; Vol. IX, p 545 and references therein.

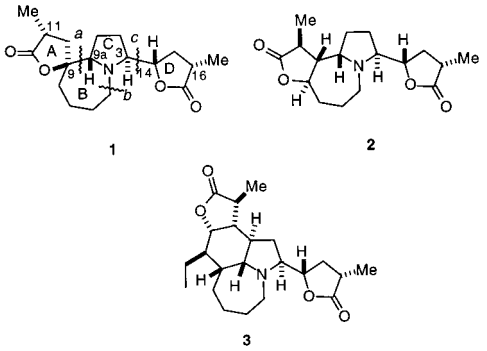
(2) For leading references to structural and biological investigations of the *Stemona* alkaloids, see: (a) Koyanma, H.; Oda, K. *J. Chem. Soc. (B)* **1970**, 268. (b) Lizuka, H.; Irie, H.; Masaki, N.; Osaki, K.; Uyeo, S. *J. Chem. Soc., Chem. Commun.* **1973**, 125. (c) Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. In *Natural Products Chemistry*; Academic Press: New York, 1975; Vol. 2, p 292 ff. (d) Sakata, K.; Aoki, K.; Chang, C.-F.; Sakaurai, A.; Tamura, S.; Mukakoshi, S. *Agric. Biol. Chem.* **1978**, *42*, 457. (e) Noro, T.; Fukushima, S.; Ueno, A.; Litaka, Y.; Saiki, Y. *Chem. Pharm. Bull.* **1979**, *27*, 1495. (f) Xu, R.-S.; Lu, Y.-J.; Chu, J.-H.; Iwashita, T.; Naoki, H.; Naya, Y.; Nakanishi, K. *Tetrahedron* **1982**, *38*, 2667. (g) Tereda, M.; Sano, M.; Ishii, A. I.; Kino, H.; Fukushima, S.; Noro, T. *J. Pharm. Soc. Jpn.* **1982**, *79*, 93. (h) Cheng, D.; Guo, J.; Chu, T. T.; Röder, E. *J. Nat. Prod.* **1988**, *51*, 202. (i) Lin, W.-H.; Ye, Y.; Xu, R.-S. *J. Nat. Prod.* **1992**, *55*, 571. (j) Ye, Y.; Qin, G.; Xu, R. *Phytochemistry* **1994**, *37*, 1201, 1205.

(3) (a) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923. (b) Chen, C.-y.; Hart, D. J. *J. Org. Chem.* **1990**, *55*, 6236. (c) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477. (d) Morimoto, Y.; Nishida, K.; Hayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 5773. (e) Chen, C.-y.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 3840. (f) Williams, D. R.; Reddy, J. P.; Amato, G. S. *Tetrahedron Lett.* **1994**, *35*, 6417. (g) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106. (h) Morimoto, Y.; Iwahashi, M. *Synlett* **1995**, 1221. (i) Goldstein, D. M.; Wipf, P. *Tetrahedron Lett.* **1996**, *37*, 739. (j) Kohno, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2063. (k) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356; *Heterocycles* **1997**, *46*, 287. (l) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **1997**, *119*, 3409. (m) Rigby, J. H.; Laurent, S.; Cavezza, A.; Heeg, M. J. *J. Org. Chem.* **1998**, *63*, 5587.

(4) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299.

(5) (a) Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, 55. (b) Martin, S. F.; Bur, S. K. *Tetrahedron Lett.* **1997**, *38*, 7641.

10.1021/ja990077r CCC: $18.00
Published on Web 07/14/1999



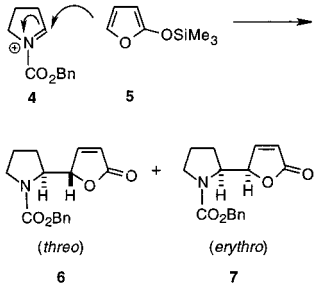
1 2 3

A and D butyrolactone rings in **1**, might be appended to the pyrrolidine core C via vinylogous Mannich reactions to form bonds ***a*** and ***c***. At some stage in the synthesis, the seven-membered B ring would be constructed via an intramolecular *N*-alkylation to make bond ***b***.

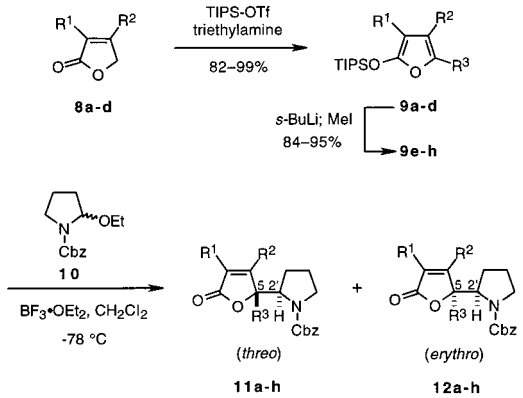
The key to the successful implementation of this novel plan lay in the feasibility and the stereoselectivity of the vinylogous Mannich reactions of silyloxyfurans with cyclic iminium salts.[8] As a preliminary step toward examining these two issues, we found that 2-trimethylsilyloxyfuran (**5**) added to the iminium ion **4** to give a mixture (5:1) of the *threo* and *erythro* adducts **6** and **7**, respectively, in which the *threo* isomer dominated (Scheme 1).[5a] Significantly, the relative stereochemistry at the newly created stereogenic centers in the major adduct **6** corresponds to the pairwise relationships at C(9)−C(9a) and C(3)−C(14) of (+)-croomine (**1**). Thus, the critical reactivity and stereochemical elements in our strategy for the synthesis of **1** had been validated, and it then remained to reduce these discoveries to practice. In tandem with our efforts directed toward the synthesis of the *Stemona* and other alkaloids, we were interested in developing a better understanding of the factors that controlled the stereochemical course in the vinylogous Mannich reactions of substituted silyloxyfurans with cyclic iminium salts.[5c] We now report the details of these stereochemical studies, together with an account of the successful implementation of two sequential vinylogous Mannich reactions in completing convergent and extraordinarily concise, enantioselective syntheses of (+)-croomine (**1**).

Stereochemical Studies of Vinylogous Mannich Reactions. In early studies of the vinylogous Mannich reactions of silyloxyfurans with cyclic iminium, we found that there was a preference for formation of the *threo* adduct.[5a] However, we were interested in determining the basis for this preference and what effect the position and the number of substitutents on the furan ring had on the stereochemical course of the process. To address this issue, we prepared the series of methyl-substituted triisopropylsilyloxyfurans **9a**−**h**. The starting butenolides **8a,b** are commercially available, and **8c,d** were prepared by modification of known procedures.[9] Reaction of **8a**−**d** with TIPS−OTf in the presence of Et_3N then furnished the corresponding silyloxyfurans **9a**−**d**.[10,11] Metalation of **9a**−**d** followed by methylation then gave **9e**−**h** (Scheme 2).

