De Novo Design, Synthesis, and X-ray Crystal Structures of Pyrrolinone-Based β-Strand Peptidomimetics†

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Abstract: The de novo design and synthesis of a novel non-peptide scaffolding for β-strand/sheet mimics are described. The scaffold consists of repeating 3,5,5-trisubstituted pyrrolinone (enaminone) units punctuated with appropriate amino acid side chains. The iterative construction of the pyrrolinones exploits a highly efficient cyclization of metalloimines, the latter derived from C-terminal aldehydes and readily available α-substituted α-amino ester building blocks. As predicted by interactive computer modeling and confirmed by X-ray crystallography, the polypyrrolinones present the side chains and carbonyl hydrogen-bond acceptors in a solid-state conformation which mimics polypeptide β-sheets. Importantly, the enaminone NH protons form hydrogen bonds both intramolecularly, stabilizing the β-strand conformation, and intermolecularly, promoting sheet formation. The presence or absence of the nitrogen protecting group controlled antiparallel versus parallel sheet formation.

Introduction

Whereas few small peptides adopt preferred conformations in solution, proteins fold into well-defined secondary and tertiary structures, either spontaneously,[1] as determined by their amino acid sequences, or under the influence of chaperones.[2] Attempts to determine whether individual amino acids tend to favor specific secondary structures have given ambiguous results.[3] Of the three types of secondary structures, α-helices and the various turns have received the most study. On the other hand, there have been relatively few investigations of β-sheet model systems, as their propensity to form insoluble aggregates renders them experimentally intractable. However, recent work has explored the requirements for nucleation of β-sheets,[4,5] and modified primary structures have been created to promote the requisite extended conformation.[6–8]

It has been known for some time that proteases bind their substrates and inhibitors by generating β-sheets/strands. This conformational requirement has been exploited in the design of inhibitors of the aspartic acid protease renin[9] and of HIV-1 protease.[10] Cascading β-sheets have also been suggested as the cause of the insoluble amyloid fibrils associated with Alzheimer's disease.[11] In addition, protein–DNA interactions can occur with the protein interface in a β-strand conformation.[12] Further explication of these phenomena, and of the more general issues of protein folding and ligand binding by proteases, will require greater fundamental knowledge of β-sheets.

Peptidomimetics comprise valuable probes for the study of turns and β-sheets in peptides and proteins. The latter mimics are exemplified by the aforementioned inhibitors[9,10] and β-sheet mimics.[4–8] However, traditional peptidyl peptidomimetics suffer from a critical drawback: they contain secondary amide bonds. This polar functionality may account for the poor oral bioavailability of peptide-based pharmaceuticals,[13–15a] not to mention the susceptibility of amides to in vivo degradation by proteases. To address these deficiencies, we have for several years investigated the design and synthesis of novel, non-peptide peptidomimetics,

† This paper is dedicated to the memory of Dr. Johannes A. Meienhofer whose untimely death on October 23, 1993, deprived the international peptide community of one of its most productive and respected colleagues.

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(1) Williamson, M. P.; Waltho, J. P. *Chem. Soc. Rev.* **1992**, 227.

(2) Ellis, R. J. *Nature* **1987**, *328*, 378. For a review, see: Ellis, R. J.; Hemmingsen, S. M. *Trends Biochem. Sic.* **1989**, *14*, 339. Hendrick, J. P.; Hartl, F.-U. In *Annual Review of Biochemistry*; Richardson, C. C.; Abelson, J. N.; Meister, A., Walsh, C. T., Eds.; Annual Reviews, Inc.: Palo Alto, CA, 1993; Vol. 62, p 349.

(3) Levitt, M. *Biochemistry* **1978**, *17*, 4277. Chou, P. Y.; Fasman, G. D. *Biochemistry* **1974**, *13*, 211, 222.

(4) Diaz, H.; Tsang, K. Y.; Choo, D.; Espina, J. R.; Kelly, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 3790 and references cited therein.

(5) Kemp, D. S.; Bowen, B. R.; Muendel, C. C. *J. Org. Chem.* **1990**, *55*, 4650 and references cited therein.

(6) Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Baker, W. R.; Condon, S. L.; deLara, E.; Rosenberg, S. H.; Spina, K. P.; Stein, H. H.; Cohen, J.; Kleinert, H. D. *J. Med. Chem.* **1992**, *35*, 1710.

(7) Hagihara, M.; Anthony, N. H.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568.

(8) Simon, R. J.; Kania, R. S.; Zuckermann, R. N.; Huebner, V. D.; Jewell, K. A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C. K.; Spellmeyer, D. C.; Tan, R.; Frankel, A. D.; Santi, D. V.; Cohen, F. E.; Bartlett, P. A. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 9367.

(9) Kleinert, H. D.; Rosenberg, S. H.; Baker, W. R.; Stein, H. H.; Klinghofer, V.; Barlow, J.; Spina, K.; Polakowski, J.; Kovar, P.; Cohen, J.; Denissen, J. *Science* **1992**, *257*, 1940.

(10) (a) McQuade, T. J.; Tomasselli, A. G.; Liu, L.; Karacostas, V.; Moss, B.; Sawyer, T. K.; Heinikson, R. L.; Tarpley, W. G. *Science* **1990**, *247*, 454. (b) Rich, D. H.; Sun, C.-Q.; Vara Prasad, J. V. N.; Pathiasseril, A.; Toth, M. V.; Marshall, G. R.; Clare, M.; Mueller, R. A.; Houseman, K. *J. Med. Chem.* **1991**, *34*, 1224. (c) Vacca, J. P.; Guare, J. P.; deSolms, S. J.; Sanders, W. M.; Giuliani, E. A.; Young, S. D.; Darke, P. L.; Zugay, J.; Sigal, I. S.; Schleif, W. A.; Quintero, J. C.; Emini, E. A.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1991**, *34*, 1225. (d) deSolms, S. J.; Giuliani, E. A.; Guare, J. P.; Vacca, J. P.; Sanders, W. M.; Graham, S. L.; Wiggins, J. M.; Darke, P. L.; Sigal, I. S.; Zugay, J.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2852 and references cited therein. (e) Askin, D.; Wallace, M. A.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771. (f) Thompson, W. J.; Fitzgerald, P. M. D.; Holloway, M. K.; Emini, E. A.; Darke, P. L.; McKeever, B. M.; Schleif, W. A.; Quintero, J. C.; Zugay, J. C.; Tucker, T. J.; Schwering, J. E.; Homnick, C. F.; Nunberg, J.; Springer, J. P.; Huff, J. R. *J. Med. Chem.* **1992**, *35*, 1685. (g) Young, S. D.; Payne, L. S.; Thompson, W. J.; Gaffin, N.; Lyle, T. A.; Britcher, S. F.; Graham, S. L.; Schultz, T. H.; Deana, A. A.; Darke, P. L.; Zugay, J.; Schleif, W. A.; Quintero, J. C.; Emini, E. A.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1992**, *35*, 1702.

(11) Colon, W.; Kelly, J. W. *Biochemistry* **1992**, *31*, 8654.

(12) Somers, W. S.; Phillips, S. E. V. *Nature* **1992**, *359*, 387.

(13) Hirschmann, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1278.

(14) The cyclic hexapeptide MK-678 exhibits unsatisfactory pharmacokinetics despite its stability to proteolytic enzymes: Veber, D. F.; Saperstein, R.; Nutt, R. F.; Freidinger, R. M.; Brady, S. F.; Curley, P.; Perlow, D. S.; Paleveda, W. J.; Colton, C. D.; Zacchei, A. G.; Tocco, D. J.; Hoff, D. R.; Vandlen, R. L.; Gerich, J. E.; Hall, L.; Mandarino, L.; Cordes, E. H.; Anderson, P. F.; Hirschmann, R. *Life Sci.* **1984**, *34*, 1371. In contrast, cyclosporin contains mostly N-methylated amide bonds and is orally bioavailable: Yoshimura, N.; Matsui, S.; Hamashima, T.; Oka, T. *Transplantation* **1989**, *47*, 351.

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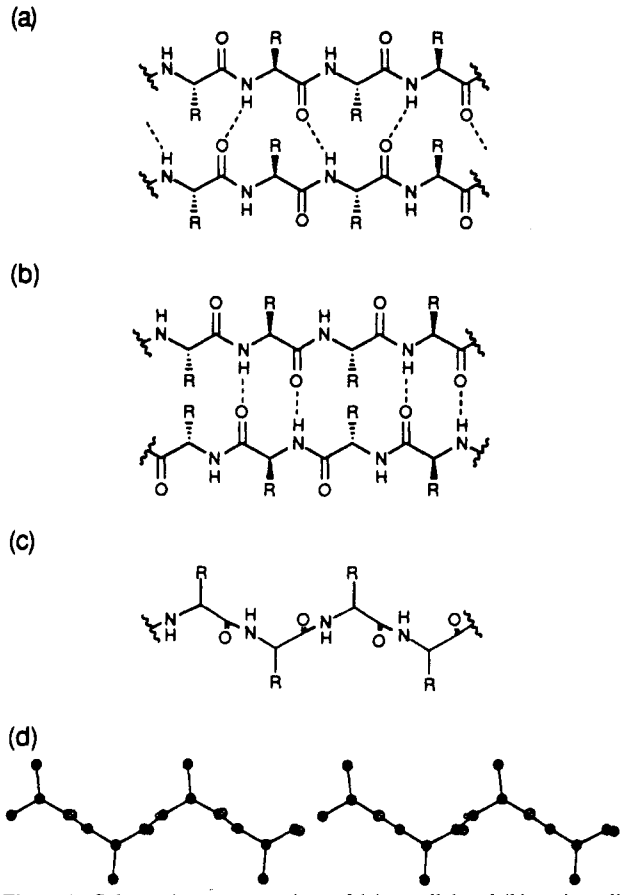


Figure 1. Schematic representations of (a) parallel and (b) antiparallel β-pleated sheets. (c) Top view of one strand of a β-sheet showing the parallel but opposite orientations of adjacent side chains. (d) Stereoview of a β-sheet.

with one program aimed at hormone/neurotransmitter receptor agonists and antagonists[16] and a complementary effort targeting enzyme inhibitors.[15] In an effort to optimize the pharmacokinetic properties of the mimetics, we have sought to eliminate secondary amide backbone linkages altogether.

Design

There are two possible orientations of the peptide chains in β-sheets. When the strands extend in the same direction (N-to-C), the sheet is designated as parallel; in an antiparallel sheet the strands run in opposite directions (Figure 1a,b). In either case, the side chains are oriented orthogonal to the sheet surface (Figure 1c), with an antiperiplanar disposition of adjacent side chains on the same strand. The three-dimensionality of β-strands becomes critical in the active sites of proteases, where both side chains and hydrogen bonds appear to be essential for binding (Figure 2).[17] Thus, a successful β-strand mimic must incorporate not only appropriate side-chain trajectories, but also hydrogen-bonding capabilities.[18] These requirements present an even more formidable challenge than mimicking agonist/antagonist ligands of non-enzyme receptors, for which the natural ligand–receptor interactions are thought for the most part not to involve interactions with the peptide backbones.[19] We also elected to incorporate a repeating backbone structural unit allowing for an iterative synthetic strategy and facilitating application of the scaffolding to the broad spectrum of problems that could potentially be addressed.

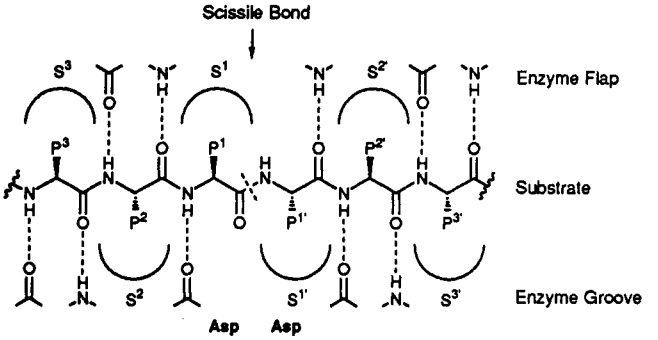


Figure 2. Typical aspartic acid protease active site: row 1, enzyme flap; row 2, substrate; row 3, enzyme groove. The scissile bond of the substrate is shown as a dotted line.

Consideration of these requirements and of the proteolytic stability problem led us to the enaminone functionality. A juxtaposition of peptide and vinylogous amide bonds (Figure 3) reveals the following key elements: (i) the nitrogens have comparable basicity,[20] (ii) the carbonyls possess similar hydrogen-bonding ability, and (iii) the rigid olefin linkage provides an element of rigidity which might confer a degree of conformational

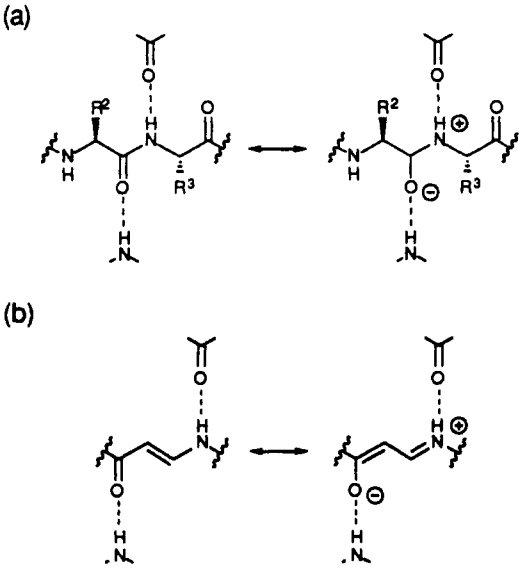


Figure 3. Comparison of amide (a) and enaminone (b) moieties.

(15) (a) Smith, A. B., III; Hirschmann, R.; Pasternak, A.; Akaishi, R.; Guzman, M. C.; Jones, D. R.; Keenan, T. P.; Sprengeler, P. A.; Darke, P. L.; Emini, E. A.; Holloway, M. K.; Schleif, W. A. *J. Med. Chem.* **1994**, *37*, 215. (b) Smith, A. B., III; Akaishi, R.; Jones, D. R.; Keenen, T. P.; Guzman, M. C.; Holcomb, R. C.; Sprengeler, P. A.; Wood, J. L.; Hirschmann, R.; Holloway, M. K. *Peptide Sci.*, in press. For a preliminary account of this work, see: (c) Smith, A. B., III; Keenan, T. P.; Holcomb, R. C.; Sprengeler, P. A.; Guzman, M. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1992**, *114*, 10672. See also: (d) Wood, J. L.; Jones, D. R.; Hirschmann, R.; Smith, A. B., III. *Tetrahedron Lett.* **1990**, *31*, 6329.

(16) (a) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Salvino, J.; Arison, B.; Cichy, M. A.; Spoors, P. G.; Shakespeare, W. C.; Sprengeler, P. A.; Hamley, P.; Smith, A. B., III; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R. M.; Cascieri, M. R.; Strader, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 12550. (b) Hirschmann, R.; Sprengeler, P. A.; Kawasaki, T.; Leahy, J. W.; Shakespeare, W. C.; Smith, A. B., III. *Tetrahedron Symp. Print* **1993**, *49*, 3665. (c) Hirschmann, R.; Sprengeler, P. A.; Kawasaki, T.; Leahy, J. W.; Shakespeare, W. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **1992**, *114*, 9699. (d) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Salvino, J.; Leahy, E. M.; Sprengeler, P. A.; Furst, G.; Smith, A. B., III; Strader, C. D.; Cascieri, M. A.; Candelore, M. R.; Donaldson, C.; Vale, W.; Maechler, L. *J. Am. Chem. Soc.* **1992**, *114*, 9217. (e) Nicolaou, K. C.; Salvino, J. M.; Raynor, K.; Pietranico, S.; Reisine, T.; Freidinger, R. M.; Hirschmann, R. In *Peptides - Chemistry, Structure and Biology: Proceedings of the 11th American Peptide Symposium*; Rivier, J. E., Marshall, G. R., Eds.; ESCOM: Leiden, 1990; p 881.

(17) Rich, D. H. In *Comprehensive Medicinal Chemistry*; Sammes, P. G., Taylor, J. B., Eds.; Pergamon: New York, 1990; Vol. 4, p 391.

(18) Rudinger, J. In *Drug Design*; Areins, E. J., Ed.; Academic: New York, 1971; Vol. 2, p 319.

(19) Walter, R. *Fed. Proc.* **1977**, *36*, 1872.

(20) Meyers, A. I.; Reine, A. H.; Gault, R. *J. Org. Chem.* **1969**, *34*, 698. Also see: Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277.

stability. The design of an enaminone-based β-strand mimic was initiated with the native peptide in the extended conformation (Figure 4). Displacement of the amide nitrogens from the

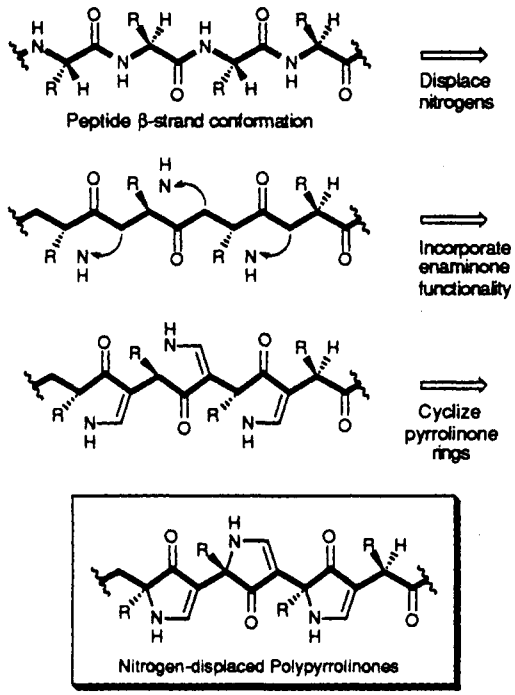


Figure 4. Conceptual derivation of pyrrolinone-based β-sheet mimics.

backbone allowed for incorporation of the olefins, and cyclization of the nitrogens onto the backbone then generated pyrrolinone rings. Because the NH's were displaced relative to a native peptide backbone, we could not predict whether they would participate in β-sheet formation. Via similar conceptual manipulations, we also designed carbonyl-displaced pyrrolinones (Figure 5), but we

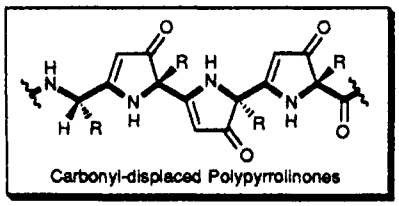


Figure 5. β-Strand mimetic design incorporating carbonyl-displaced 2,5,5-substituted pyrrolinones.

selected the nitrogen-displaced heterocycles for our initial investigations.[21] The additional rigidity imparted by the cyclic structure of the repeating unit is noteworthy. Although Farmer has advised against rigid structures in the search for a peptidomimetic lead compound,[22] we envisioned that the conformational constraints imposed upon the backbone could be offset by confinement of the side chains to suitable trajectories. Moreover, the side chains themselves could freely rotate, allowing for induced fit into an enzyme active site as observed for the native substrates.

Computer Modeling

To determine whether a series of 3,5-linked pyrrolinone rings could adopt an energetically favorable conformation mimicking a peptide β-strand, we performed a variety of molecular mechanics calculations[23] with the MM2 force field.[24] Upon comparison of dipeptide **1** with bispyrrolinone **2**, it was immediately apparent that significantly fewer degrees of freedom are available to **2** (Figure 6). Dipeptide **1** contains three backbone bonds (ψ_1, ϕ_2, and ψ_2) with 360° rotational mobility, plus two ω bonds which can be cis or trans. In contrast, the ψ and ω bonds of bispyrrolinone **2** are locked at 120° and 180°, respectively; only φ can rotate through 360°. Calculation of the energy of rotation about the φ bond in **2** revealed an overall minimum at 310° (vide infra) and a local minimum of slightly higher energy at ca. 205°, the latter mimicking the desired β-strand φ angle (Figure 7). Another local minimum at 80° was predicted to be far less favorable energetically.

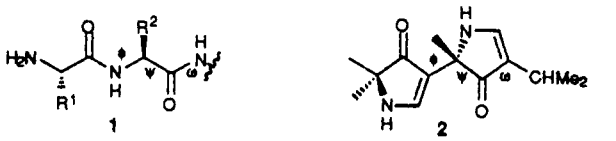


Figure 6. Rotational degrees of freedom for dipeptide **1** and bispyrrolinone **2**.

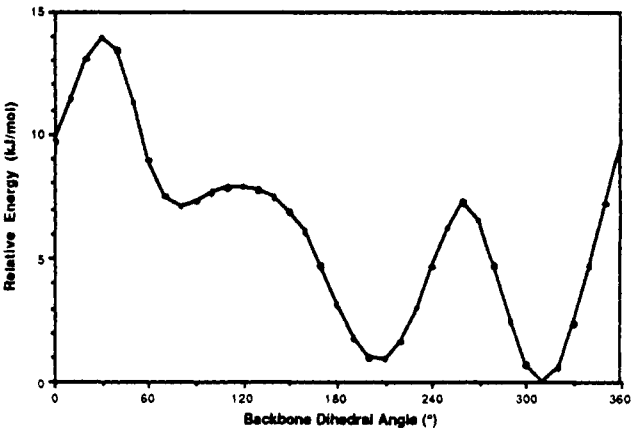


Figure 7. Calculated energy of rotation about φ of **2** at 10° resolution.

To evaluate the backbone conformations for a series of linked pyrrolinones, we undertook a Monte Carlo conformational search[25] on tetrapyrrolinone **3** containing methyl groups. Three classes of structures resulted (Figure 8) differentiated by the dihedral angle φ between the two central rings. The linear arrangement (φ = ca. 200°), analogous to a peptide β-strand, and turned (φ = ca. 310°) and twisted (φ = ca. 60°) rotamers were all found in approximately equal proportions. These dihedral angles correspond quite closely to the three minima calculated for **2** (Figure 7). Examination of pairs of adjacent pyrrolinones in the lowest energy linear conformation of **3** (i.e., **3a**) reveals a six-membered-ring hydrogen bond between a carbonyl oxygen and the NH of the neighboring ring (Figure 9). We believe that this repetitive intrachain H-bonding significantly stabilizes the extended (linear) conformation of our polypyrrolinones (vide infra), whereas in the absence of this interaction, steric repulsion between the oxygen and hydrogen atoms would disfavor the desired rotamers. This analysis further suggests that *N*-methyl substitution which stabilizes turn conformations, employed extensively in the study of peptidyl β-sheets, would be problematic for pyrrolinones if linearity is to be retained.

Prior to initiating the synthesis of a potential protease inhibitor, we sought experimental support for β-sheet formation, exploiting

(21) The cross-conjugated relationship between the adjacent enaminone functional units in the nitrogen-displaced pyrrolinones suggested that they would not be susceptible to nucleophilic cleavage whereas the carbonyl-displaced pyrrolinone enaminones might experience ring opening upon exposure to nucleophiles.

(22) Farmer, P. S. In *Drug Design*; Areins, E. J., Ed.; Academic: New York, 1971; Vol. 10, p 119.

(23) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Henderickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(24) The 1987 version of the MM2 force field was used: Bowen, J. P.; Pathiaseril, A.; Profeta, S., Jr.; Allinger, N. L. *J. Org. Chem.* **1987**, *52*, 5162. See also: Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

(25) Goodman, J. M.; Still, W. C. *J. Comput. Chem.* **1991**, *12*, 1110. See also: Saunders, M.; Houk, K. N.; Wu, Y.-D.; Still, W. C.; Lipton, M.; Chang, G.; Guida, W. C. *J. Am. Chem. Soc.* **1990**, *112*, 1419.

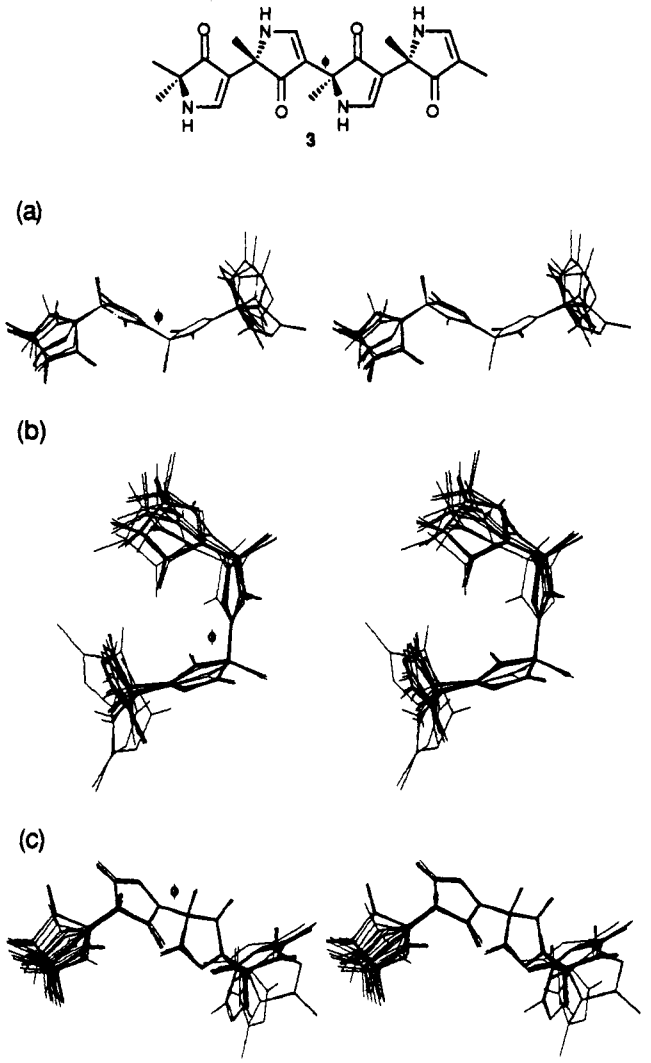


Figure 8. Monte Carlo-generated backbone conformations for tetrapyrrolinone **3**: (a) linear (ϕ = 200°); (b) turned (ϕ = 310°); (c) twisted (ϕ = 60°).

the above design (vide infra). We were in particular concerned that displacement of the secondary amide nitrogen might preclude intermolecular hydrogen bonding to a protease, as required for enzyme inhibition.

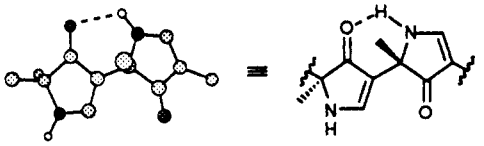


Figure 9. Six-membered-ring hydrogen bond linking adjacent pyrrolinones in the lowest energy linear conformation of **3**.

Selection of an Initial β-Strand Target

In 1987, Precigoux and co-workers[26] reported that the tetrapeptide methyl ester **4** (H-Leu-Leu-Val-Tyr-OMe), a fragment of equine angiotensinogen, crystallizes as a parallel β-sheet (Figure 10). A minor distortion from the ideal β-strand conformation was caused by an intermolecular hydrogen bond between the C-terminal tyrosine hydroxyl and the N-terminus of an adjacent strand in the unit cell. Least-squares comparison of the lowest energy linear conformation obtained for **3** with the crystal structure of tetrapeptide **4** afforded an excellent correspondence

(26) Precigoux, G.; Courseille, C.; Geoffre, S.; Leroy, F. *J. Am. Chem. Soc.* **1987**, *109*, 7463.

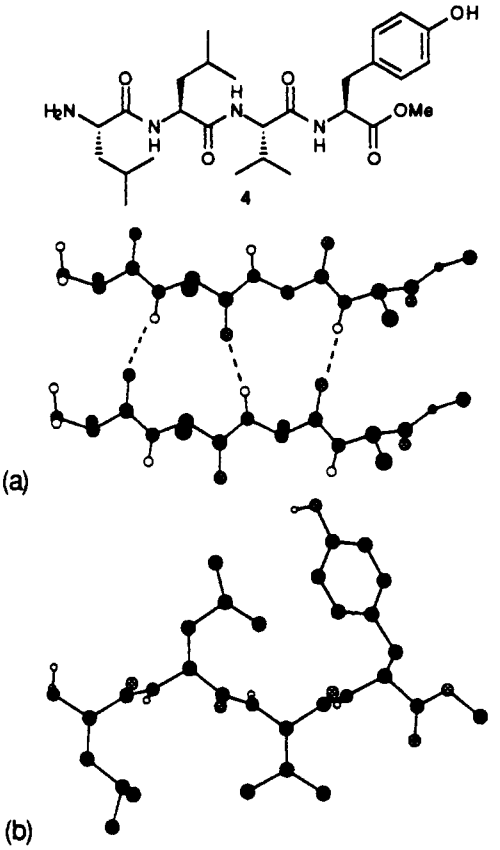


Figure 10. X-ray crystal structure of tetrapeptide **4**:[26] (a) side view; (b) view down the sheet axis.

between backbone atoms and side chains except, as expected, at the C-terminus (Figure 11).

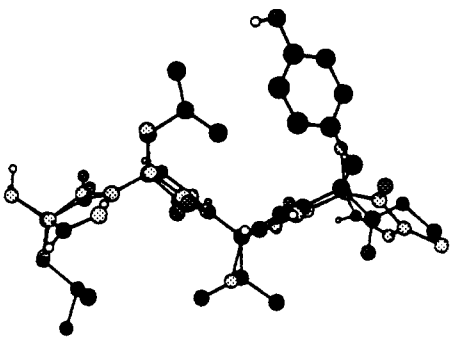


Figure 11. Least-squares overlay of the linear conformation of **3** (gray) and the X-ray structure of **4** (black).

We next undertook the modeling of **5** (Figure 12), a pyrrolinone-based analog of **4**, in the hope that it or a closely related derivative [vide infra, Scheme 10, (–)-**45**] would crystallize and thus prove amenable to study by X-ray diffraction. We excluded the Tyr hydroxyl group primarily to simplify the synthesis. To investigate the effect of the side chains upon the profile of backbone conformations, we performed a Monte Carlo search which revealed only two families of low-energy backbone conformations of **5** similar to the linear and turned conformers computed for **3** (Figure 12). As anticipated, side-chain rotations resulted in a larger number of accessible conformations for **5** than were found for **3**. Few twisted conformers were observed in structures within 8 kJ/mol of the minimum. Least-squares comparison of the lowest energy linear conformation of **5** with the crystal structure of **4** (Figure 13) again revealed a remarkable correspondence between the backbone and side-chain atoms.

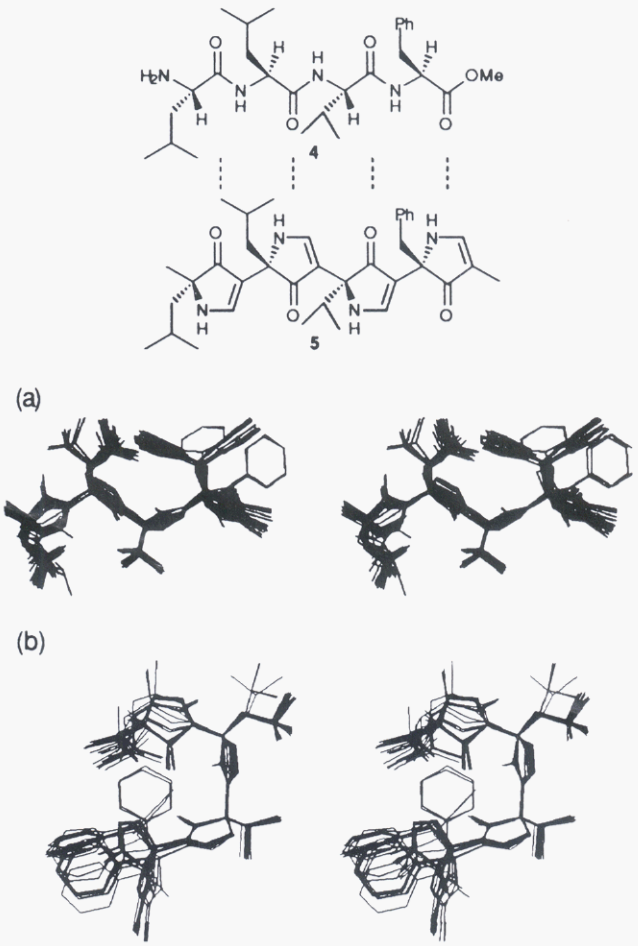
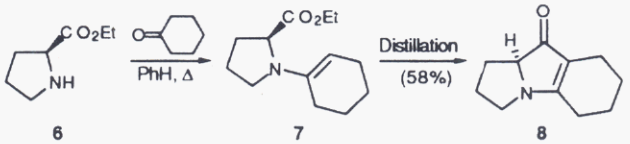


Figure 12. Families of Monte Carlo-generated backbone conformations for **5**: (a) linear and (b) turned.