Scheme 1



Scheme 2



Series **a:** R^1 = H; R^2 = H; R^3 = H
b: R^1 = Me; R^2 = H; R^3 = H
c: R^1 = H; R^2 = Me; R^3 = H
d: R^1 = Me; R^2 = Me; R^3 = H
e: R^1 = H; R^2 = H; R^3 = Me
f: R^1 = Me; R^2 = H; R^3 = Me
g: R^1 = H; R^2 = Me; R^3 = Me
h: R^1 = Me; R^2 = Me; R^3 = Me

The reactions of the furans **9a**−**h** with the iminium ion that was generated in situ upon treatment of the ethoxy carbamate **10**[12] with $BF_3{\cdot}OEt_2$ were then examined using a standard set of conditions similar to those reported previously.[5a] Mixtures of the *threo* and *erythro* adducts **11a**−**h** and **12a**−**h**, respectively, were obtained, and the results of these experiments are summarized in Table 1. The diastereomeric ratios were obtained by integrating several diagnostic signals in the ^{1}H NMR spectrum of crude reaction mixtures. Typically, the protons having distinct chemical shifts were the α- and *β*-butenolide protons and the protons α to nitrogen at C(2′). Because this analysis was complicated by the presence of rotamers when the spectra were acquired at room temperature, it was necessary to obtain the spectra at 100 °C. At this elevated temperature, the diagnostic signals assigned to rotational isomers coalesced, and integrals arising from each diastereomer could be reproducibly measured.

(6) (a) Martin, S. F.; Liras, S. *J. Am. Chem. Soc.* **1993**, *115*, 10450. (b) Martin, S. F.; Clark, C. W.; Corbett, J. W. *J. Org. Chem.* **1995**, *60*, 3236. (c) Martin, S. F.; Clark, C. W.; Ito, M.; Mortimore, M. *J. Am. Chem. Soc.* **1996**, *118*, 9804. (d) Martin, S. F.; Bur, S. K. *Tetrahedron*, in press.

(7) For a recent review of the Mannich reaction, see: Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1045.

(8) 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: Asymmetry* **1994**, *5*, 1745. (e) Hanessian, S.; Raghavan, S. *Biorg. Med. Chem. Lett.* **1994**, *4*, 1697. (f) Pichon, M.; Figadére, B.; Cavé, A. *Tetrahedron Lett.* **1996**, *37*, 7963.

(9) (a) Stewart, J. M.; Woolley, D. W. *J. Am. Chem. Soc.* **1959**, *81*, 4951. (b) Epstein, W. W.; Sonntag, A. C. *J. Org. Chem.* **1967**, *32*, 3390.

(10) The structure assigned to each compound is in full accord with its spectral (^{1}H and ^{13}C NMR, IR, mass) characteristics; the 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 **11b**−**g, 14c, 18**, **19**, **24**, and **26** were determined by X-ray crystallography.

(11) (a) Brimble, M. A.; Brimble, M. T.; Gibson, J. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 179. (b) Jefford, C. W.; Sledeski, A. W.; Rossier, J.-C.; Boukouvalas, J. *Tetrahedron Lett.* **1990**, *31*, 5741. (c) Boukouvalas, J.; Lachance, N. *Synlett* **1998**, 31.

(12) Nagasaka, T.; Tamano, H.; Hamaguchi, F. *Heterocycles* **1986**, *24*, 1231.

Table 1. Stereoselectivity of Vinylogous Mannich Reaction of Furans **9a**−**h**

entry	furan **9**	yield (%)[a]	**11:12**[b]
1	**a**	70	15:1
2	**b**	87	8:1
3	**c**	88	9:1
4	**d**	80	5:1
5	**e**	70	3.5:1
6	**f**	96	3:1
7	**g**	88	5:1
8	**h**	83	3.5:1

[a] Yields are of purified material and are unoptimized. [b] Ratios of **11a**−**h**:**12a**−**h** were determined by ^{1}H NMR analysis of the crude reaction mixtures.

As is evident from examination of Table 1, the introduction of methyl groups at any position on the furan ring resulted in somewhat lower diastereoselectivity, although the yields remained high (70−96%). Substitution at C(5) of the furan ring (entries 5−8) had the greatest effect upon lowering the stereoselectivity of the addition. Moreover, the presence of a methyl group at C(5) on the furan significantly decreased the rate of the reaction.

The major *threo* diastereomers **11b**−**g** were isolated as crystalline solids whose structures were determined by single-crystal X-ray analysis, whereas the structure of **11a** had been previously determined by X-ray analysis of a crystalline derivative.[5a] The structures of **11h** and **12h** were assigned by comparisons of their ^{13}C and ^{1}H NMR spectra with those of other adducts, as some apparent trends were observed. For example, the ^{13}C chemical shifts of the C(5) carbon of **11a**−**d** were deshielded relative to those of the C(5) carbon in **12a**−**d**. However, in compounds having a C(5) methyl substituent, the trend was reversed as the chemical shifts of the C(5) carbon in **11g,h** were shielded relative to those of **12g,h**; the signals for the C(5) carbon in **11e,f** and **12e,f** overlapped. Some relationships in the observed chemical shifts in the ^{1}H NMR spectra for the protons at C(2′) and C(5) were also predictive. For example, the C(2′) proton in **11a**−**d** was deshielded relative to the C(2′) proton in **12a**−**d**, whereas the C(2′) proton in compounds **11e**−**h**, having a methyl group at C(5), was shielded relative to that in **12e**−**h**.

The structure of the cyclic iminium ion also appears to have an effect on the stereochemical course of the vinylogous Mannich reaction. For example, we found that the iminium ion generated from the ethoxy pyrrolidinone **13** underwent additions with the methyl silyloxyfurans **9a**−**c,e**, albeit with low diastereoselectivity (1.1−2.8:1). The reactions of **13** required higher temperatures and longer reaction times than the related additions involving **10**. Although it was not possible to make unequivocal structure assignments to the products on the basis of their NMR spectra, we did obtain an X-ray crystal structure of **14c**, which was the major product from the reaction of **13** with **9c**. We presume that the major products of the other reactions are also the *threo* adducts **14a,b,e.** Because these processes were not very stereoselective, they were not examined in greater detail (Scheme 3).

At the outset of these studies, we had hoped to identify some of the stereochemical control elements and to gain insights regarding geometric features of the transition states for vinylogous Mannich reactions. Examination of the data in Table 1 clearly reveals that the presence of alkyl substituents on the furan ring does affect the stereochemical course of the reaction. However, because of the relatively small energetic differences between the competing transition states, it is not possible to conclude with certainty whether these additions proceed via

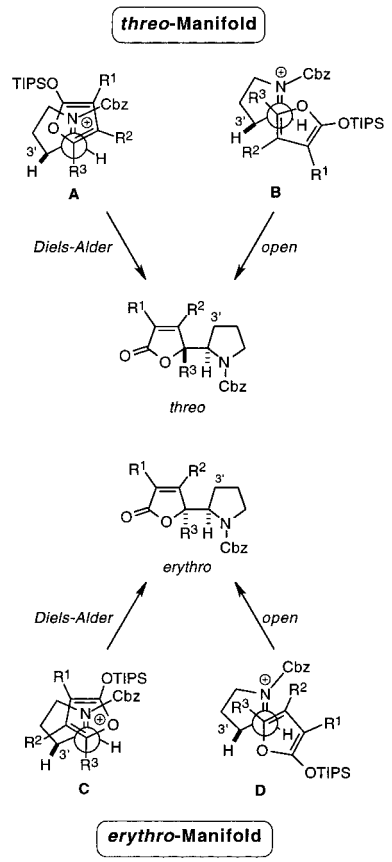
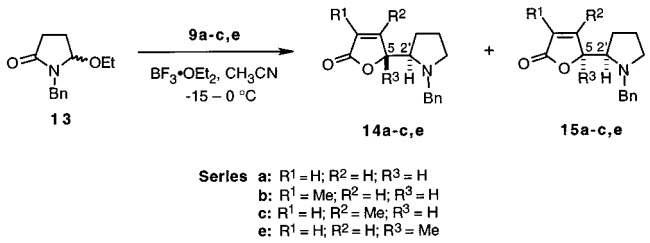


Figure 1. Limiting transition states for the addition of silyloxyfurans to cyclic iminium ions.