Iterative Construction of Scalemic Polypyrrolinones

In view of the very promising computational evalulation of linked 3,5,5-substituted pyrrolinones as β-strand mimics, we sought to develop an iterative synthetic approach to the target compounds. Many procedures were available for the preparation of racemic pyrrolinones,[27] but only a single scalemic example had been reported. Hiroi et al. discovered that enamine **7**, the condensation product of L-proline ethyl ester (**6**) with cyclohexanone, cyclized unexpectedly upon distillation to generate the tricyclic pyrrolinone **8** in 58% yield (Scheme 1).[28]

Scheme 1



6 **7** **8**

An analogous retrosynthetic disconnection of the simple monopyrrolinone **9** led to α-substituted α-amino ester **12** and aldehyde **13** (Scheme 2). Condensation of primary amine **12** with **13** was expected to give imine **11** rather than the corresponding enamine.[29] We envisioned, however, that thermolysis of the imine might induce tautomerization to enamine **10**, whereupon cyclization could furnish **9**. Extension of this analysis to polypyrrolinone **14** (Scheme 3) indicated the potential for iterative synthesis via either "C-terminal" or "N-terminal" chain extension. N-terminal disconnection (path a) generates α-alkylated amino ester **12** and aldehyde **15**, the latter accessible by oxidative cleavage of olefin **16**. Repetition of this sequence would furnish monopyrrolinone **17**; similar disconnection of the latter leads in turn to amino ester **12** and aldehyde **18**, available via N–protection of **12** and ozonolysis. C-terminal disconnection

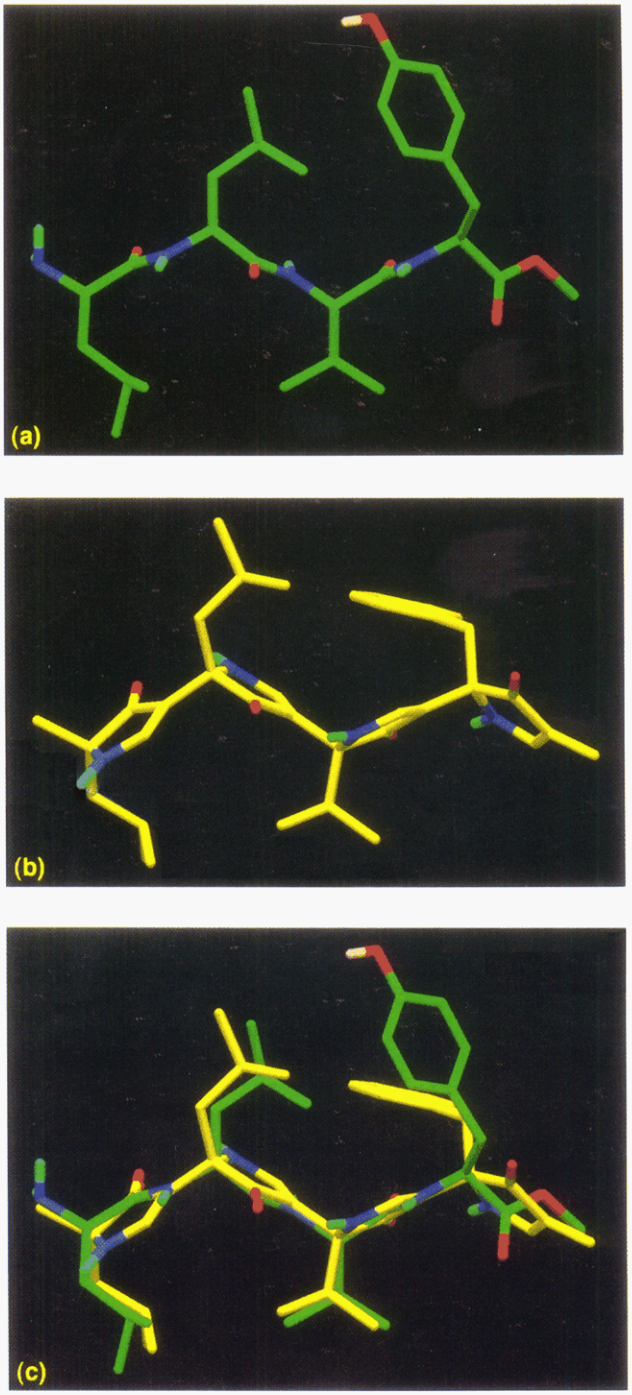


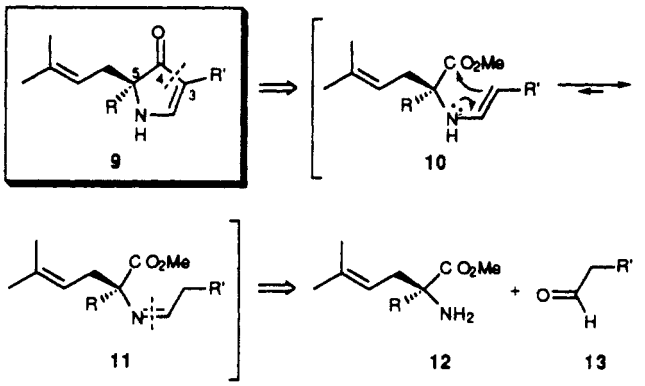
Figure 13. (a) X-ray structure of peptide **4**. (b) Monte Carlo lowest energy linear conformer of **5**. (c) Least-squares overlay of (a) (green) and (b) (yellow).

(27) (a) Flitsch, W.; Hampel, K.; Hohenhorst, M. *Tetrahedron Lett.* **1987**, *28*, 4395. (b) McNab, H.; Monahan, L. C. *J. Chem. Soc., Chem. Commun.* **1985**, 213. (c) Momose, T.; Tanaka, T.; Yokota, T. *Heterocycles* **1977**, 1827. (d) Pfeiffer, G.; Bauer, H. *Liebigs Ann. Chem.* **1976**, 383.

(28) Hiroi, K.; Achiwa, K.; Yamada, S.-I. *Chem. Pharm. Bull.* **1972**, *20*, 246. A similar cyclization of a more highly substituted cyclohexanone was reported previously: Hickmott, P. W.; Woodward, K. N.; Urbani, R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1885.

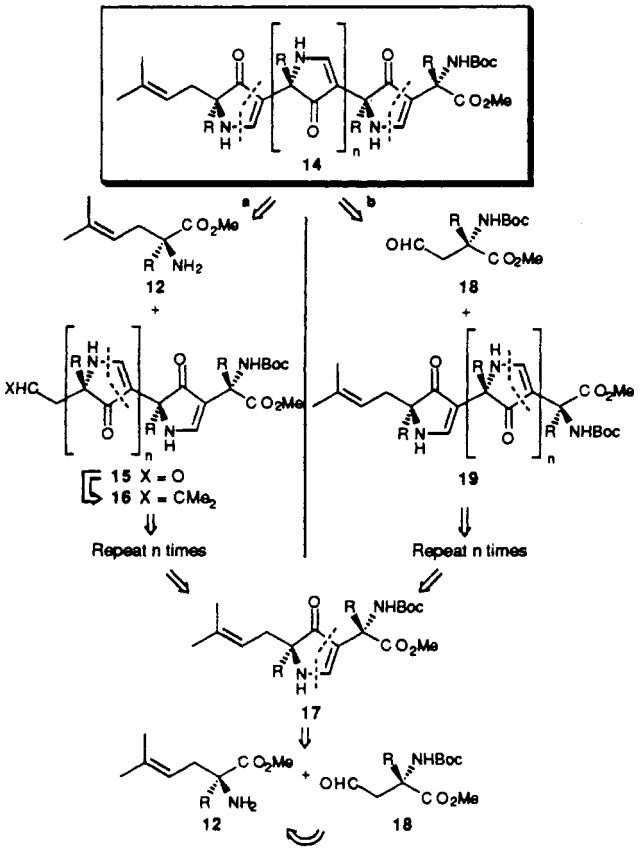
(29) (a) Bianchetti, G.; Dalla Croce, P.; Pocar, D. *Tetrahedron Lett.* **1965**, 2043. (b) Nelson, D. A.; Worman, J. J. *J. Chem. Soc., Chem. Commun.* **1966**, 487. (c) Ahlbrecht, H. *Tetrahedron Lett.* **1968**, 4421. (d) Ahlbrecht, H.; Blecher, J.; Kröhnke, F. *Tetrahedron Lett.* **1969**, 439.

Scheme 2



(path b) yields **18** and amino ester **19**; repetition would then afford **17** as before.

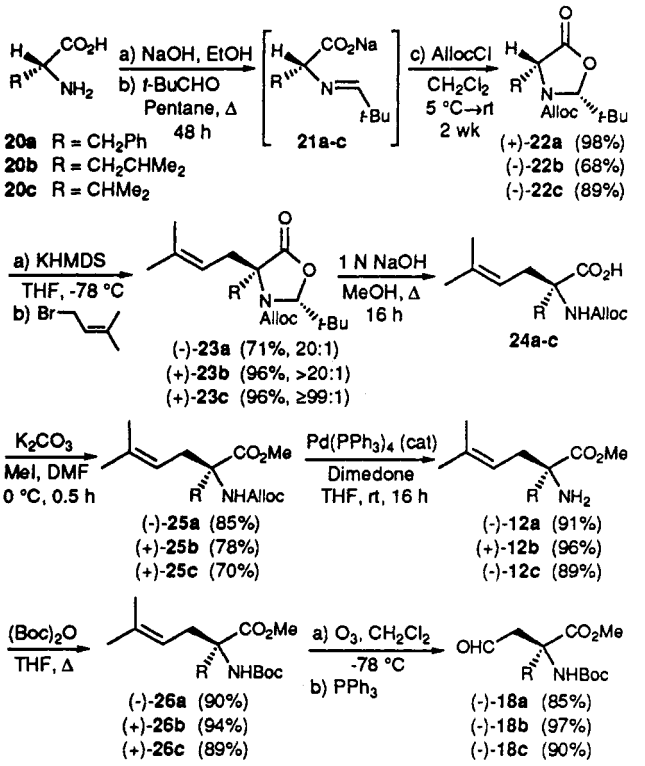
Scheme 3



The above strategy would require an efficient preparation of α-alkylated amino esters such as **12**, amenable to the incorporation of peptidyl side chains. Both Seebach and co-workers[30] and Karady and associates[31] successfully prepared the corresponding amino acids via enantioretentive alkylation of *cis*-oxazolidinones. The latter heterocycles were prepared by N-acylation of imines derived from amino acid sodium salts and pivaldehyde or, alternatively, from Cbz-protected amino acids and aromatic aldehydes. Unfortunately, the Cbz protecting group would be incompatible with our proposed synthesis. Furthermore, the water solubility of the α-alkylated amino acids generated in both approaches proved inconvenient in preparative experiments. We therefore devised an alternative procedure which directly furnished the required amino esters.[32]

The Seebach procedure was employed for imine formation between pivaldehyde and the sodium salts of the D-amino acids phenylalanine, leucine, and valine (Scheme 4). Diverging from

Scheme 4



the earlier sequence, the resultant Schiff bases were cyclized to the corresponding *cis*-oxazolidinones by N-acylation with allyl chloroformate,[33] rather than benzoyl chloride. Seebach's procedure for enantioretentive alkylation (KHMDS, THF, −78 °C; prenyl bromide) then afforded the alkylated oxazolidinones **23a–c** with ≥20:1 diastereoselectivity. Hydrolysis under the conditions developed at Merck (1 N NaOH, MeOH, reflux, 16 h) furnished the Alloc-protected amino acids, which were immediately esterified (MeI, K_2CO_3, DMF). The Alloc protecting group was then removed via selective isomerization of the allyl double bond with catalytic $Pd(PPh_3)_4$ in the presence of dimedone.[34] Finally, Kugelrohr distillation of amino ester building blocks **12a–c** brought this efficient synthesis to fruition (42–52% yields for the six steps; up to 100-g scale). As anticipated, these compounds could be readily converted to aldehydes **18a–c** by Boc N-protection followed by ozonolysis with reductive workup.

With both the scalemic α-amino esters and aldehyde building blocks in hand, the viability of our strategy for the preparation of pyrrolinones could be tested. We initially employed hydrocinnamaldehyde as a model aldehyde; condensation with amino ester (−)-**12a** (benzene or toluene, 15 min) gave the Schiff base **27a** (Scheme 5). Heating according to the Hiroi procedure,[28] neat or in benzene, led only to recovery of starting material or decomposition. Moreover, formation of the tautomeric enamine, the proposed cyclization substrate, could not be demonstrated analytically, suggesting that an amide, carbamate, or secondary amine intermediate might be required. Further functionalization of nitrogen could in principle be performed either before or after reaction with the aldehyde; both routes were investigated (Scheme

(30) (a) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243. (b) Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194.

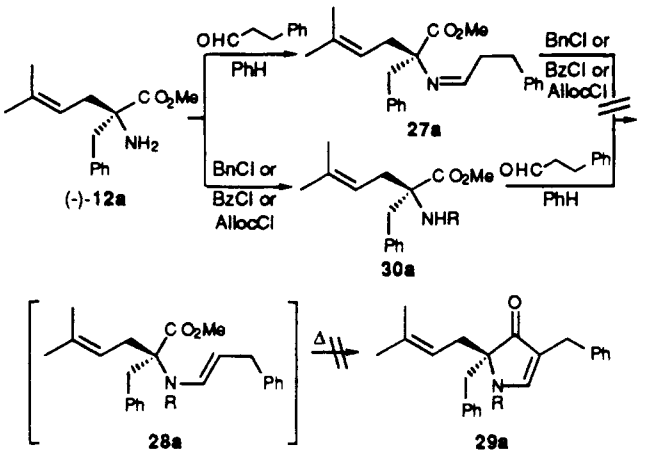
(31) Karady, S.; Amato, J. S.; Weinstock, L. M. *Tetrahedron Lett.* **1984**, *25*, 4337. Amato, J. S.; Weinstock, L. M.; Karady, S. U.S. Patent 4 508 921, 1985.

(32) Smith, A. B., III; Holcomb, R. C.; Guzman, M. C.; Keenan, T. P.; Sprengeler, P. A.; Hirschmann, R. *Tetrahedron Lett.* **1993**, *34*, 63.

(33) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3223.

(34) Kunz, H.; Unverzagt, C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 436.

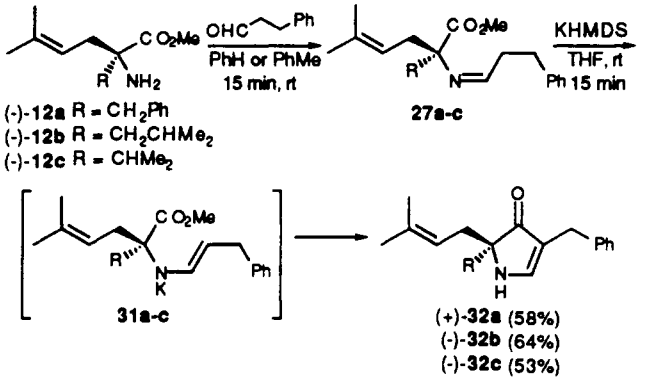
Scheme 5



5). Unfortunately, thermolysis of **28a**, the condensation product of hydrocinnamaldehyde with either the alkylated or acylated amine **30a**, did not afford pyrrolinones. Attempted alkylation and acylation of imine **27a** likewise proved ineffective.