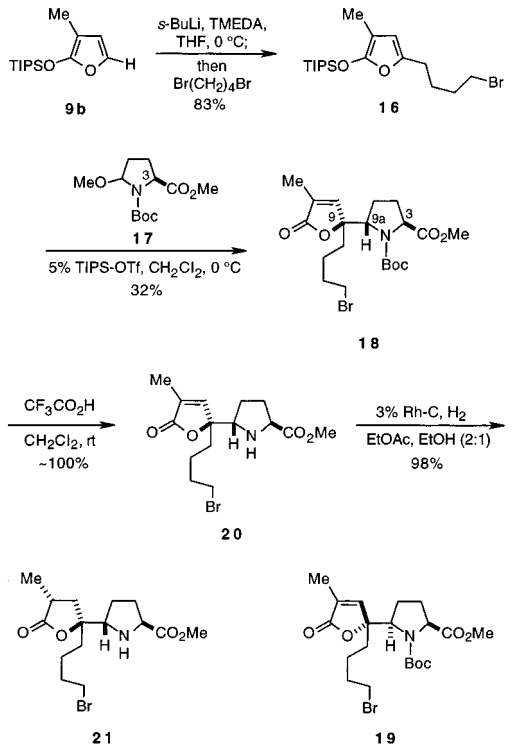
Scheme 3



limiting Diels−Alder, **A** and **C**, or open geometries, **B** and **D** (Figure 1). It is nonetheless possible to identify some apparent stereochemical features associated with these processes that will require further testing. For example, the loss of diastereoselectivity observed in the vinylogous Mannich reaction of **9b**, which has a methyl group as the R^1 substituent at C(3), seems to be more consistent with a Diels−Alder transition state than an open one. Namely, a group $R^1 \neq H$ clearly incurs steric interactions with the iminium ion in transition states **A** and **C**, whereas there are no such interactions apparent in **B** and **D**. Thus, if an open transition state were operative, one would not expect to observe any difference in the stereochemical outcome of the addition depending upon the nature of R^1. Modeling suggests that $R^2 \neq H$ would sterically encounter the proton at C(3′) of the iminium ion in transition states **B** and **C**, whereas this interaction is absent in **A** and **D**. That the *threo* adduct is the major product whenever $R^2 = Me$ (entries 3, 7, and 8; Table 1) suggests that the Diels−Alder transition state **A** is preferred.

First-Generation Synthesis of (+)-Croomine (1). The application of vinylogous Mannich reactions to the enantioselective synthesis of (+)-croomine required the trialkylsilyloxy furan **9b** as the common precursor of both the A and D rings.

Scheme 4



The stage for the first of these was set by preparing the furan **16** in 83% yield by alkylation of the lithio derivative of **9b** with 1,4-dibromobutane (Scheme 4).[13] It was also necessary to select a suitable iminium ion precursor, and the known methoxypyrrolidine **17**[14] appeared to be ideally suited to the task. Namely, we envisioned that the carboxyl function at C(3) in the iminium ion produced by loss of the methoxy group from **17** would direct the furan nucleophile to the opposite face, thereby setting the absolute stereochemistry at C(9a) of croomine.[15] The carboxyl function would later serve as a functional handle to direct the formation of the iminium ion in the second vinylogous Mannich reaction (vide infra). In the event, when **16** was allowed to react with the chiral acyl iminium ion generated in situ by the triisopropylsilyl triflate-catalyzed ionization of **17**, a mixture was obtained from which the *threo* adduct **18** crystallized in 32% yield; the structure of **18** was unequivocally established by X-ray crystallography. Despite considerable experimentation with different Lewis acid promoters and solvents, we were unable to improve the efficiency of this key addition. Nevertheless, it is noteworthy that the requisite absolute stereochemical relationships at C(9) and C(9a) of croomine were secured in a single step via a vinylogous Mannich reaction proceeding via a *threo* manifold in which the furan approached the iminium ion from the face opposite the carboxyl function at C(3).

The ^{1}H and ^{13}C NMR spectra of the crude mixture from the reaction of **16** with **17** were complex, but only one diagnostic singlet, corresponding to the β-proton on the butenolide moiety, was readily visible in the ^{1}H NMR spectrum (δ 7.17 ppm), suggesting the primary formation of only one adduct. Repeated separation of the mixture by column and HPLC chromatography

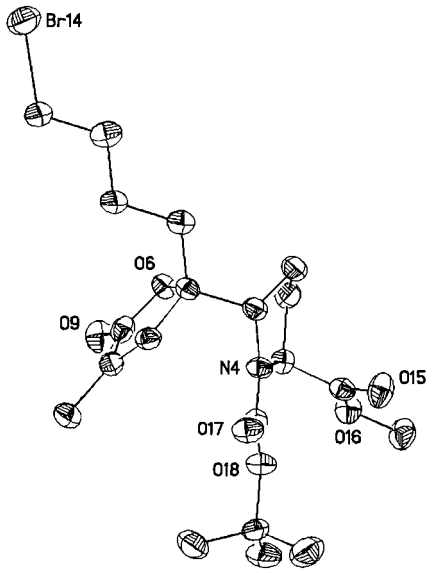


Figure 2. ORTEP plot of compound **18**.

eventually afforded the *threo* adduct **19**, albeit in less than 1% yield. The structural assignment of **19**, which was produced by the nucleophilic addition of the furan **16** to the *more* hindered face of the intermediate acyl iminium ion, was confirmed by X-ray crystallography. Although neither of the two possible *erythro* isomers was isolated, it is not possible to exclude their formation. The failure to identify *erythro* adducts in the mixture is all the more puzzling because we have recently found that both *threo* and *erythro* adducts were formed in a related vinylogous Mannich reaction.[6d]

Attempted reduction of the carbon−carbon double bond in **18** by catalytic hydrogenation using Pd/C, Pd(OH$_2$)/C, Ru/C, and Rh/C under 1 atm of H_2 was unsuccessful, and some hydrogenolysis of the alkyl bromide group was observed when using various palladium catalysts. The reluctance of **18** to undergo hydrogenation may be rationalized upon examination of the X-ray structure (Figure 2), which suggests that both faces of the butenolide double bond are highly sterically encumbered. On the other hand, reduction of the amine **20**, which was prepared by the acid-catalyzed removal of the *tert*-butyloxycarbonyl protecting group from **18**, proceeded stereoselectively to give the saturated amine **21** as the only detectable stereoisomer in >96% overall yield. The stereochemical course of this reduction is consistent with steric approach control, but it is also possible that the hydrogenation is directed by the basic nitrogen of the pyrrolidine ring.[16]

At this juncture, the seven-membered B ring of croomine was formed by heating **21** in refluxing dimethylformamide (DMF) in the presence of *N*-methylmorpholine (NMM) to give **22** (80% yield) (Scheme 5). When stronger bases, such as Hünig's base or triethylamine, were used to effect this cyclization, significant epimerization at C(11) occurred to give **25**. In a separate study, a mixture (2:1) of **22** and **25** was equilibrated with methanolic NaOMe to return a new mixture (1:2) of diastereoisomers in which **23** was the major product; no epimerization of the center α to the methyl ester at C(3) was observed. Thus, the unnatural configuration at C(11) in these tricyclic intermediates is thermodynamically preferred.

The plan to complete the total synthesis of (+)-croomine required that the carboxyl group at C(3) of **22** would serve as a precursor of a regioselectively generated iminium ion that

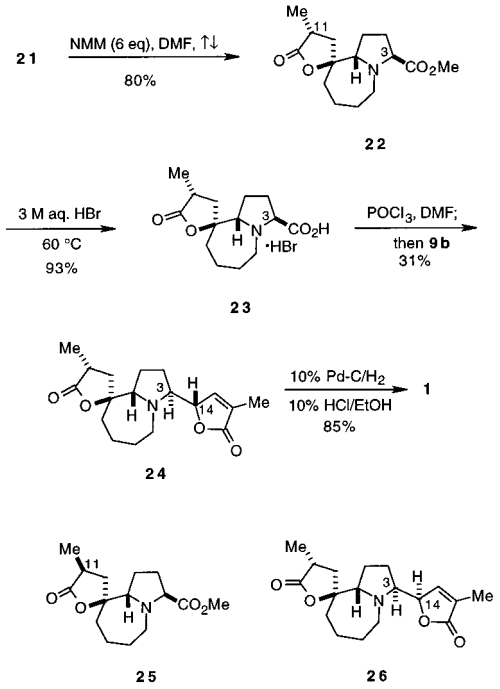
(13) Cf.: Perron, F.; Albizati, K. F. *J. Org. Chem.* **1989**, *54*, 2044.

(14) Shono, T.; Matsumura, Y.; Tsubatya, K.; Sugihara, Y.; Shin-ichiro, Y.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697. See also ref 8e.

(15) Numbering of all intermediates corresponds to the numbering scheme shown for croomine (**1**).

(16) Brown, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190.

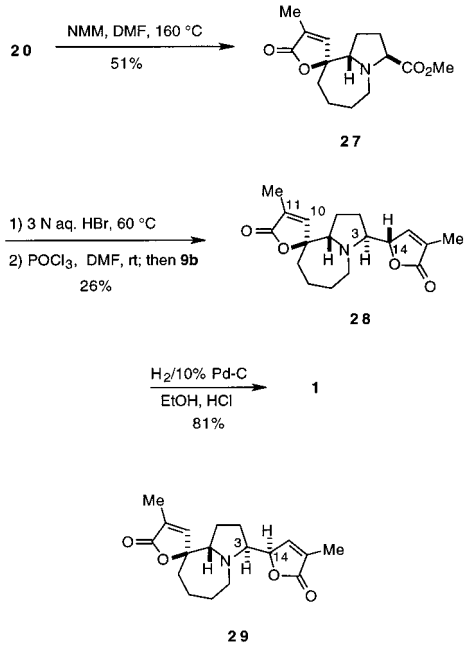
Scheme 5



would undergo a vinylogous Mannich reaction to form the C(3)−C(14) bond and introduce the pendant butyrolactone D ring. As precedent for this critical transformation, Rapoport reported that acid chlorides derived from tertiary α-amino acids are thermally unstable and decarbonylate to give iminium salts that may be trapped with nucleophiles;[17] similar reactions have been reported by others.[18] Although the base-induced hydrolysis of the methyl ester in **22** afforded mixtures of products, hydrolysis in refluxing aqueous 3 M HBr cleanly furnished the carboxylic acid **23** in 93% yield. Treatment of **23** with $POCl_3$ in DMF at room temperature and subsequent reaction of the intermediate iminium salt in situ with the furan **9b** gave a separable mixture (ca. 2:1) of the requisite *threo* adduct **24**, together with the *erythro* product **26** in 47% combined yield.[19] Both **24** and **26** were characterized by X-ray crystallography. The synthesis was then completed by the stereoselective hydrogenation from the less hindered face of the hydrochloride salt of **24** 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.[2e,3a]

Second-Generation Synthesis of (+)-Croomine (1). Despite the remarkable brevity of this asymmetric synthesis of croomine (**1**), we were intrigued by the possibility of devising an even shorter route. It thus occurred to us that postponing the hydrogenation of the C(10)−C(11) carbon−carbon double bond until the last step in the synthesis would trim one step from the sequence. This maneuver was not without risk, however, as a preliminary examination of molecular models of **28**, the penultimate intermediate in the new route, suggested that reduction of the C(10)−C(11) carbon−carbon double bond would *not* be expected to occur from either face with a high level of selectivity, as both faces appeared approximately equally accessible. Indeed, we found that catalytic hydrogenation of **27** (H_2/10% Pd−C, EtOH, HCl) gave an inseparable mixture (2:1) of **22** and its C(11) epimer **25**. The aforementioned equilibration studies with **22** and **25** also offered no encouragement that the configuration at C(11) corresponding to that found in croomine was more stable. However, we judged these negative omens as insufficient to deter our interest and enthusiasm in the potential reward of an even shorter synthesis of croomine.

Scheme 6



The feasibility of applying this modified plan was evaluated in unoptimized series of reactions in which **20** was first cyclized in the presence of *N*-methylmorpholine (NMM) to give the unsaturated tricycle **27** (Scheme 6). Acid-catalyzed hydrolysis of the methyl ester as before, followed by reaction of the intermediate iminium ion with the furan **9b**, then furnished the expected mixture (ca. 2:1) of **28** and **29**. To our considerable delight and surprise, catalytic hydrogenation of **28** delivered croomine (**1**) as the *only* isolable product in 81% yield; synthetic samples of croomine (**1**) from both routes gave identical ^{1}H and ^{13}C NMR spectra.

To explore the possible basis for this remarkable result, we undertook a series of computational studies to verify whether our original molecular models were misleading. Perhaps we had missed a low-energy conformation in which there was a clear steric bias about the C(10)−C(11) double bond that would favor the observed stereochemical mode of addition of hydrogen. A search of conformational space for **26** was therefore performed by both Monte Carlo methods and stochastic dynamics using MM2[20] and Tripos[21] force fields. Under the acidic conditions of the reduction, the central nitrogen atom is protonated, and the calculations suggested that protonation syn to the bridgehead methine at C(9a) to give a cis-fused [5.3.0] bicyclic array was several kilocalories per mole lower in energy than the corresponding anti configuration. A low-energy conformation of

(17) (a) Dean, R. T.; Padgett, H. C.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 7448. (b) Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1979**, *101*, 1259. (c) Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 4914.

(18) For example, see: (a) Wasserman, H.; Tremper, A. W. *Tetrahedron Lett.* **1977**, 1449. (b) van Tamelen, E. E.; Haarstead, V. B.; Orvis, R. L. *Tetrahedron* **1967**, *24*, 687. (c) van Tamelen, E. E.; Oliver, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 2136; *Bioorg. Chem.* **1976**, *5*, 309.

(19) Approximately 5% of another stereoisomer that was not identified was also isolated.

(20) As implemented by MacroModel v6.0, available from Columbia University. See: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. *J. Comput. Chem.* **1990**, *11*, 440.