At this juncture we decided to explore the cyclization of a more reactive metalloimine derivative. Whereas this functionality has been extensively exploited in alkylation reactions,[35] the acylation of metalated imines had been reported only twice previously.[36] Bartoli et al.[37] independently expanded on these precedents while our work was in progress. As we had hoped, treatment of imine **27a**, prepared in THF as described above, with potassium hexamethyldisilazide (KHMDS) in toluene (room temperature, 15 min) furnished the desired pyrrolinone (+)-**32a** in 58% yield overall from amino ester **12a** (Scheme 6).

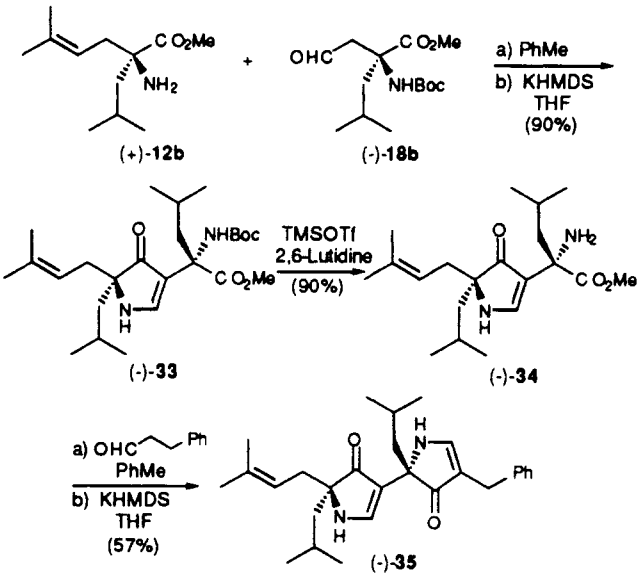
Scheme 6



Heterocycles (–)-**32b** and (–)-**32c** could likewise be prepared with comparable efficiency from the corresponding amino esters. The alternative bases LDA, LiHMDS, and NaHMDS all afforded lower yields of the pyrrolinones.

In similar fashion, coupling of (+)-**12b** with the functionalized aldehyde building block (+)-**18b** furnished monopyrrolinone (–)-**33** (Scheme 7). However, selective cleavage of the prenyl olefin to the corresponding aldehyde, as required for chain extension in the C-to-N direction, could not be achieved by ozonolysis, even in the presence of 1 equiv of ozone; oxidation of the ring double bond undoubtedly interfered. Removal of the *tert*-butyl carbamate in **33** (TMSOTf, CH_2Cl_2, 0 °C) did yield the monopyrrolinone amine (–)-**34**, which was viewed as a prospective

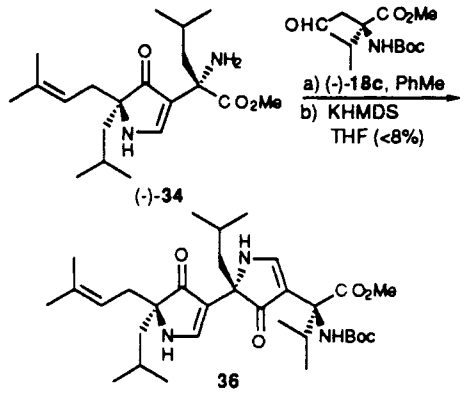
Scheme 7



substrate for N-to-C chain extension. Bispyrrolinone (–)-**35** was then obtained in 57% yield by coupling with hydrocinnamaldehyde.

Unfortunately, the generation of bispyrrolinone **36** via analogous coupling of (–)-**34** with the valine-derived aldehyde **18c** was beset with difficulties (Scheme 8). Combination of amino ester

Scheme 8



34 with aldehyde **18c** in toluene or benzene produced an insoluble gel. *In vacuo* concentration afforded a solid which, by NMR analysis, contained a high proportion of starting materials in addition to the desired imine. The use of chloroform as cosolvent had no effect. Efforts to improve the efficiency of imine formation, via azeotropic removal of water (benzene, reflux, atmospheric pressure), addition of molecular sieves, or use of aza-Wittig procedures, resulted instead in the isolation of an unwanted product. The latter arose via decomposition of monopyrrolinone **34**, and could also be obtained by heating a benzene solution of **34** at reflux. On the basis of ^1H NMR analysis (250 MHz), which showed disappearance of the amine protons and two new vinylic resonances, we tentatively assigned the isomeric structures **40**; these species could arise via the mechanism shown in Scheme 9.

The solid imine also proved to be insoluble in THF, the usual cyclization solvent. Suspensions of the impure material were treated with a variety of bases, furnishing a mixture of starting materials and a new byproduct. Although solubilization of the

(35) For a review, see: Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517.

(36) (a) Wittig, G.; Reiff, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 7. (b) Dannhardt, G.; Geyer, Y.; Obergrusberger, R.; Ziereis, K. *Chem.—Ztg.* **1987**, *111*, 237.

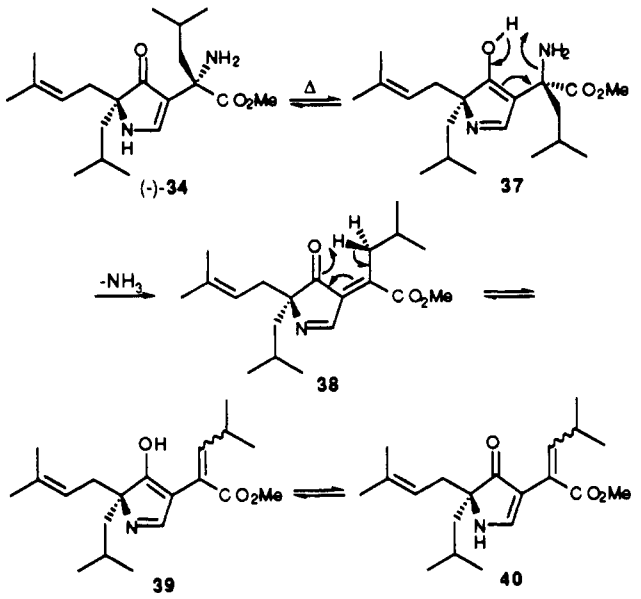
(37) Bartoli, G.; Cimarelli, C.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Synthesis* **1990**, 895.

(38) Van Rheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973–1976.

(39) Criegee, R.; Kraft, L.; Rank, B. *Liebigs Ann. Chem.* **1933**, *507*, 159–197.

(40) Roush, W. R.; Adam, M. A.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, *24*, 1377.

Scheme 9



imine with TMEDA resulted in a 20% yield of the desired bispyrrolinone **36**, the unidentified compound accounted for ca. 23% of the mass balance. This substance appeared to be an α,β-unsaturated γ-lactam, derived from N-acylation of the imine by the ester moiety of **18c**.

Confronted with the problems of gel formation, ammonia elimination in the preparation of imines from pyrrolinone amino esters, and poor chemoselectivity during cyclization, we turned

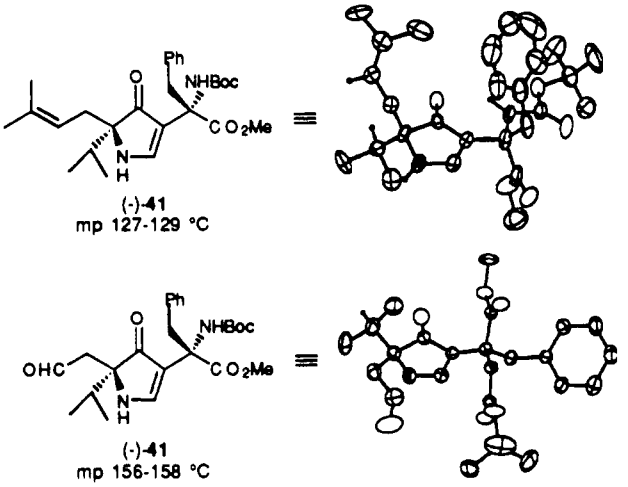
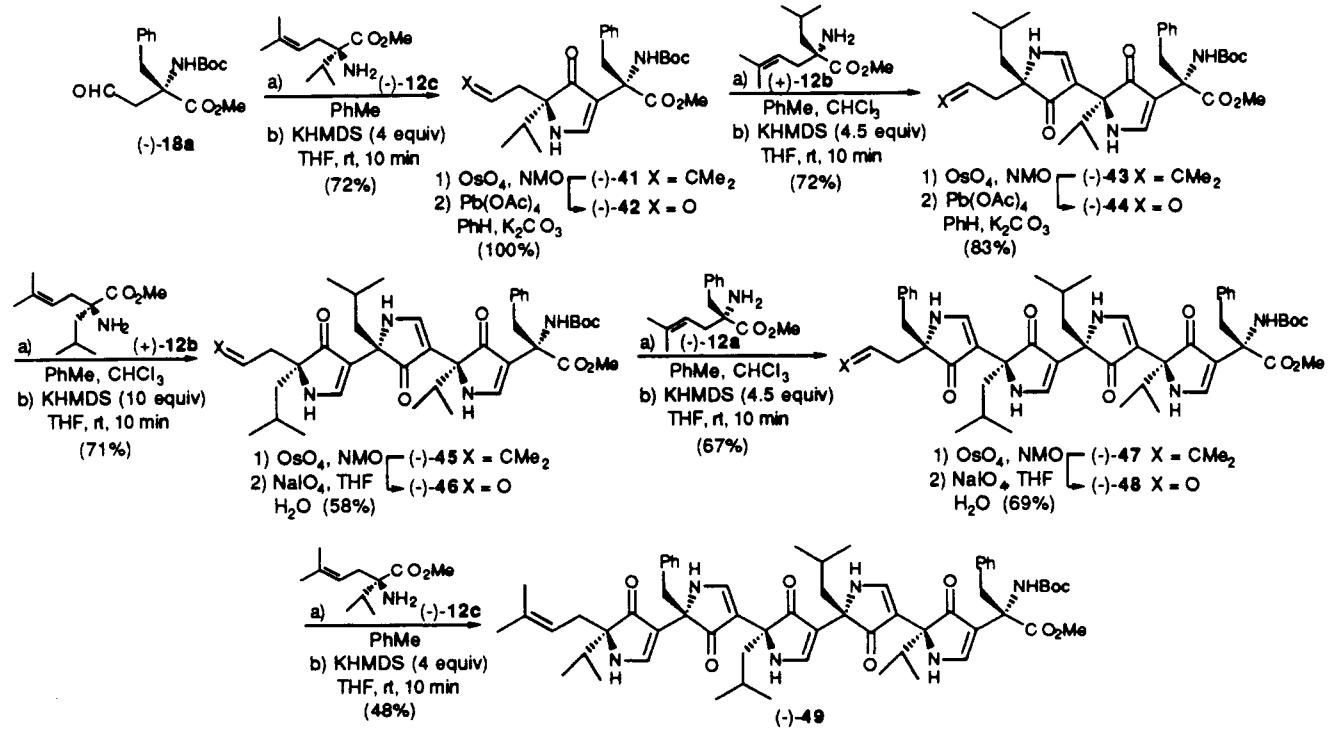


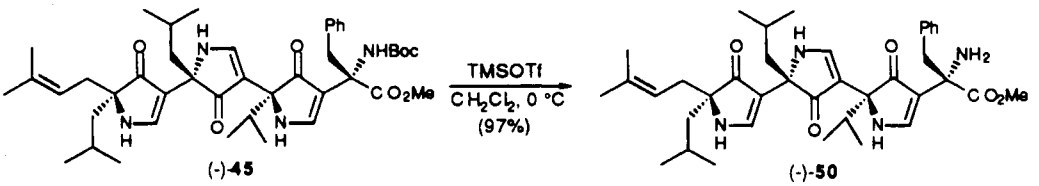
Figure 14. ORTEP plots for monopyrrolinone amides (-)-**41** and (-)-**42**.

once again to the C-to-N chain extension strategy. To circumvent the indiscriminate ozonolysis, we envisioned a two-step protocol for oxidative cleavage of the prenyl group. In the event, monopyrrolinone (-)-**41** (Scheme 10), prepared via the standard KHMDS cyclization procedure, reacted cleanly with catalytic osmium tetraoxide (*N*-methylmorpholine *N*-oxide cooxidant, 8:1 acetone/H_2O, room temperature, 24 h)[38] to furnish a mixture of diastereomeric diols. Treatment with either lead tetraacetate (CH_2Cl_2, 0 °C, 15 min)[39] or sodium periodate (4:1 THF/H_2O, room temperature, 2 h)[40] then provided the requisite monopyrrolinone aldehyde (-)-**42**. Condensation with amino ester (+)-**12b** and cyclization of the resultant imine with KHMDS gave

Scheme 10



Scheme 11



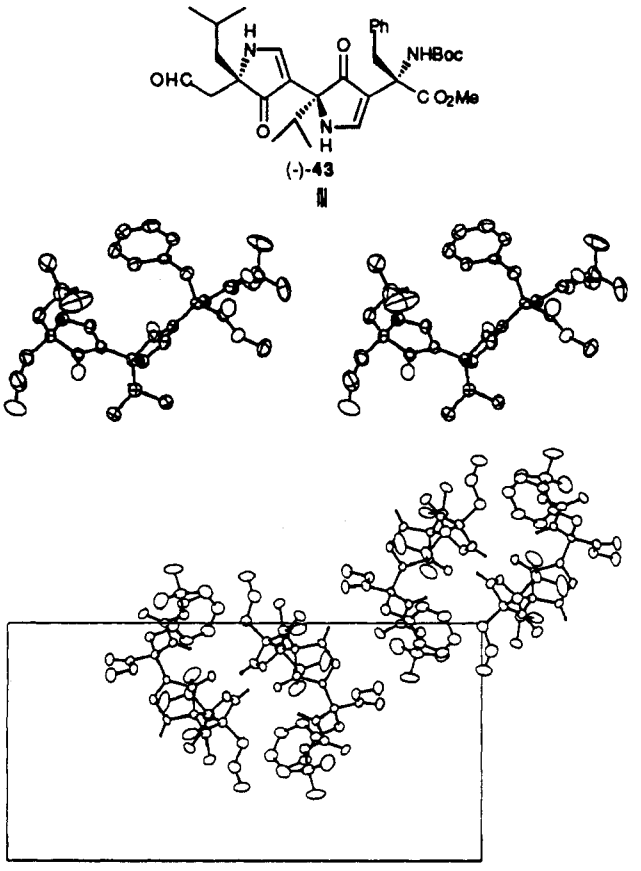


Figure 15. Stereo ORTEP plot and unit cell for bispyrrolinone (–)-**43**.

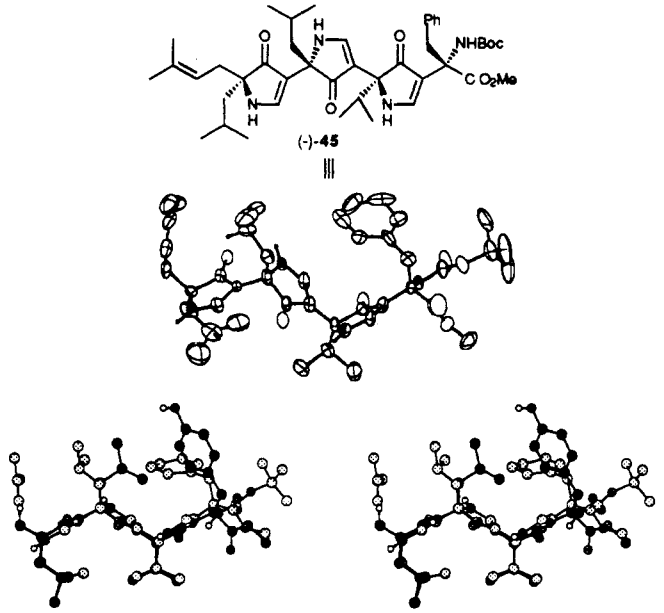


Figure 16. ORTEP plot of trispyrrolinone (–)-**45** and least-squares overlap with the crystal structure of tetrapeptide **4** (stereoview).

bispyrrolinone (–)-**43**; a single iteration of this sequence with **12b** then afforded the previously reported trispyrrolinone (–)-**45**.[15c] We have recently expanded the scope of this stretegy by synthesizing the tetra- and pentapyrrolinones (–)-**47** and (–)-**49**, as outlined in Scheme 10. Finally, the Boc protecting group in **45** was removed as shown in Scheme 11 to afford (–)-**50** (vide infra).