(21) As implemented by CONFORT v2 from Dr. Robert Pearlman at the University of Texas at Austin.

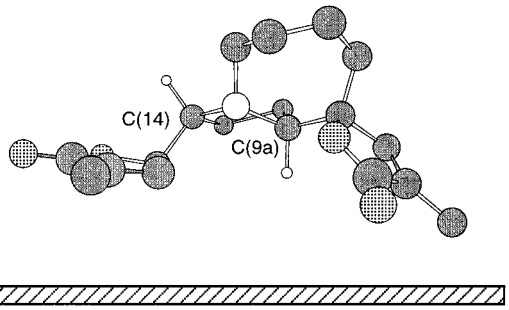


Figure 3. Low-energy conformer of **28**.

protonated **28** was thus identified in which the face of each double bond that is syn to the hydrogen at C(9a) and anti to the hydrogen at C(14) can be simultaneously presented to the surface of the catalyst (Figure 3). If one then presumes that the substrate is not released from the surface of the catalyst prior to the second reduction, the stereoselective reduction of both olefinic functions can produce the observed product.

These asymmetric syntheses of the complex alkaloid (+)-croomine (**1**) are remarkably concise and highlight the power of vinylogous Mannich reactions in alkaloid synthesis. The first requires only 9 steps in the longest linear sequence, with a total of 11 steps from commercially available starting materials, whereas the second contains 8 steps in the longest linear sequence and a total of 10 steps. All of the chirality in the target was derived from L-pyroglutamic acid. Although the two key vinylogous Mannich constructions proceeded with modest efficiencies, this useful methodology allows for the rapid assembly of the skeletal framework of alkaloids of the *Stemonaceae* family. Other novel applications of vinylogous Mannich reactions will be reported in due course.

Experimental Section

General Procedures. Boron trifluoride etherate ($BF_3{\cdot}OEt_2$), dichloromethane (CH_2Cl_2), dimethylformamide (DMF), *N*-methylmorpholine (NMM), tetramethylethylenediamine (TMEDA), and triethylamine (Et_3N) were distilled from CaH_2 prior to use. Thionyl chloride was distilled from quinoline immediately prior to use. Tetrahydrofuran (THF) was distilled from sodium benzoquinone ketyl prior to use. All other solvents and reagents were available from commercial sources and were used without further purification. All reactions involving organometallic reagents or other moisture-sensitive reactants were executed under an atmosphere of dry nitrogen or argon using oven-dried glassware. Flash chromatography was performed using silica gel 60 (230−400 mesh ASTM) with the indicated solvent. Melting points are uncorrected. HPLC was performed on a Waters 2000 system. ^{1}H and ^{13}C NMR spectra of compounds were recorded at the indicated field strength as solutions in deuteriochloroform ($CDCl_3$) unless otherwise indicated. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) ($\delta = 0.00$ ppm) and referenced to the solvent. Splitting patterns are recorded as singlet (s), doublet (d), triplet (t), quartet (q), pentuplet (p), septet (sept), multiplet (m), complex multiplet composed of chemically nonequivalent ^{1}H's (comp), broad (br), and apparent (app). IR spectra were recorded either as films on sodium chloride plates or as solutions in $CHCl_3$ as indicated and reported in wavenumbers (cm^{-1}). Optical rotations were recorded in $CHCl_3$ that was stabilized with 1% ethanol unless otherwise indicated.

5-(4-Bromobut-1-yl)-3-methyl-2-(triisopropylsilyloxy)furan (16). *sec*-Butyllithium (98.2 mL of a 1.10 M solution in cyclohexane, 108 mmol) was slowly added to a solution of **9b** (15.3 g, 60.0 mmol) and TMEDA (12.6 g, 108 mmol) in THF (300 mL) at 0 °C. After 2 h, 1,4-dibromobutane (51.8 g, 240 mmol) was added and the mixture stirred for 14 h at 0 °C. A mixture (2:1) of H_2O and saturated, aqueous $NaHCO_3$ was added, and the resulting mixture was extracted with Et_2O (3 × 200 mL). The organic layer was dried ($MgSO_4$) and then concentrated under reduced pressure (80 °C, 0.1 mmHg) to provide a gold oil with a suspended precipitate. A small volume of pentane was added, the mixture was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure to give 19.4 g (83%) of **16** as a gold oil that was pure by NMR and was used directly in the next step: ^{1}H NMR (250 MHz) δ 1.09 (d, $J = 6.5$ Hz, 18 H), 1.22 (sept, $J = 6.5$ Hz, 3 H), 1.66−1.73 (m, 2 H), 1.79 (s, 3 H), 1.82−1.90 (m, 2 H), 2.48 (t, $J = 7.1$ Hz, 2 H), 3.40 (t, $J = 6.7$ Hz, 2 H), 5.69 (s, 1 H); ^{13}C NMR (62.5 MHz) δ 8.5, 12.3, 17.6, 26.8, 27.0, 31.9, 33.5, 91.4, 108.9, 142.8, 151.3; IR (film) 1265, 1406, 1463, 1590, 1661 cm^{-1}; HRMS (CI) *m*/*z* 388.1430 ($C_{18}H_{33}BrO_2Si$ requires 388.1433).

[5(*S*),2′(*S*),5′(*S*)]-5-(4″-Bromobut-1″yl)-5-[*N*-(*tert*-butoxycarbonyl)-2′-(methoxycarbonyl)pyrrolidin-5′-yl]-3-methyl-2(5*H*)-furanone (18). TIPSOTf (0.61 g, 2.00 mmol) was slowly added to a solution of **17** (10.4 g, 40.0 mmol) and **16** (15.9 g, 40.0 mmol) in dry CH_2Cl_2 (120 mL) at 0 °C. After 16 h, saturated, aqueous $NaHCO_3$ (40 mL) was added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 60 mL), and the combined organic portions were dried ($MgSO_4$) and concentrated under reduced pressure. Recrystallization of the residual oil from pentane/ether (1:1) afforded 5.89 g (32%) of **18** as colorless crystals. Alternatively, purification of the residue by flash column chromatography, eluting with hexane/EtOAc (gradient elution with 80:20 and 70:30), provided 5.16 g (28%) of **18** as a white powder and a mixture that was further purified by HPLC, eluting with hexane/EtOAc (70:30), to provide 99 mg (0.5%) of **19** as colorless crystals.

For **18**: mp 152.5−155.5 °C; $[\alpha]_D$ −90.8° ($c = 0.97$, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.23-1.42 (comp, 11 H), 1.73−1.89 (comp, 8 H), 2.05−2.19 (m, 2 H), 2.48−2.59 (m, 1 H), 3.36 (t, $J = 6.6$ Hz, 2 H), 3.69 (s, 3 H), 4.18 (d, $J = 9.3$ Hz, 1 H), 4.24 (d, $J = 7.8$ Hz, 1 H), 7.17 (s, 1 H); ^{13}C NMR (125 MHz) δ 10.2, 22.1, 25.0, 27.9, 29.3, 32.6, 32.8, 33.6, 51.9, 60.3, 61.7, 80.4, 91.3, 127.5, 151.2, 154.3, 173.7, 174.0; IR (film) 1697, 1740, 1750 cm^{-1}; HRMS (CI) *m*/*z* 460.1308 ($C_{20}H_{30}BrNO_6$ requires 460.1335).