Solid-State Conformations

Throughout our investigation, single-crystal X-ray analyses of intermediates were performed whenever possible. We were able

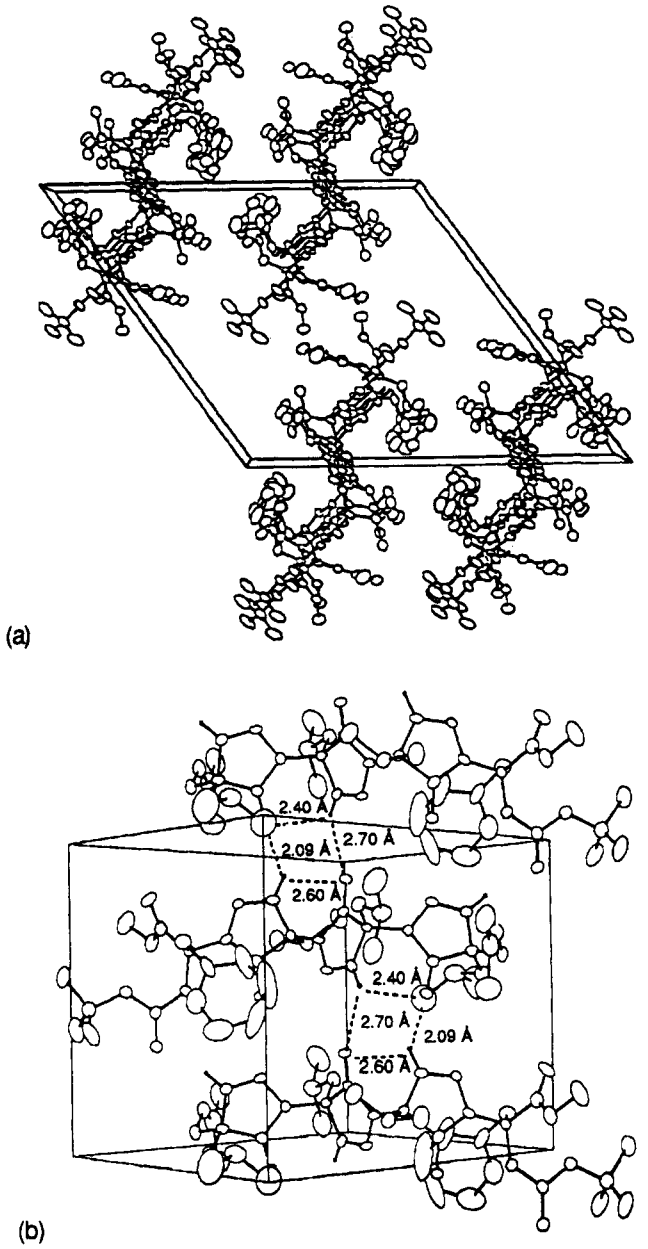


Figure 17. (a) ORTEP plot of the unit cell for trispyrrolinone (–)-**45**. (b) Intra- and intermolecular H-bonding pattern of the unit cell for (–)-**45**.

to determine the solid-state conformations of five compounds in all, as shown in Figures 14–18. The modeling studies had suggested that intramolecular H-bonds joining at least two pyrrolinones would be required to stabilize the desired β-strand conformation. However, the crystal structures of monopyrrolinone amides (–)-**41** and (–)-**42** demonstrated that H-bonding between a carbamate NH and a pyrrolinone carbonyl oxygen likewise can give rise to a β-strand (Figure 14). Bispyrrolinone (–)-**43** followed suit, with the three side chains and three carbonyls directed along the expected trajectories (Figure 15). Unlike the monopyrrolinone amides, the bispyrrolinone does hydrogen bond intermolecularly, albeit not as a β-sheet. Instead, the solid-state structure is dimeric, with the strands oriented at an angle close to 90°. Presumably the unfavorable steric interactions of the *tert*-butyl carbamates interfere with sheet formation.

Our target tetrapeptide mimic, trispyrrolinone (–)-**45**, also adopts the β-strand conformation in the solid state; moreover, both the side-chain trajectories and carbonyl orientations overlap remarkably well with the X-ray structure of tetrapeptide **4** (Figure 16). Importantly, the unit cell reveals head-to-tail molecular stacking in conjunction with interstrand H-bonding, similar to

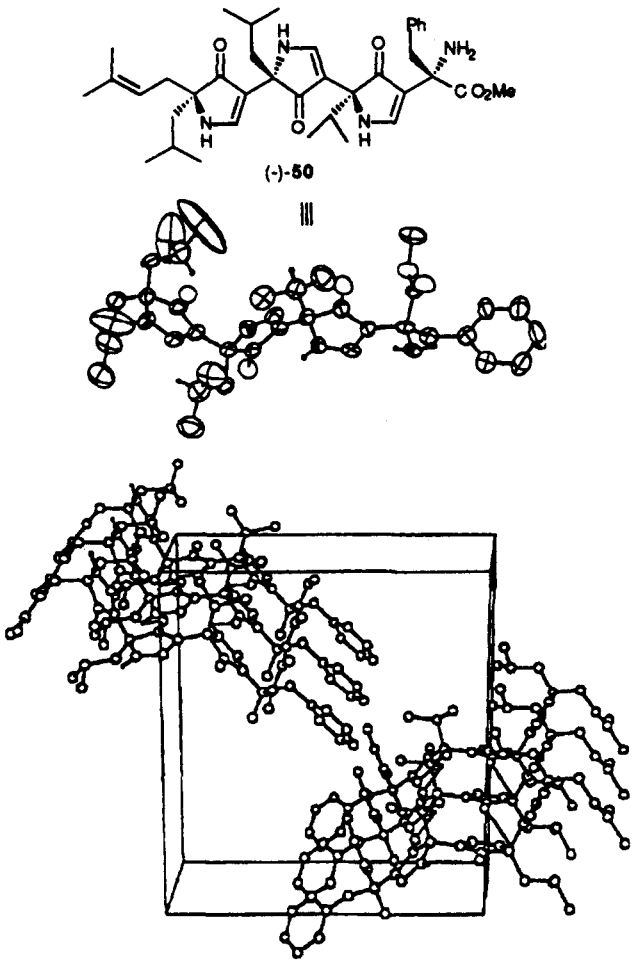


Figure 18. ORTEP plot and unit cell for bispyrrolinone (–)-**50**.

the arrangement found in antiparallel β-sheets (Figure 17). Taken together, these results provide for the first time experimental evidence that the pyrrolinone NH proton, displaced from the peptide backbone, can form a hydrogen bond with the carbonyl of a neighboring strand. This result all but assured that the pyrrolinones would also H-bond with proteases and thus serve as effective enzyme inhibitors.[15a,b]

Finally, the X-ray structure of bispyrrolinone **43**, in conjunction with the parallel-sheet orientation of crystalline tetrapeptide **4**, suggested that removal of the *tert*-butyl carbamate in **45** (Scheme 11) might lead to parallel sheet formation. Indeed, as shown in Figure 18, the deprotected trispyrrolinone (–)-**50** hydrogen bonds intermolecularly to form parallel β-sheets. Interestingly, the primary amine does not intramolecularly H-bond to the adjacent pyrrolinone carbonyl, causing a deviation from the β-strand conformation at the C-terminus. The β-strand conformation of the individual molecules is also apparent.

Conclusion

We have for the first time designed and synthesized a novel enaminone-based scaffolding that with appropriate peptidyl side chains mimics β-strands/sheets. In addition, we have shown that enaminone NH protons can hydrogen bond both intramolecularly, to stabilize the requisite β-strand conformation, and intermolecularly, promoting β-sheet formation. Interactive computer modeling predicted that linked 3,5,5-trisubstituted pyrrolinones (enaminones) would adopt side-chain trajectories and carbonyl H-bond acceptor orientations similar to those of a natural tetrapeptide which crystallizes as a β-sheet. The repeating pyrrolinone unit favored an iterative synthetic approach, and to this end we developed a new protocol for generation of the pyrrolinone ring system via cyclization of metalated imino esters. The first examples of linked tris-, tetra-, and pentapyrrolinones were then prepared in scalemic form. Single-crystal X-ray analysis confirmed that a suitably substituted trispyrrolinone does indeed mimic the solid-state conformation of the tetrapeptide β-sheet. Finally, removal of a Boc protecting group in the trispyrrolinone could be exploited to dictate parallel and antiparallel sheet formation.

Goals for future studies include (a) determination of the solution structures of polypyrrolinones, (b) preparation and evaluation of carbonyl-displaced pyrrolinone mimics, (c) crystallization of pyrrolinone–protein complexes, including those in the active sites of renin and HIV-1 protease, and (d) synthesis of a designed substrate of a protease exploiting the pyrrolinone motif. Our efforts directed toward pyrrolinone-based aspartic acid protease inhibitors will be reported elsewhere.[15b]

Experimental Section[41]

Oxazolidinone (–)-22b. A suspension of D-leucine (**20b**) (25 g, 191 mmol) in absolute ethanol (400 mL) was treated with a solution of NaOH (7.62 g, 191 mmol) in H_2O (45 mL). The resultant mixture homogenized while stirring at room temperature for 0.5 h. After evaporation of most of the solvent in vacuo, the oily concentrate was diluted with pentane (500 mL). Pivaldehyde (31.0 mL, 286 mmol) was then added and the mixture heated at reflux under a Dean-Stark trap until H_2O generation ceased (ca. 48 h). The mixture was cooled to room temperature and concentrated in vacuo, affording a white powder which was dried azeotropically with toluene (3 × 200 mL) and stored under vacuum overnight.

A suspension of the dried salt in CH_2Cl_2 (500 mL) was cooled to 0 °C, allyl chloroformate (30.0 mL, 286 mmol) was added, and the slurry was stirred at 5 °C for 16 days. After dilution with H_2O (200 mL), DMAP (50 mg) was introduced to catalyze the hydrolysis of excess chloroformate. The mixture was stirred for 24 h and then extracted with EtOAc (1 L). The organic layer was washed with 10% aqueous $NaHSO_4$, saturated aqueous $NaHCO_3$, and brine (500 mL each), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (10% EtOAc/hexanes) afforded (–)-**22b** (36.6 g, 68% yield), a single diastereomer, as an opaque solid: mp 37–39 °C; $[\alpha]^{20}_D$ –43.9° (*c* 3.05, $CHCl_3$); IR ($CHCl_3$) 3000 (s), 2880 (m), 1800 (s), 1720 (s), 1655 (w), 1470 (m) cm^{-1}; ^1H NMR(500 MHz, $CDCl_3$) δ 5.97–5.89 (m, 1 H), 5.55 (s, 1 H), 5.35 (dd, *J* = 17.2, 1.3 Hz, 1 H), 5.28 (dd, *J* = 10.4, 0.6 Hz, 1 H), 4.65 (d, *J* = 6.0 Hz, 2 H), 4.35 (dd, *J* = 7.4, 6.6 Hz 1 H), 2.07–2.03 (m, 1 H), 1.84–1.78 (m, 1 H), 1.70–1.65 (m, 1 H), 1.01 (d, *J* = 1.9 Hz, 3 H), 0.99 (d, *J* = 1.9 Hz, 3 H), 0.99 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.95, 155.87, 131.72, 119.16, 96.23, 67.08, 55.49, 42.43, 36.88, 25.01, 24.93 (3 C), 22.73, 22.04; high-resolution mass spectrum (CI, methane) *m/z* 284.1839 [(M + H)$^+$], calcd for $C_{15}H_{26}NO_4$ 284.1862. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.81; H, 8.90; N, 4.83.

Oxazolidinone (+)-22a. Following the procedure described above for (–)-**22b**, reaction of D-phenylalanine (**20a**) (25 g, 151 mmol), NaOH (6.05 g, 151 mmol), and pivaldehyde (25.0 mL, 227 mmol) afforded the corresponding imine carboxylate. Treatment with allyl chloroformate (24.0 mL, 227 mmol; 5 °C, 16 days), workup, and flash chromatography (10% EtOAc/hexanes) provided (–)-**22a**, (36.7 g, 98% yield) as a colorless oil: $[\alpha]^{20}_D$ +5.69° (*c* 8.84, $CHCl_3$); IR ($CHCl_3$) 3040 (m), 2990 (s), 1800 (s), 1725 (s), 1480 (m), 1450 (m), 1380 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.20 (m, 5 H), 5.80–5.72 (m, 1 H), 5.56 (s, 1 H), 5.28–5.21 (m, 2 H), 4.54 (dd, *J* = 12.9, 6.1 Hz, 1 H), 4.51 (dd, *J* = 7.4, 5.9 Hz, 1 H), 4.43 (dd, *J* = 12.4, 5.7 Hz, 1 H), 3.25 (dd, *J* = 13.9, 7.4 Hz, 1 H), 3.13 (dd, *J* = 13.9, 5.9 Hz, 1 H), 1.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.87, 155.69, 136.84, 131.64, 129.49 (2 C), 128.44 (2 C), 126.94, 119.04, 96.24, 67.05, 58.91, 39.21, 37.03, 24.92 (3 C); high-resolution mass spectrum (CI, NH_3) *m/z* 335.1970 [(M + NH_4)$^+$], calcd for $C_{18}H_{27}N_2O_4$ 335.1970. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.23; H, 7.44; N, 4.60.

Oxazolidinone (–)-22c. Following the procedure described above for (–)-**22b**, reaction of D-valine (**20c**) (25.0 g, 213 mmol), NaOH (8.54 g, 213 mmol), and pivaldehyde (34.8 mL, 320 mmol) generated the corresponding imine carboxylate. Treatment with allyl chloroformate (34.0 mL, 320 mmol; 5 °C; 14 days), workup, and flash chromatography (10% EtOAc/hexanes) afforded (–)-**22c**, (51.0 g, 89% yield) as a colorless oil: $[\alpha]^{20}_D$ –14.4° (*c* 12.8, $CHCl_3$); IR ($CHCl_3$) 3040 (m), 2990 (s), 1785 (s), 1710 (s), 1465 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.97–5.89 (m, 1 H), 5.56 (s, 1 H), 5.35 (ddd, *J* = 17.2, 2.8, 1.4 Hz, 1 H), 5.29

(ddd, J = 11.6, 2.4, 1.2 Hz, 1 H), 4.65 (dt, J = 5.9, 1.3 Hz, 2 H), 3.98 (d, J = 10.9 Hz, 1 H), 2.05–1.98 (m, 1 H), 1.27 (d, J = 6.4 Hz, 3 H), 1.09 (d, J = 6.9 Hz, 3 H), 1.00 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.17, 156.50, 131.70, 119.01, 96.21, 67.18, 61.94, 36.59, 31.94, 24.95 (3 C), 19.80, 19.52; high-resolution mass spectrum (CI, NH_3) m/z 270.1683 [$(M + H)^+$], calcd for $C_{14}H_{24}NO_4$ 270.1705. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.70; H, 8.57; N, 4.83.