For **19**: mp 108.0−108.5 °C; $[\alpha]_D$ +84.6° ($c = 1.35$, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.25-1.43 (comp, 11 H), 1.75−1.92 (comp, 8 H), 1.97−2.05 (m, 1 H), 2.13−2.17 (comp, 2 H), 3.36 (t, $J = 6.6$ Hz, 2 H) 3.68 (s, 3 H), 4.10−4.18 (m, 2 H), 7.20 (s, 1 H); ^{13}C NMR (125 MHz) δ 9.6 21.3, 25.8, 27.3, 28.7, 32.0, 32.2, 33.7, 51.4, 60.2, 61.5, 80.0, 90.3, 128.3, 149.2, 153.8, 171.8, 173.4); IR (film) 2979, 1757, 1698, 1381, 1155 cm^{-1}; HRMS (CI) *m*/*z* 460.1319 ($C_{20}H_{30}BrNO_6$ requires 460.1335).

[5(*S*),2′(*S*),5′(*S*)]-5-(4″-Bromobut-1″-yl)-5-[2′-(methoxycarbonyl)-pyrrolidin-5′-yl]-3-methyl-2(5*H*)-furanone (20). Neat CF_3CO_2H (11.4 g, 100 mmol) was slowly added with stirring to a solution of **18** (4.60 g, 10.00 mmol) in CH_2Cl_2 (30 mL) at room temperature. After 5 h, the mixture was concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (30 mL). The solution was *carefully* washed with saturated $NaHCO_3$ (30 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure to provide 3.60 g (100%) of crude **20** as a clear, colorless oil that was pure by NMR and was used directly in the next step: $[\alpha]_D$ −28.5° ($c = 1.07$, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.24-1.44 (m, 2 H), 1.52−1.59 (m, 1 H), 1.77−1.92 (comp, 6 H), 1.94 (s, 3 H), 2.03−2.10 (m, 1 H), 2.46 (br s, 1 H), 3.37 (t, $J = 6.6$ Hz, 2 H), 3.63 (app t, $J = 7.1$ Hz, 1 H), 3.72 (s, 3 H), 3.76 (dd, $J = 5.2$, 8.4 Hz, 1 H), 6.94 (s, 1 H);^{13}C NMR (125 MHz) δ 10.6, 21.8, 25.7, 29.9, 32.6, 33.0, 33.5, 52.1, 60.0, 62.3, 90.2, 131.3, 149.5, 173.7, 175.5; IR (film) 2951, 1748, 1434, 1216 cm^{-1}; HRMS (CI) *m*/*z* 360.0806 ($C_{15}H_{23}BrNO_4$ requires 360.0810).

5-(*S*)-(Methoxycarbonyl)-2-(*S*)-[α-(*R*)-methyl-γ-(bromobutyl)-(*S*)-lacton-γ-yl]pyrrolidine (21). A mixture of **20** (1.08 g, 3.00 mmol) and 5% Rh/C (0.185 g, 0.09 mmol) in EtOAc/EtOH (2:1, 30 mL) was stirred under H_2 (1 atm) for 4 h. The mixture was then filtered through Celite, and the pad was rinsed with EtOAc/EtOH (2:1, 10−15 mL). The filtrate was concentrated under reduced pressure to provide a pale amber oil that was purified by flash chromatography eluting with pentane/Et_2O (2:3) to provide 1.06 g (98%) of **21** as a clear, colorless oil: $[\alpha]_D$ −20.4° ($c = 1.10$, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.23 (d, $J = 7.8$ Hz, 3 H), 1.45−1.52 (m, 2 H), 1.58−1.77 (comp, 4 H), 1.78−1.95 (comp, 4 H), 2.20 (dt, $J = 5.0$, 17.3 Hz, 1 H), 2.30 (br s, 1 H),

2.40 (dd, J = 10.3, 13.1 Hz, 1 H), 3.07−3.17 (m, 1 H), 3.42 (t, J = 6.6 Hz, 2 H), 3.48 (app t, J = 7.5 Hz, 1 H), 3.70 (app t, J = 7.0 Hz, 1 H), 3.72 (s, 3 H); ^{13}C NMR (125 MHz) δ 17.1, 21.7, 26.2, 31.3, 32.6, 33.2, 35.8, 36.5, 38.2, 52.1, 60.1, 64.3, 87.2, 175.8, 180.4; IR (film) 3626, 3507, 3342, 2850, 1740, 1732, 1453 cm^{-1}; HRMS (CI) m/z 362.0965 ($C_{15}H_{25}BrNO_4$ requires 360.0810).

[3′*S*-[3′α,9′α(*S),9′aα]]-Decahydro-4-methyl-5-oxospiro[furan-2(3*H*),9′-[9*H*]pyrrolo[1,2-*a*]azepin]-3′-carboxylic Acid, Methyl Ester (22).** A solution of **21** (0.388 g, 1.00 mmol) and NMM (0.607 g, 6.00 mmol) in DMF (10 mL) was heated to reflux. After 30 min, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. A mixture (3:1) of saturated, aqueous $NaHCO_3$ and brine (10 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with pentane/Et_2O (1:1) to afford 0.281 g (80%) of **22** as a clear, colorless oil: $[\alpha]_D$ −44.0° (c = 0.99, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.32 (d, J = 7.3 Hz, 3 H), 1.47−1.58 (m, 3 H), 1.58−1.67 (m, 1 H), 1.67−1.78 (m, 2 H), 1.78−1.86 (m, 2 H), 1.88−1.94 (m, 1 H), 2.01−2.08 (m, 1 H), 2.22−2.30 (m, 1 H), 2.61 (dd, J = 11.0, 13.8 Hz, 1 H), 2.68−2.87 (m, 1 H), 2.82−2.87 (comp, 2 H), 3.53 (dd, J = 3.2, 9.4 Hz, 1 H), 3.69 (s, 3 H), 3.86 (dd, J = 1.3, 7.6 Hz, 1 H); ^{13}C NMR (125 MHz) δ 18.3, 20.6, 26.7, 28.3, 28.8, 35.7, 36.2, 43.4, 49.4, 51.2, 67.0, 67.5, 88.8, 174.6, 179.5; IR (film) 1731, 1766 cm^{-1}; HRMS (CI) m/z 282.1702 ($C_{15}H_{23}NO_4$ requires 282.1705).

[3′*S*-[3′α,9′α(*S),9′aα]]-Decahydro-4-methyl-5-oxospiro[furan-2(3*H*),9′-[9*H*]pyrrolo[1,2-*a*]azepin]-3′-carboxylic Acid, Hydrobromide Salt (23).** A solution of **22** (0.281 g, 1.00 mmol) in 3 M aqueous HBr (3 mL) was heated to 80 °C for 4 h, and then the solution was concentrated under reduced pressure. The residue was recrystallized from hot acetonitrile to give 0.324 g (93%) of **23** as colorless crystals: mp 238.0−239.0 °C; $[\alpha]_D$ −24.0° (c = 0.82, H_2O); ^{1}H NMR (500 MHz, D_2O/DDS) δ 1.28 (d, J = 9.3 Hz, 3 H), 1.72−1.87 (m, 2 H), 1.87−2.04 (comp, 3 H), 2.04−2.16 (comp, 2 H), 2.16−2.32 (comp, 2 H), 2.36−2.43 (m, 1 H), 2.58−2.66 (m, 2 H), 3.04 (dd, J = 9.5, 16.8 Hz, 1 H), 3.46 (dd, J = 6.6, 13.8 Hz, 1 H), 3.71 (dd, J = 9.6, 14.4 Hz, 1 H), 4.22 (dd, J = 6.0, 12.4 Hz, 1 H), 4.59 (dd, J = 7.0, 11.4 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O/DDS) δ 18.1, 24.8, 25.2, 30.4, 30.8, 37.2, 39.0, 43.9, 57.2, 71.2, 75.2, 89.3, 173.0, 184.9; IR (KBr) 1778, 1738, 1187 cm^{-1}; HRMS (CI) m/z 346.06542 ($C_{14}H_{21}NO_4Br$ requires 346.0654).

[3′*S*-[3′α(*R),9′α(*S**),9′aα]]-3′-(2,5-Dihydro-4-methyl-5-oxo-2-furanyl)decahydro-4-methylspiro[furan-2(5*H*),9′-[9*H*]pyrrolo[1,2-*a*]azepin-5-one (24) and [3′*S*-[3′α(*S**),9′α(*S**),9′aα]]-3′-(2,5-Dihydro-4-methyl-5-oxo-2-furanyl)decahydro-4-methylspiro[furan-2(5*H*),9′-[9*H*]pyrrolo[1,2-*a*]azepin-5-one (26).** $POCl_3$ (94 mg, 0.60 mmol) was slowly added to a solution of **23** (0.174 g, 0.50 mmol) in anhydrous DMF (5 mL) at room temperature, upon which gas evolution was observed. After 15 min, the mixture was concentrated under reduced pressure to provide a dark residue that was dissolved in DMF (5 mL). Furan **9b** (0.509 g, 2.00 mmol) was added, and the resulting mixture was stirred for 6 h at room temperature. Saturated, aqueous $NaHCO_3$ (10 mL) was carefully added, and the mixture was extracted with Et_2O/MeCN (1:1, 4 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. The residual mixture was initially separated by flash column chromatography, eluting with hexane/EtOAc (2:3), and then by HPLC, eluting with hexane/EtOAc (7:3), to give 49 mg (31%) of **24** and 25 mg (16%) of **26** as clear oils.

For **24**: mp 142.1−142.3 °C; $[\alpha]_D$ 58.8° (c = 0.94, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.31 (d, J = 77.4 Hz, 3 H), 1.43−1.68 (comp, 5 H), 1.64 (dd, J = 7.8, 13.6 Hz, 1 H), 1.68−1.97 (comp, 5 H), 1.93 (s, 3 H), 2.41 (dd, J = 10.6, 13.6 Hz, 1 H), 2.67−2.75 (m, 1 H), 3.04−3.10 (m, 1 H), 3.15−3.22 (m, 1 H), 3.47−3.52 (comp, 2 H), 4.98−5.02 (m, 1 H), 7.00 (m, 1 H); ^{13}C NMR (125 MHz) δ 10.7, 17.9, 22.1, 25.8, 27.2, 27.8, 35.8, 27.3, 40.9, 48.3, 65.2, 68.5, 82.5, 89.2, 131.2, 146.4, 173.9, 179.2; IR (KBr) 1757, 1658, 1454, 1190 cm^{-1}; HRMS (CI) m/z 320.1871 ($C_{18}H_{26}NO_4$ requires 320.1862).

For **26**: mp 150.5−151.5 °C; $[\alpha]_D$ +94.1° (c = 4.23, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.28 (d, J = 7.4 Hz, 3 H), 1.40−1.50 (comp, 2 H), 1.51−1.58 (m, 1 H), 1.55−1.62 (m, 1 H), 1.62−1.67 (m, 1 H), 1.67−1.80 (comp, 3 H), 1.82−1.87 (m, 1 H), 1.88−1.94 (m, 1 H), 1.94 (s, 3 H), 1.96−2.03 (m, 1 H), 2.50 (dd, J = 10.8, 13.7 Hz, 1 H), 2.66−2.74 (m, 1 H), 2.93−2.98 (m, 1 H), 3.07−3.13 (m, 1 H), 3.45−3.50 (comp, 2 H), 5.15−5.18 (m, 1 H), 6.97−6.99 (m, 1 H); ^{13}C NMR (125 MHz) δ 10.8, 18.0, 21.5, 24.6, 27.6, 27.9, 36.0, 36.9, 41.6, 48.1, 65.2, 68.0, 81.2, 88.8, 130.8, 147.1, 174.1, 179.3; IR (KBr) 1754, 1454 cm^{-1}; HRMS (CI) m/z 320.1859 ($C_{18}H_{26}NO_4$ requires 320.1862).

[3′*S*-[3′α,9′α(*S),9′aα]]-1′,2′,3′,5′,6′,7′,8′-Octahydro-4-methyl-5-oxospiro[furan-2(5*H*),9′-[9*H*]pyrrolo[1,2-*a*]azepin]-3′-carboxylic Acid, Methyl Ester (27).** A solution of **20** (1.09 g, 3.00 mmol) and NMM (1.82 g, 18.00 mmol) in DMF (30 mL) was heated at reflux for 30 min, whereupon the mixture was cooled to room temperature and then concentrated under reduced pressure. A mixture (3:1) of saturated, aqueous $NaHCO_3$ and brine (30 mL) was added to the residue, and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with hexane/EtOAc (7:3), to afford 0.43 g (51%) of **27** as a clear, colorless oil that solidified upon standing: mp 121−122 °C; $[\alpha]_D$ +3.85° (c = 1.04, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.23−1.28 (m, 1 H), 1.58−1.74 (comp, 4 H), 1.75−1.88 (comp, 4 H), 1.93 (s, 3 H), 2.12−2.20 (m, 1 H), 2.83−2.88 (m, 1 H), 2.88−2.94 (m, 1 H), 3.64 (dd, J = 1.6, 9.5 Hz, 1 H), 3.68 (s, 3 H), 3.78−3.81 (m, 1 H), 7.21 (d, J = 1.4 Hz, 1 H); ^{13}C NMR (125 MHz) δ 10.7, 21.6, 23.6, 29.0, 29.5, 39.6, 49.7, 51.2, 65.3, 67.5, 90.7, 130.4, 150.9, 173.5, 174.2; IR (KBr) 2932, 1740, 1448, 1160, 754 cm^{-1}; HRMS (CI) m/z 280.1538 ($C_{15}H_{21}NO_4$ requires 280.1549).

[3′*S*-[3′α,9′α(*S),9′aα]]-1′,2′,3′,5′,6′,7′,8′-Octahydro-4-methyl-5-oxospiro[furan-2(5*H*),9′-[9*H*]pyrrolo[1,2-*a*]azepin]-3′-carboxylic Acid, Hydrobromide Salt.** A solution of **27** (0.279 g, 1.00 mmol) in 3 M aqueous HBr (3 mL) was heated at 85 °C for 4 h, whereupon the water was removed under reduced pressure. Recrystallization of the residue from hot MeCN provided 0.329 g (95%) of the hydrobromide salt of the amino acid as colorless crystals: mp 203 °C dec; $[\alpha]_D$ +144.2° (c = 0.89, H_2O); ^{1}H NMR (500 MHz, D_2O/DDS) δ 1.72−1.92 (comp, 6 H), 1.92−2.13 (comp, 4 H), 2.55−2.68 (m, 1 H), 3.53−3.67 (m, 1 H), 3.75−3.88 (m, 1 H), 4.06 (dd, J = 6.9, 11.2 Hz, 1 H), 4.63 (dd, J = 6.8, 11.0 Hz, 1 H), 7.50 (s, 1 H); ^{13}C NMR (125 MHz, D_2O/DDS) δ 12.2, 25.2, 26.0, 30.5, 30.6, 35.1, 56.4, 70.1, 74.2, 90.7, 132.7, 154.5, 172.5, 177.7; IR (KBr) 2923, 1765, 1727, 1460, 1358, 1218, 1195 cm^{-1}; HRMS (CI) m/z 344.0488 ($C_{14}H_{19}NO_4Br$ requires 344.0497).