Prenyloxazolidinone (+)-23b. A solution of oxazolidinone (–)-**22b** (11.5 g, 40.6 mmol) in THF (150 mL) was cooled to –78 °C, and 0.5 M KHMDS in toluene (97.4 mL, 48.7 mmol) was added via a dropping funnel at a rate that maintained an internal temperature of –70 °C. The resultant yellow solution was stirred for 15 min and then treated dropwise with 1-bromo-3-methyl-2-butene (12.1 mL, 81.2 mmol), again maintaining an internal temperature no higher than –70 °C. The reaction was stirred 30 min further at –78 °C and quenched at low temperature (–78 °C) with 10% aqueous $NaHSO_4$ (300 mL). Following extraction with EtOAc (2 × 100 mL), the combined organic phases were washed with 10% aqueous $NaHSO_4$ (2 × 200 mL), saturated aqueous $NaHCO_3$ (200 mL), and brine (200 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (10% EtOAc/hexanes) afforded (+)-**23b**, (13.8 g, 96% yield) as a colorless oil: $[\alpha]^{20}_D$ + 25.6° (c 6.13, $CHCl_3$); IR ($CHCl_3$) 1790 (s), 1720 (s), 1450 (m), 1390 (m), 1190 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96–5.90 (m, 1 H), 5.43 (s, 1 H), 5.36 (dd, J = 17.1, 0.7 Hz, 1 H), 5.28 (dd, J = 10.4, 0.8 Hz, 1 H), 4.82 (t, J = 6.9 Hz, 1 H), 4.68 (dd, J = 12.9, 5.6 Hz, 1 H), 4.51 (dd, J = 12.8, 5.7 Hz, 1 H), 3.10 (br s, 1 H), 2.47 (dd, J = 14.0, 5.5 Hz, 1 H), 2.10 (br s, 1 H), 1.96 (dd, J = 14.5, 5.7 Hz, 1 H), 1.90 (dd, J = 14.6, 5.2 Hz, 1 H), 1.68 (s, 3 H), 1.58 (s, 3 H), 1.06–0.91 (m, 15 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.75, 154.91 (br), 137.86, 131.84, 118.93, 116.03, 95.13, 67.39, 66.49, 46.18, 37.96, 35.50 (br), 26.12, 25.66 (3 C), 24.88, 24.63, 23.73, 18.05; high-resolution mass spectrum (CI, NH_3) m/z 369.2727 [$(M + NH_4)^+$], calcd for $C_{20}H_{37}N_2O_4$ 369.2753. Anal. Calcd for $C_{20}H_{33}NO_4$: C, 68.34; H, 9.46; N, 3.99. Found: C, 68.33; H, 9.81; N, 3.75.

Prenyloxazolidinone (–)-23a. Following the procedure described above for (+)-**23b**, reaction of oxazolidinone (+)-**22a** (6.00 g, 18.9 mmol), 0.5 M KHMDS in toluene (45.4 mL, 22.7 mmol), and 1-bromo-3-methyl-2-butene (5.63 g, 37.8 mmol) followed by workup and flash chromatography (10% EtOAc/hexanes) provided (–)-**23a** (5.19 g, 71% yield) as a colorless oil: $[\alpha]^{20}_D$ –19.7° (c 13.6, $CHCl_3$); IR ($CHCl_3$) 1795 (s), 1720 (s), 1490 (m), 1450 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.18 (m, 5 H), 5.98–5.92 (m, 1 H), 5.45–5.25 (m, 3 H), 4.89 (dd, J = 8.1, 7.2 Hz, 1 H), 4.73 (dd, J = 12.9, 5.9 Hz, 1 H), 4.58 (br m, 1 H), 3.38 (br s, 1 H), 3.30 (d, J = 13.7 Hz, 1 H), 3.05 (br s, 1 H), 2.48 (br s, 1 H), 1.69 (s, 3 H), 1.58 (s, 3 H), 0.55 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.68, 155.40 (br), 138.24, 135.86, 131.67, 130.99 (2 C), 128.24 (2 C), 127.10, 119.24, 115.53, 95.18, 69.13, 66.61, 42.07, 37.52, 36.28 (br), 26.08, 24.95 (3 C), 17.93; high-resolution mass spectrum (CI, NH_3) m/z 403.2529 [$(M + NH_4)^+$], calcd for $C_{23}H_{35}N_2O_4$ 403.2596. Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.10; N, 3.63. Found: C, 71.50; H, 8.39; N, 3.63.

Prenyloxazolidinone (+)-23c. Following the procedure described above for (+)-**23b**, reaction of oxazolidinone (–)-**22c** (6.70 g, 24.9 mmol), 0.5 M KHMDS in toluene (60.0 mL, 29.9 mmol), and 1-bromo-3-methyl-2-butene (7.45 g, 50.0 mmol) followed by workup and flash chromatography (10% EtOAc/hexanes) gave (+)-**23c** (8.08 g, 96% yield) as a colorless oil: $[\alpha]^{20}_D$ +16.4° (c 13.2, $CHCl_3$); IR ($CHCl_3$) 1785 (s), 1710 (s), 1450 (m), 1380 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95–5.87 (m, 1 H), 5.48 (s, 1 H), 5.34 (ddd, J = 17.2, 2.8, 1.4 Hz, 1 H), 5.28 (ddd, J = 10.4, 2.3, 1.0 Hz, 1 H), 4.75–4.71 (m, 1 H), 4.66 (ddt, J = 13.0, 5.9, 1.2 Hz, 1 H), 4.46 (ddt, J = 13.0, 6.0, 1.2 Hz, 1 H), 3.08 (dd, J = 14.4, 8.0 Hz, 1 H), 2.55 (dd, J = 14.7, 6.1 Hz, 1 H), 2.38–2.32 (m, 1 H), 1.77 (s, 3 H), 1.60 (s, 3 H), 1.17 (d, J = 3.3 Hz, 3 H), 1.16 (d, J = 3.2 Hz, 3 H), 0.99 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.30, 154.98, 137.69, 131.94, 118.93, 116.27, 95.09, 70.09, 66.58, 37.72, 35.54, 29.98 (br), 26.16, 25.94 (3 C), 18.82, 18.52, 18.19; high-resolution mass spectrum (CI, methane) m/z 338.2298 [$(M + H)^+$], calcd for $C_{19}H_{32}NO_4$ 338.2331. Anal. Calcd for $C_{19}H_{31}NO_4$: C, 67.63; H, 9.26; N, 4.15. Found: C, 67.77; H, 9.44; N, 4.15.

Alloc-Protected Amino Ester (+)-25b. A solution of oxazolidinone (+)-**23b** (2.00 g, 5.69 mmol) in a mixture of methanol and 1 N aqueous NaOH (30 mL each) was heated at reflux for 16 h. The mixture was cooled to room temperature and concentrated in vacuo, and the resultant mixture was acidified with 10% aqueous $NaHSO_4$ to pH 1 and then extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with H_2O and brine (50 mL each), dried over $MgSO_4$, and concentrated in vacuo.

A solution of the crude residue in DMF (5.0 mL) was treated with anhydrous K_2CO_3 (2.0 g) and cooled to 0 °C. Iodomethane (0.71 mL, 11.4 mmol) was slowly added and the resultant yellow mixture stirred at 0 °C for 30 min and at room temperature for 30 min. The reaction mixture was quenched with H_2O (10 mL) and extracted with ether (2 × 50 mL). The combined extracts were washed with H_2O (4 × 50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (10% EtOAc/hexanes) provided (+)-**25b** (1.31 g, 78% yield) as a colorless oil: $[\alpha]^{20}_D$ +41.8° (c 16.1, $CHCl_3$); IR ($CHCl_3$) 3500 (w), 3420 (s), 2900 (s), 1720 (s), 1650 (w), 1500 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93–5.88 (m, 2 H), 5.30 (d, J = 17.2 Hz, 1 H), 5.20 (d, J = 10.3, 1 H), 4.89 (br t, 1 H), 4.53 (d, J = 3.8 Hz, 2 H), 3.73 (s, 3 H), 3.02 (dd, J = 14.1, 7.1 Hz, 1 H), 2.42–2.38 (m, 2 H), 1.71–1.66 (m, 1 H), 1.66 (s, 3 H), 1.60–1.56 (m, 1 H), 1.58 (s, 3 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.78 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.58, 153.70, 135.44, 132.98, 117.57, 117.15, 64.80, 63.45, 52.24, 43.62, 35.28, 25.82, 24.45, 23.70, 22.35, 17.65; high-resolution mass spectrum (CI, methane) m/z 298.2019 [$(M + H)^+$], calcd for $C_{16}H_{28}NO_4$ 298.2018. Anal. Calcd for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71. Found: C, 64.95; H, 9.23; N, 4.64.

Alloc-Protected Amino Ester (–)-25a. Following the procedure described above for (+)-**25b**, oxazolidinone (–)-**23a** (5.00 g, 13.0 mmol) was hydrolyzed with 1 N NaOH and methanol (65 mL each). Esterification with anhydrous K_2CO_3 (5.0 g) in DMF (5 mL) and iodomethane (1.62 mL, 26.0 mmol) followed by workup and flash chromatography (10% EtOAc/hexanes) afforded (–)-**25a** (3.76 g, 85% yield) as a colorless oil: $[\alpha]^{20}_D$ –23.6° (c 7.24, $CHCl_3$); IR ($CHCl_3$) 3500 (w), 3460 (m), 2900 (m), 1725 (s), 1650 (w), 1500 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.20 (m, 5 H), 5.97–5.88 (m, 1 H), 5.59 (s, 1 H), 5.30 (d, J = 17.2 Hz, 1 H), 5.21 (d, J = 10.5 Hz, 1 H), 4.96 (t, J = 7.3, 1 H), 4.61 (dd, J = 13.5, 5.4 Hz, 1 H), 4.54 (dd, J = 13.4, 5.2 Hz, 1 H), 3.72 (s, 3 H), 3.65 (d, J = 13.6 Hz, 1 H), 3.20–3.13 (m, 1 H), 3.13 (d, J = 13.6 Hz, 1 H), 2.59 (dd, J = 14.1, 7.1 Hz, 1 H), 1.67 (s, 3 H), 1.60 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.93, 154.08, 136.20, 135.71, 132.93, 129.59 (2 C), 128.06 (2 C), 126.71, 117.46, 117.23, 65.09, 64.87, 52.27, 40.50, 34.39, 25.84, 17.76; high-resolution mass spectrum (CI, NH_3) m/z 332.1841 [$(M + H)^+$], calcd for $C_{19}H_{26}NO_4$ 332.1862. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.76; H, 7.49; N, 3.92.

Alloc-Protected Amino Ester (+)-25c. Following the procedure described above for (+)-**25b**, oxazolidinone (+)-**23c** (17.7 g, 52.4 mmol) was hydrolyzed with 1 N NaOH and methanol (150 mL each). Esterification with anhydrous K_2CO_3 (14 g) in DMF (30 mL) and iodomethane (22.4 g, 157 mmol) followed by workup and flash chromatography (10% EtOAc/hexanes) gave (+)-**25c** (10.4 g, 70% yield) as a colorless oil: $[\alpha]^{20}_D$ +22.4° (c 18.4, $CHCl_3$); IR ($CHCl_3$) 3460 (s), 2900 (s), 1720 (s), 1650 (m), 1490 (s), 1440 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94–5.86 (m, 1 H), 5.75 (br s, 1 H), 5.29 (ddd, J = 17.3,

(41) Materials and Methods: All reactions were carried out under argon with dry, freshly distilled solvents, vacuum-flamed glassware, and magnetic stirring, unless otherwise stated. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone, benzene and toluene were distilled from sodium, and dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Triethylamine, diisopropylethylamine, and pyridine were distilled from calcium hydride and stored over KOH. Dimethyl sulfoxide was distilled from calcium hydride and stored over 4-Å molecular sieves. *n*-Butyllithium and cyclohexylmethyllithium were standardized by titration with diphenylacetic acid. All reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck precoated silica gel plates. Flash chromatography was performed with the indicated solvents and E. Merck silica gel 60 (particle size 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds, except as otherwise indicated. All melting points were obtained on a Thomas-Hoover apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 283B spectrophotometer. Proton NMR spectra were recorded on a Bruker AM-500 spectrometer; ^{13}C NMR spectra were recorded on a Bruker WH-250 or WH-500 instrument. Chemical shifts are reported in δ values relative to tetramethylsilane. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter in the solvent indicated. High-resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Center on either a VG Micromass 70/70H or VG ZAB-E spectrometer. High-performance liquid chromatography was performed on a Ranin system equipped with a Dynamax Method Manager, Rabbit MPX solvent delivery system, Rheodyne injector, and Gilson Model 131 refractive index detector or Gilson Model 115 variable-wavelength UV detector. The columns employed were 4.0, 10.0, or 25.0 mm × 25 cm with 8-μm (60-Å) normal-phase packing. Microanalyses were performed by Robertson Labs, Madison, NJ.

3.1, 1.5 Hz, 1 H), 5.19 (dd, J = 10.5, 1.3 Hz, 1 H), 4.90 (m, J = 6.0 Hz, 1 H), 4.56–4.45 (m, 2 H), 3.73 (s, 3 H), 3.12 (dd, J = 13.7, 6.6 Hz, 1 H), 2.65 (dd, J = 14.5, 7.3 Hz, 1 H), 2.50–2.44 (m, 1 H), 1.65 (s, 3 H), 1.58 (s, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.90 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.01, 153.76, 134.60, 132.86, 118.20, 116.79, 67.03, 64.61, 51.86, 33.44, 30.69, 25.68, 17.57, 17.51, 17.46; high-resolution mass spectrum (CI, methane) m/z 284.1877 [(M + H)$^+$], calcd for $C_{15}H_{26}NO_4$ 284.1862. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.67; H, 9.17; N, 4.83.

Primary Amine (+)-12b. A mixture of alloc derivative (+)-**25b** (3.33 g, 11.2 mmol), dimedone (7.9 g, 56 mmol), and $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (50 mL) was stirred at room temperature for 16 h. Following dilution with ether (100 mL) and extraction with 1 N HCl (5 × 75 mL), the combined aqueous layers were made basic by addition of solid K_2CO_3, and additional base was added to facilitate extraction of the product. The resultant mixture was extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine (100 mL, each), dried over magnesium sulfate, and concentrated in vacuo. Kugelrohr distillation (heat gun, 0.01 mmHg) provided (+)-**12b** (2.30 g, 96% yield) as a colorless oil: $[\alpha]^{20}_D$ +34.4° (c 7.48, $CHCl_3$); IR ($CHCl_3$) 3380 (w), 3220 (w), 2980 (s), 1735 (s), 1605 (m), 1450 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01–4.98 (m, 1 H), 3.69 (s, 3 H), 2.43 (dd, J = 14.0, 6.6 Hz, 1 H), 2.25 (dd, J = 14.0, 8.7 Hz, 1 H), 1.76–1.71 (m, 2 H), 1.70 (s, 3 H), 1.62 (s, 3 H), 1.61–1.50 (m, 4 H), 0.94 (d, J = 6.4 Hz, 3 H), 0.82 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.74, 135.60, 117.72, 60.47, 51.30, 48.32, 39.47, 25.59, 24.23, 23.82, 22.19, 17.54; high-resolution mass spectrum (CI, methane) m/z 214.1790 [(M + H)$^+$], calcd for $C_{12}H_{24}NO_2$ 214.1807. Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.58; H, 11.00; N, 6.51.

Primary Amine (−)-12a. Following the procedure described above for (+)-**12b**, reaction of alloc derivative (−)-**25a** (11.9 g, 35.9 mmol), dimedone (15.1 g, 108 mmol), and $Pd(PPh_3)_4$ (750 mg, 0.65 mmol) afforded (−)-**12a** (8.18 g, 91% yield) as an opaque crystalline solid after workup and Kugelrohr distillation: mp 44–45 °C; $[\alpha]^{20}_D$ −2.6° (c 4.53, $CHCl_3$); IR ($CHCl_3$) 3360 (w), 2980 (m), 1735 (s), 1600 (m), 1500 (w), 1445 (m) cm^{-1}; ^{1}H NMR (500 MHz), $CDCl_3$) δ 7.30–7.10 (m, 5 H), 5.07–5.03 (m, 1 H), 3.68 (s, 3 H), 3.18 (d, J = 13.1 Hz, 1 H), 2.79 (d, J = 13.2 Hz, 1 H), 2.60 (dd, J = 14.1, 6.7 Hz, 1 H), 2.48 (dd, J = 14.1, 8.5 Hz, 1 H), 1.73 (s, 3 H), 1.67 (s, 3 H), 1.53 (br s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.92, 136.50, 136.37, 129.84 (2 C), 128.32 (2 C), 126.86, 117.95, 62.57, 51.84, 45.92, 38.73, 26.04, 18.05; high-resolution mass spectrum (CI, NH_3) m/z 248.1654 [(M + H)$^+$], calcd for $C_{15}H_{22}NO_2$ 248.1650. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.89; H, 8.70; N, 5.65.

Primary Amine (−)-12c. Following the procedure described above for (+)-**12b**, reaction of alloc derivative (+)-**25c** (20.0 g, 70.3 mmol), dimedone (19.7 g, 141 mmol), and $Pd(PPh_3)_4$ (406 mg, 0.035 mmol) afforded (−)-**12c** (12.0 g, 86% yield) as a viscous, colorless oil after workup and Kugelrohr distillation: $[\alpha]^{20}_D$ −10.8° (c 13.2, $CHCl_3$); IR ($CHCl_3$) 3500 (w), 3380 (w), 3300 (w), 2985 (s), 1720 (s), 1600 (m), 1445 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (m, 1 H), 3.70 (s, 3 H), 2.39 (dd, J = 14.1, 6.7 Hz, 1 H), 2.32 (dd, J = 14.1, 8.4 Hz, 1 H), 2.03 (m, 1 H), 1.70 (s, 3 H), 1.64 (s, 3 H), 1.43 (br s, 1 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.84 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.48, 136.50, 118.48, 64.29, 51.49, 35.98, 35.17, 25.77, 17.68, 17.62, 15.94; high-resolution mass spectrum (CI, methane) m/z 200.1658 [(M + H)$^+$], calcd for $C_{11}H_{22}NO_2$ 200.1650. Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.30; H, 10.62; N, 7.03. Found: C, 66.06; H, 10.57; N, 7.00.

Boc Derivative (+)-26b. A solution of amine (+)-**12b** (1.72 g, 8.06 mmol) and di-*tert*-butyl dicarbonate (2.20 g, 10.1 mmol) in THF (15 mL) was heated at reflux for 16 h and then allowed to cool. H_2O (15 mL) and DMAP (20 mg) were added to hydrolyze excess dicarbonate. After 30 min the mixture was extracted with EtOAc (2 × 25 mL), and the combined organic layers were washed with 10% aqueous $NaHSO_4$, saturated aqueous $NaHCO_3$, and brine (2 × 25 mL each), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (10% EtOAc/hexanes) provided (+)-**26b** (2.37 g, 94% yield) as a clear, colorless oil: $[\alpha]^{20}_D$ + 34.6° (c 7.48, $CHCl_3$); IR ($CHCl_3$) 3420 (s), 1720 (s), 1500 (s), 1450 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (br s, 1 H), 4.88 (br s, 1 H), 3.74 (s, 3 H), 3.04 (dd, J = 13.8, 7.7 Hz, 1 H), 2.41–2.33 (m, 2 H), 1.68 (s, 3 H), 1.68–1.64 (m, 1 H), 1.59 (s, 3 H), 1.44 (s, 9 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.78 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.87, 153.66, 135.32, 117.91, 78.73, 63.33, 52.19, 43.65, 35.27, 28.31 (3 C), 25.93, 24.54, 23.70, 22.72, 17.73; high-resolution mass spectrum (CI, NH_3) m/z 314.2322 [(M + H)$^+$], calcd for $C_{17}H_{32}NO_4$ 314.2331.

Boc Derivative (−)-26a. Following the procedure described above for (+)-**26b**, reaction of amine (−)-**12a** (1.50 g, 60.6 mmol) and di-*tert*-butyl dicarbonate (1.65 g, 75.8 mmol) afforded (−)-**26a** (1.90 g, 90% yield) as a colorless oil after workup and flash chromatography (10% EtOAc/hexanes): $[\alpha]^{24}_D$ −25.5° (c 1.41, $CHCl_3$); IR ($CHCl_3$) 3425 (s), 2990 (s), 1745 (s), 1710 (s), 1500 (s), 1450 (s), 1370 (s), 1235 (m), 1165 (s), 1075 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.19 (m, 3 H), 7.06–7.04 (m, 2 H), 5.30 (br s, 1 H), 4.95 (br t, 1 H), 3.74 (s, 3 H), 3.65 (d, J = 18.9 Hz, 1 H), 3.16–3.11 (m, 2 H), 2.51 (dd, J = 11.6, 4.5 Hz, 1 H), 1.69 (s, 3 H), 1.61 (s, 3 H), 1.47 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.19, 153.95, 136.54, 135.61, 129.68 (2 C), 128.01 (2 C), 126.63, 117.70, 78.92, 64.87, 52.17, 40.46, 34.46, 28.30 (3 C), 25.92, 17.78; high-resolution mass spectrum (CI, methane) m/z 348.2173 [(M + H)$^+$], calcd for $C_{20}H_{30}NO_4$ 348.2175.

Boc Derivative (+)-26c. Following the procedure described above for (+)-**26b**, reaction of amine (−)-**12c** (632 mg, 3.17 mmol) and di-*tert*-butyl dicarbonate (864 mg, 3.96 mmol) furnished (+)-**26c** (846 mg, 89% yield) as an opaque solid after workup and flash chromatography (10% EtOAc/hexanes): mp 67–69 °C; $[\alpha]^{20}_D$ +13.4° (c 2.26, $CHCl_3$); IR ($CHCl_3$) 3420 (m), 3000 (m), 1710 (s), 1490 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50 (br s, 1 H), 4.93 (br s, 1 H), 3.74 (s, 3 H), 3.12 (br s, 1 H), 2.65 (dd, J = 14.4, 7.0 Hz, 1 H), 2.47 (br s, 1 H), 1.68 (s, 3 H), 1.62 (s, 3 H), 1.44 (s, 9 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.92 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.64, 154.00, 134.77, 118.73, 78.85, 67.05, 52.07, 33.66, 31.04, 28.36 (3 C), 26.07, 17.92, 17.85, 17.79; high-resolution mass spectrum (CI, methane) m/z 300.2152 [(M + H)$^+$], calcd for $C_{16}H_{30}NO_4$ 300.2175. Anal. Calcd for $C_{16}H_{29}NO_4$: C, 64.19; H, 9.76; N, 4.68. Found: C, 64.03; H, 9.76; N, 4.68.

Aldehyde (−)-18b. A solution of olefin (+)-**26b** (7.22 g, 23.0 mmol) in CH_2Cl_2 (100 mL) was cooled to −78 °C, and ozone was bubbled into the reaction until a blue color persisted. After excess ozone was purged with argon, triphenylphosphine (6.03 g, 23.0 mmol) was added and the solution allowed to warm to room temperature. Concentration in vacuo and flash chromatography (20% EtOAc/hexanes) gave (−)-**18b** (6.40 g, 97% yield) as a clear, colorless oil: $[\alpha]^{20}_D$ −4.1° (c 16.7, $CHCl_3$); IR ($CHCl_3$) 3600 (w), 3410 (s), 1720 (br, s), 1500 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1 H), 5.77 (br s, 1 H), 3.77 (s, 3 H), 3.69 (br d, J = 17.5 Hz, 1 H), 2.90 (d, J = 17.6 Hz, 1 H), 2.34 (d, J = 10.4 Hz, 1 H), 1.62–1.52 (m, 2 H), 1.42 (s, 9 H), 0.92 (d, J = 6.5 Hz, 3 H), 0.81 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.29, 173.50, 153.87, 79.51, 59.36, 52.71, 49.71, 43.97, 28.22 (3 C), 23.86, 23.56, 23.23; high-resolution mass spectrum (CI, methane) m/z 288.1812 [(M + H)$^+$], calcd for $C_{14}H_{26}NO_5$ 288.1811.

Aldehyde (−)-18a. Following the procedure described above for (−)-**18b**, ozonolysis of olefin (−)-**26a** (3.64 g, 10.5 mmol) provided (−)-**18a** (2.87 g, 85% yield) as a colorless solid after workup and flash chromatography (10% EtOAc/hexanes): mp 73–75 °C; $[\alpha]^{24}_D$ −72.5° (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3420 (w), 3000 (w), 1750 (s), 1735 (s), 1710 (s), 1500 (s), 1210 (s), 1170 (s), 1080 (m), 1060 (m), 725 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1 H), 7.29–7.25 (m, 3 H), 7.02–7.00 (m, 2 H), 5.54 (br s, 1 H), 3.84 (d, J = 18.4 Hz, 1 H), 3.74 (s, 3 H), 3.61 (d, J = 13.3 Hz, 1 H), 3.07 (d, J = 17.7 Hz, 1 H), 2.98 (d, J = 13.4 Hz, 1 H), 1.45 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.03, 172.11, 154.13, 134.80, 129.72 (2 C), 128.25 (2 C), 127.22, 79.73, 60.80, 52.71, 48.70, 41.39, 28.27 (3 C); high-resolution mass spectrum (CI, NH_3) m/z 322.1634 [(M + H)$^+$], calcd for $C_{17}H_{24}NO_5$ 322.1654. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.58; H, 7.11; N, 4.28.

Aldehyde (−)-18c. Following the procedure described above for (−)-**18b**, ozonolysis of olefin (+)-**26c** (1.00 g, 3.33 mmol) gave (−)-**18c** (0.819 g, 90% yield) as a colorless oil after workup and flash chromatography (10% EtOAc/hexanes): $[\alpha]^{20}_D$ −4.8° (c 2.65, $CHCl_3$); IR ($CHCl_3$) 3600 (w), 3420 (m), 1720 (br, s), 1490 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (br s, 1 H), 5.60 (br s, 1 H), 3.77 (s, 3 H), 3.68 (m, 1 H), 3.06 (d, J = 17.6 Hz, 1 H), 2.32 (m, 1 H), 1.41 (m, 11 H), 0.92 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.67, 172.31, 154.47, 79.71, 63.07, 52.52, 46.18, 34.62, 28.24 (3 C), 17.42, 17.23; high-resolution mass spectrum (CI, methane) m/z 274.1622 [(M + H)$^+$], calcd for $C_{13}H_{24}NO_5$ 274.1654. Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.13. Found: C, 57.21; H, 8.69; N, 4.93.

Monopyrrolinone (+)-32a. At room temperature a solution of amino ester (−)-**12a** (500 mg, 2.03 mmol) in toluene (8.1 mL) was treated with hydrocinnamaldehyde (0.29 mL, 2.23 mmol). Condensation was effected

via concentration in vacuo followed by azeotropic dehydration with additional toluene (5 × 8 mL). The resultant oil was then dissolved in THF (20 mL), and 0.5 M KHMDS in toluene (10.1 mL, 5.07 mmol) was added dropwise rapidly at room temperature The dark green reaction mixture was stirred for 15 min, quenched with 10% aqueous $NaHSO_4$ (25 mL), and extracted with EtOAc (3 × 25 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine (75 mL each), dried over $MgSO_4$, and concentrated in vacuo. Crystallization of the resultant oil (50% CH_2Cl_2/hexanes) gave (+)-**32a** (389 mg, 58% yield) as a yellow crystalline solid: mp 140.5–142.5 °C (EtOAc/hexanes); $[\alpha]^{20}_D$ +22.0° (*c* 1.43, $CHCl_3$); IR ($CHCl_3$) 3470 (m), 2990 (m), 1660 (s), 1580 (s), 1490 (w), 1450 (m), 1420 (m), 1145 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 3.7 Hz, 1 H), 7.22–6.90 (m, 10 H), 5.34 (d, *J* = 2.9 Hz, 1 H), 5.00 (m, 1 H), 3.35 (s, 2 H), 3.00 (d, *J* = 13.4 Hz, 1 H), 2.86 (d, *J* = 13.4 Hz, 1 H), 2.44 (dd, *J* = 14.5, 7.2 Hz, 1 H), 2.36 (dd, *J* = 14.5, 7.5 Hz, 1 H), 1.66 (s, 3 H), 1.58 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 161.5, 140.7, 135.8, 135.6, 130.0 (2 C), 128.3 (2 C), 128.2 (2 C), 127.9 (2 C), 126.6, 125.6, 117.4, 113.7, 70.4, 42.1, 34.9, 28.1, 25.8, 18.1; high-resolution mass spectrum (CI, NH_3) *m/z* 332.2034 [(M + H)$^+$], calcd for $C_{23}H_{26}NO$ 332.2014.

Monopyrrolinone (–)-32b. Following the procedure described above for (+)-**32a**, condensation of amino ester (+)-**12b** (500 mg, 2.34 mmol) with hydrocinnamaldehyde (0.34 mL, 2.58 mmol) followed by reaction with 0.5 M KHMDS (11.7 mL, 5.86 mmol) provided (–)-**32b** (450 mg, 64% yield) as a light yellow solid after workup and crystallization. Recrystallization afforded a white solid: mp 82–83 °C (hexanes); $[\alpha]^{20}_D$ –64.4° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 3440 (m), 2975 (m), 1655 (s), 1580 (s), 1490 (w), 1450 (m), 1415 (m), 1150 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 2.0 Hz, 1 H), 7.28–7.15 (m, 5 H), 5.02 (br s, 1 H), 4.99–4.95 (m, 1 H), 3.49 (apparent q, *J* = 15.8 Hz, 2 H), 2.28 (apparent d, *J* = 7.9 Hz, 2 H), 1.69–1.54 (m, 3 H), 1.66 (s, 3 H), 1.58 (s, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H), 0.80 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 161.2, 140.9, 135.4, 128.5 (2 C), 128.3 (2 C), 125.8, 117.7, 113.5, 70.4, 44.6, 36.4, 28.4, 25.8, 24.5, 24.3, 23.8, 18.0; high-resolution mass spectrum (CI, NH_3) *m/z* 297.2074 [M$^+$], calcd for $C_{20}H_{27}NO$ 297.2093.

Monopyrrolinone (–)-32c. Following the procedure described above for (+)-**32a**, condensation of amino ester (–)-**12c** (500 mg, 2.52 mmol) with hydrocinnamaldehyde (0.37 mL, 2.77 mmol) followed by cyclization with 0.5 M KHMDS (12.6 mL, 6.30 mmol) afforded (–)-**32c** (376 mg, 53% yield) as a tan crystalline solid after workup and crystallization: mp 96–97 °C (5% EtOAc/hexanes); $[\alpha]^{20}_D$ –22.5° (*c* 0.78, $CHCl_3$); IR ($CHCl_3$) 3450 (m), 2980 (m), 1655 (s), 1590 (s), 1495 (w), 1450 (m), 1160 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 3.3 Hz, 1 H), 7.26–7.14 (m, 5 H), 4.97 (br s, 1 H), 4.93–4.89 (m, 1 H), 3.50 (d, *J* = 15.8 Hz, 1 H), 3.40 (d, *J* = 15.8 Hz, 1 H), 2.44 (dd, *J* = 14.5, 7.9 Hz, 1 H), 2.36 (dd, *J* = 14.5, 7.9 Hz, 1 H), 2.00 (heptet, *J* = 6.6 Hz, 1 H), 1.61 (s, 3 H), 1.57 (s, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.80 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 162.2, 141.1, 134.6, 128.4 (2 C), 128.2 (2 C), 125.7, 117.5, 114.4, 72.8, 33.5, 28.2, 25.8, 18.0, 17.1, 16.5; high-resolution mass spectrum (CI, NH_3) *m/z* 283.1948 [M$^+$], calcd for $C_{19}H_{25}NO$ 283.1936.