[3′*S*-[3′α(*R),9′α(*S**),9′aα]]-3′-(2,5-Dihydro-4-methyl-5-oxo-2-furanyl)-1′,2′,3′,5′,6′,7′,8′-octahydro-4-methylspiro[furan-2(5*H*),9′-[9*H*]pyrrolo[1,2-*a*]azepin]-5-one (28) and [3′*S*-[3′α(*S**),9′α(*S**),9′aα]]-3′-(2,5-Dihydro-4-methyl-5-oxo-2-furanyl)-1′,2′,3′,5′,6′,7′,8′-octahydro-4-methylspiro[furan-2(5*H*),9′-[9*H*]pyrrolo[1,2-*a*]azepin]-5-one (29).** Phosphorus oxychloride (69 mg, 0.20 mmol) was slowly added to a solution of the amino acid hydrobromide salt from the preceding experiment (37 mg, 0.24 mmol) in DMF (2 mL); gas evolution was observed. After 15 min, the mixture was concentrated under reduced pressure to provide a dark residue that was redissolved in DMF (5 mL), and furan **9b** (0.203 g, 0.80 mmol) was added. After the mixture was stirred for 6 h at room temperature, saturated, aqueous $NaHCO_3$ (2 mL) was carefully added. The mixture was extracted with Et_2O/MeCN (1:1, 4 × 2 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was partially purified by flash column chromatography, eluting with hexane/EtOAc (2:3), to give a mixture of **28** and **29** that was separated by HPLC, eluting with hexane/EtOAc (7:3), to give 21 mg (27%) of **28** and 9 mg (12%) of **29** as clear oils.

For **28**: $[\alpha]_D$ +43.9° (c = 0.23, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.31−1.37 (m, 1 H), 1.37−1.43 (m, 1 H), 1.52−1.63 (comp, 3 H), 1.63−1.74 (comp, 2 H), 1.74−1.84 (m, 1 H), 1.84−1.90 (comp, 2 H), 1.92 (s, 3 H), 1.93 (s, 3 H), 3.12−3.20 (m, 1 H), 3.21−3.28 (m, 1 H), 3.34−3.38 (m, 1 H), 3.56 (dd, J = 3.5, 8.2 Hz, 1 H), 4.98−5.02 (m, 1 H), 6.97 (s, 1 H), 7.06 (s, 1 H); ^{13}C NMR (125 MHz) δ 10.8, 22.8, 25.8, 26.4 27.8, 38.6, 48.9, 65.1, 66.8, 81.9, 90.9, 130.6, 131.2, 146.3, 150.4, 173.1, 173.8; IR (film) 2928, 1745, 1659, 1447 cm^{-1}; HRMS (CI) m/z 317.1633 ($C_{18}H_{23}NO_4$ requires 317.1627).

For **29**: $[\alpha]_D$ −163.8° (c = 0.37, $CHCl_3$); ^{1}H NMR (500 MHz) δ

1.17−1.32 (comp, 2 H), 1.32−1.52 (comp, 2 H), 1.52−1.99 (comp, 12 H), 2.95−3.05 (m, 1 H), 3.12−3.27 (m, 1 H), 3.38−3.44 (m, 1 H), 3.62 (dd, J = 2.6, 8.7 Hz, 1 H), 5.24 (m, 1 H), 6.94 (s, 1 H), 7.14 (s, 1 H); ^{13}C NMR (125 MHz) δ 10.8, 22.1, 24.8, 26.5, 28.8, 39.2, 48.2, 64.9, 66.1, 80.9, 90.7, 130.4, 130.9, 147.0, 150.8, 173.3, 174.0; IR (film) 2927, 1747, 1656, 1447 cm^{-1}; HRMS (CI) m/z 317.1623 ($C_{18}H_{23}NO_4$ requires 317.1627).

Croomine (1). Method A. A solution of **24** (32 mg, 0.10 mmol) and 10% Pd/C (27 mg) in 10% concentrated HCl/EtOH (2 mL) was stirred under H_2 (1 atm) for 8 h, and the mixture was filtered through a Celite pad that was washed with MeOH (1 mL). Saturated, aqueous $NaHCO_3$ (12 mL) was added to the filtrate, and the mixture was extracted with CH_2Cl_2 (6 × 2 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to provide 27 mg (85%) of croomine as a clear, colorless oil: $[\alpha]_D$ +15.6° (c = 0.34, $CHCl_3$), lit.[1d] $[\alpha]_D$ +9.8° (c = 0.11, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.26 (d, J = 7.0 Hz, 3 H), 1.31 (d, J = 7.4 Hz, 3 H), 1.45−1.60 (comp, 3 H), 1.65 (dd, J = 7.6, 13.7 Hz, 1 H), 1.65−1.82 (m, 4 H), 1.82−1.93 (m, 3 H), 1.93−2.02 (m, 1 H), 2.34−2.39 (m, 1 H), 2.54 (dd, J = 10.7, 13.7 Hz), 2.56−2.65 (m, 1 H), 2.68−2.74 (m, 1 H), 3.08−3.17 (comp, 2 H), 3.36 (dd, J = 6.6, 13.8 Hz, 1 H), 3.49 (app t, J = 7.2 Hz, 1 H), 4.29−4.34 (m, 1 H); ^{13}C NMR (125 MHz) δ 14.9 18.0, 22.0, 26.3, 27.1, 27.7, 34.8, 35.0, 36.0, 37.1, 41.1, 48.5, 66.9, 68.8, 80.6, 89.5, 179.4 (2 C's); IR (film) 2934, 1762, 1454, 1191 cm^{-1}; HRMS (CI) m/z 322.2012 ($C_{18}H_{28}NO_4$ requires 322.2018).

Method B. A solution of **28** (16 mg, 0.050 mmol) and 10% Pd/C (13 mg) in 10% concentrated HCl/EtOH (2 mL) was stirred under H_2 (1 atm) for 8 h, whereupon saturated, aqueous $NaHCO_3$ (6 mL) was added. The mixture was extracted with CH_2Cl_2 (6 × 1 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to provide 13 mg (81%) of pure croomine as a clear, colorless oil.

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 Dr. Vincent M. Lynch (The University of Texas) for performing the X-ray crystallographic analyses of compounds **11b−g, 14c, 18**, **19**, **24**, and **26**, and Dr. Robert Pearlman (The University of Texas) for help with the molecular modeling.

Supporting Information Available: Experimental procedures and spectral data for compounds **9a−h** and **11a−h**, partial spectral data for **14a−c,e** and **15a−c,e**, and X-ray crystallographic data for compounds **11b−g** and **14c** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA990077R