Monopyrrolinone (–)-33. At room temperature a solution of amino ester (+)-**12b** (1.0 g, 4.69 mmol) in toluene (20 mL) was treated with aldehyde (–)-**18b** (1.41 g, 4.92 mmol) in toluene (20 mL). Condensation was effected via concentration in vacuo followed by azeotropic dehydration with additional toluene (3 × 50 mL). The resultant oil was then dissolved in THF (75 mL), and 0.5 M KHMDS in toluene (32.8 mL, 16.4 mmol) was added dropwise. The reaction mixture was stirred for 10 min, diluted with EtOAc (200 mL), and quenched with 10% aqueous $NaHSO_4$ (200 mL). The organic phase was washed with 10% aqueous $NaHSO_4$ and saturated aqueous $NaHCO_3$ (2 × 100 mL each), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (30% EtOAc/hexanes) furnished (–)-**33** (2.36 g, 90% yield) as a glassy light yellow solid: mp 123–125 °C; $[\alpha]^{24}_D$ –66.1° (*c* 1.19, $CHCl_3$); IR ($CHCl_3$) 3450 (w), 3420 (w), 33.20 (w), 2970 (s), 1740 (s), 1720 (s), 1650 (m), 1570 (m), 1490 (s), 1370 (m), 1240 (m), 1175 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 3.6 Hz, 1 H), 6.78 (br s, 1 H), 5.31 (s, 1 H), 5.00 (t, *J* = 6.9, 1 H), 3.65 (s, 3 H), 2.29 (dd, *J* = 13.9, 5.3 Hz, 1 H), 2.18 (d, *J* = 7.2 Hz, 2 H), 2.09 (dd, *J* = 13.8, 6.0 Hz, 1 H), 1.65 (s, 3 H), 1.60 (m, 2 H), 1.55 (s, 3 H), 1.48 (m, 1 H), 1.37 (m, 1 H), 1.37 (s, 9 H), 0.88 (d, *J* = 6.7 Hz, 3 H), 0.84 (d, *J* = 6.7 Hz, 3 H), 0.82 (d, *J* = 6.6 Hz, 3 H), 0.75 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.75, 173.89, 161.92, 154.40, 135.91, 117.38, 114.39, 110.75, 78.77, 71.09, 59.77, 52.21, 44.11, 42.11, 36.54, 28.31, 25.84, 24.29, 24.20, 23.53, 17.96; high-resolution mass spectrum (CI, NH_3) *m/z* 451.3142 [(M + H)$^+$], calcd for $C_{25}H_{43}N_2O_5$ 451.3172. Anal. Calcd for $C_{25}H_{42}N_2O_5$: C, 66.64; H, 9.40; N: 6.22 found: C, 66.43; H, 9.06; N, 5.99.

Primary Amine (–)-34. At 0 °C a solution of the Boc-protected monopyrrolinone (–)-**33** (335 mg, 0.743 mmol) in CH_2Cl_2 (5.0 mL) was treated with TMSOTf (331 mg, 1.49 mmol). The cold bath was removed, and the reaction mixture was stirred for 15 min and then partitioned between CH_2Cl_2 (25 mL) and saturated aqueous $NaHCO_3$ (100 mL). The organic layer was washed with aqueous $NaHCO_3$ (100 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (20% EtOAc/hexanes) provided (–)-**34** (236 mg, 90% yield) as a yellow solid which was crystallized from hexanes/EtOAc at 0 °C: mp 108–109 °C; $[\alpha]^{24}_D$ –68.4° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 3480 (m), 3400 (w), 2985 (s), 1740 (s), 1660 (s), 1580 (s), 1440 (w), 1230 (m), 1170 (m), 910 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 3.5 Hz, 1 H), 5.18 (br s, 1 H), 5.03 (t, *J* = 1.3 Hz, 1 H), 3.67 (s, 3 H), 2.23 (d, *J* = 7.4 Hz, 1 H), 1.80–1.75 (m, 1 H), 1.69 (s, 3 H), 1.65 (dd, *J* = 14.1, 7.1 Hz, 1 H), 1.60–1.56 (m, 1 H), 1.58 (s, 3 H), 1.52 (dd, *J* = 12.5, 6.4 Hz, 1 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 0.87 (d, *J* = 6.4 Hz, 3 H), 0.86 (d, *J* = 6.5 Hz, 3 H), 0.78 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.61, 176.26, 159.88, 135.66, 117.50, 115.16, 70.86, 58.29, 51.99, 46.79, 44.02, 36.47, 25.87, 24.71, 24.34, 24.21, 23.86, 23.63, 23.01, 18.08; high-resolution mass spectrum (CI, methane) *m/z* 351.2612 [M$^+$], calcd for $C_{20}H_{35}N_2O_3$ 351.2647. Anal. Calcd for $C_{20}H_{34}N_2O_3$: C, 68.54; H, 9.78; N, 7.99. Found: C, 68.61; H, 9.65; N, 7.75.

Bispyrrolinone (–)-35. A mixture of amino ester (–)-**34** (75 mg, 0.214 mmol) and benzene (2.14 mL) was treated with hydrocinnamaldehyde (0.056 mL, 0.428 mmol). After 15 min the solution was concentrated in vacuo and the residue azeotropically dehydrated with additional benzene (5 × 2 mL), with addition of the minimum volume of $CHCl_3$ needed to effect dissolution at each stage. A solution of the resultant solid in THF (2.14 mL) was treated with 0.5 M KHMDS in toluene (1.50 mL, 16.4 mmol). After 15 min, the emerald green solution was quenched with 10% aqueous $NaHSO_4$ (5 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL), and the combined extracts were washed with saturated aqueous $NaHCO_3$ and brine (15 mL each), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (20% EtOAc/hexanes) gave (–)-**35** (53.3 mg, 57% yield) as a yellow solid: mp 103–105 °C dec; $[\alpha]^{24}_D$ –195.4° (*c* 1.24, $CHCl_3$); IR ($CHCl_3$) 3450 (m), 3330 (w), 3000 (m), 2960 (s), 2950 (s), 1645 (s), 1580 (s), 1435 (m), 1160 (s); ^1H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 3.8 Hz, 1 H), 7.59 (d, *J* = 2.3 Hz, 1 H), 7.19 (m, 3 H), 7.13 (d, *J* = 6.8 Hz, 2 H), 5.69 (br s, 1 H). 4.95 (t, *J* = 6.9 Hz, 1 H), 3.45 (s, 3 H), 1.82 (dd, *J* = 13.8, 4.20 Hz, 1 H), 1.64 (s, 3 H), 1.62 (m, 1 H), 1.57 (s, 3 H), 1.55 (m, 2 H), 1.52 (m, 1 H), 1.41 (heptet, *J* = 6.5 Hz, 1 H), 0.85 (d, *J* = 6.7 Hz, 3 H), 0.82 (d, *J* = 6.5 Hz, 3 H), 0.77 (d, *J* = 6.7 Hz, 3 H), 0.65 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.50, 203.17, 162.70, 160.57, 140.78, 135.87, 128.87, 128.30, 125.84, 117.11, 112.14, 110.04, 71.27, 68.22, 47.89, 44.79, 36.06, 28.39, 25.88, 24.82, 24.58, 24.46, 24.22, 23.66, 23.49, 18.08; high-resolution mass spectrum (CI, methane) *m/z* 435.3024 [(M + H)$^+$], calcd for $C_{28}H_{39}N_2O_2$ 435.3011.

Monopyrrolinone (–)-40. A solution of amino ester (–)-**34** (0.0750 g, 0.214 mmol) in benzene (1.22 mL) was treated with aldehyde (–)-**18c** (0.0666 g, 0.235 mmol) in benzene (1.00 mL) at room temperature. After intermittent agitation over a 5 min period, an insoluble gel was observed. Concentration in vacuo, followed by azetropic dehydration with additional benzene (5 × 1.00 mL), resulted in a solid which was dissolved in a mixture of HMPA (1.11 mL) and THF (0.60 mL), and then added dropwise to a solution (0.51 mL) of LDA [generated from diisopropylamine (0.15 mL, 1.03 mmol) and *n*-butyllithium in hexanes (1.6 M, 0.62 mL, 0.962 mmol)] at –78 °C in THF. The reaction mixture was stirred for 1 h at 0 °C, followed by an additional 2 h at room temperature, and then quenched with 10% aqueous $NaHSO_4$ (4 mL). The resulting mixture was extracted with Et_2O (4 × 4 mL), and the combined organic phases were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl (16 mL each), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (20% EtOAc/hexanes) furnished (–)-**40** (0.0231 g, 33% yield) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 4.2 Hz, 1 H), 6.59 (d, *J* = 10.0 Hz, 1 H), 5.49 (br s, 1 H), 5.00 (t, *J* = 1.4 Hz, 1 H), 3.75 (s, 3 H), 2.84 (m, 1 H), 2.26 (dd, *J* = 14.6, 7.6 Hz, 1 H), 2.22 (dd, *J* = 15.4, 7.3 Hz, 1 H), 1.66 (s, 3 H), 1.63 (m, 1 H), 1.59 (m, 1 H), 1.56 (s, 3 H), 1.55 (m, 1 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 0.83 (d, *J* = 6.5 Hz, 3 H), 0.78 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.69, 168.50, 160.31, 142.94, 135.90, 121.70, 117.57, 116.21, 108.99, 70.91, 51.35, 44.30, 36.41, 29.28, 25.88, 24.46, 24.31, 23.89, 23.02, 18.05; high-

resolution mass spectrum (CI, NH_3) m/z 334.2373 [(M + H)$^+$], calcd for $C_{20}H_{32}NO_3$ 334.2382.

Monopyrrolinone (–)-41. Solutions of amine (–)-**12c** (886 mg, 4.45 mmol) and aldehyde (–)-**18a** (1.50 g, 4.67 mmol) in toluene (25 mL each) were combined and concentrated in vacuo, and the residue was azeotropically dehydrated with additional toluene (3 × 50 mL). The resultant oil was dissolved in THF (40 mL) and treated with 0.5 M KHMDS in toluene (35.6 mL, 17.8 mmol). After 10 min the reaction mixture was partitioned between EtOAc and 10% aqueous $NaHSO_4$ (100 mL each), and the organic phase was then washed with 10% aqueous $NaHSO_4$ and saturated aqueous $NaHCO_3$ (2 × 100 mL each), dried over $MgSO_4$, and concentration in vacuo. Flash chromatography (30% EtOAc/hexanes) afforded (–)-**41** (1.50 g, 72% yield) as a white solid which was crystallized from ether by slow evaporation: mp 127–129 °C; $[\alpha]^{21}_D$ –50.2° (*c* 1.26, $CHCl_3$); IR ($CHCl_3$) 3480 (m), 3470 (w), 3415 (w), 2990 (m), 1745 (s), 1705 (s), 1660 (m), 1580 (m), 1490 (s), 1380 (m), 1165 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 3.5 Hz, 1 H), 7.24–7.18 (m, 3 H), 7.07–7.05 (m, 2 H), 6.38 (br s, 1 H), 5.17 (br s, 1 H), 4.94 (t, J = 5.8 Hz, 1 H), 3.78 (d, J = 13.4 Hz, 1 H), 3.71 (s, 3 H), 3.39 (d, J = 13.3 Hz, 1 H), 2.41 (dd, J = 14.3, 7.1 Hz, 1 H), 2.28 (dd, J = 15.0, 8.2 Hz, 1 H), 1.99–1.93 (m, 1 H), 1.65 (s, 3 H), 1.57 (s, 3 H), 1.43 (s, 9 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.82 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.00, 172.64, 162.98, 154.37, 135.99, 134.60, 130.04 (2 C), 127.82 (2 C), 126.62, 117.00, 110.40, 78.87, 73.18, 60.54, 52.17, 39.39, 33.38, 32.99, 28.29 (3 C), 25.71, 17.86, 16.89, 15.96; high-resolution mass spectrum (CI, methane) m/z 471.2838 [(M + H)$^+$], calcd for $C_{27}H_{39}N_2O_5$ 471.2859. Anal. Calcd for $C_{27}H_{38}N_2O_5$: C, 68.91; H, 8.14; N, 5.95. Found: C, 68.85; H, 8.15; N, 5.92.

Aldehyde (–)-42. Procedure A. A solution of the prenylmonopyrrolinone (–)-**41** (1.25 g, 2.66 mmol) in acetone and H_2O (8:1, 90 mL) was treated with *N*-methylmorpholine *N*-oxide (622 mg, 5.31 mmol) and a few crystals of OsO_4 (ca. 5 mg). The mixture was stirred for 24 h and then partitioned between 10% aqueous $NaHSO_3$ (25 mL) and EtOAc (50 mL). The organic layer was washed with 10% aqueous $NaHSO_3$ and brine (2 × 25 mL each), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (50% → 100% EtOAc/hexanes, gradient elution) gave the corresponding diol (1.32 g, 96% yield) as a yellow glass. This material was dissolved in benzene (15 mL) and treated with K_2CO_3 (1.0 g) and lead tetraacetate (1.47 g, 3.32 mmol). The resultant mixture was stirred for 10 min and partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), dried over $MgSO_4$, and concentrated in vacuo. Crystallization from Et_2O at 5 °C afforded (–)-**42** (904 mg) as colorless needles. Concentration of the filtrate followed by flash chromatography (50% EtOAc/hexanes) provided additional product (73 mg, 83% overall yield from olefin) which was crystallized from ether at 0 °C.

Procedure B. A solution of (–)-**41** (2.21 g, 4.69 mmol) and *N*-methylmorpholine *N*-oxide (1.10 g, 9.39 mmol) in acetone and H_2O (8:1, 135 mL) was treated with a few crystals of OsO_4 (ca. 5 mg) and stirred for 24 h. The reaction mixture was quenched with 10% aqueous $NaHSO_3$ and extracted with EtOAc (75 mL each). The organic phase was washed with 10% aqueous $NaHSO_3$ (75 mL) solution, and the combined aqueous layers were extracted with EtOAc (75 mL). The combined organic phases were then washed with brine (75 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (1:2:8 EtOH/EtOAc/hexanes) furnished the diol (2.42 g, 100% yield) as a yellow glass. The diol was dissolved in THF and H_2O (1:1, 24 mL), and $NaIO_4$ (1.54 g, 7.04 mmol) was slowly added portionwise. After 1 h, the reaction mixture was partitioned between H_2O and ether (50 mL each), the aqueous phase was extracted with ether (2 × 50 mL), and the combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, and concentrated in vacuo. The resultant white solid (2.10 g, 100% yield) was carried forward without further purification. An analytical sample was recrystallized from ether: mp 156–158 °C; $[\alpha]^{24}_D$ –35.0° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3450 (w), 3480 (w), 2980 (w), 1750 (m), 1725 (s), 1705 (s), 1675 (m), 1580 (w), 1490 (s), 1160 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (d, J = 3.6 Hz, 1 H), 8.32 (br s, 1 H), 7.24–7.21 (m, 3 H), 7.03–7.02 (m, 2 H), 6.25 (br s, 1 H), 5.91 (br s, 1 H), 3.83 (d, J = 13.2 Hz, 1 H), 3.73 (s, 3 H), 3.35 (d, J = 13.1 Hz, 1 H), 2.74 (dd, J = 15.6, 3.9 Hz, 1 H), 2.63 (d, J = 15.5 Hz, 1 H), 2.09–2.03 (m, 1 H), 1.43 (s, 9 H), 0.95 (d, J = 6.9 Hz, 3 H), 0.84 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 199.94, 199.85, 172.17, 163.92, 154.09, 135.52, 129.89 (2 C), 128.02 (2 C), 126.90, 111.71, 79.14, 70.89, 60.03, 52.52, 48.19, 39.19, 33.96, 28.23 (3 C), 16.79, 15.56; high-resolution mass spectrum (CI, methane) m/z 445.2312 [(M + H)$^+$], calcd for $C_{24}H_{33}N_2O_6$ 445.2338. Anal. Calcd for $C_{24}H_{32}N_2O_6$: C, 64.85; H, 7.26; N, 6.30. Found: C, 64.85; H, 7.40; N, 6.39.

Bispyrrolinone (–)-43. A solution of aldehyde (–)-**42** (2.11 g, 4.75 mmol) in toluene (17 mL) was treated with amine (+)-**12b** (920 mg, 4.31 mmol). After 15 min the solution was concentrated in vacuo, and the residue was azeotropically dehydrated with toluene (5 × 17 mL) and then subjected to high vacuum for 15–20 min. The resultant oil was dissolved in THF (43 mL), and 0.5 M KHMDS in toluene 38.8 mL, 19.4 mmol) was added. The reaction mixture was stirred for 10 min and quenched with 10% aqueous $NaHSO_4$ (100 mL). The aqueous phase was extracted with EtOAc (2 × 100 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine (300 mL each), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (40% EtOAc/hexanes) provided (–)-**43** (1.88 g, 72% yield) as a clear crystalline solid: mp 164–165 °C (ether); $[\alpha]^{21}_D$ –180° (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3450 (w), 3420 (w), 3350 (w), 2975 (m), 1740 (m), 1705 (s), 1645 (s), 1575 (s), 1485 (s), 1450 (m), 1165 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 3.5 Hz, 1 H), 8.19 (d, J = 4.0 Hz, 1 H), 7.53 (d, J = 3.4 Hz, 1 H), 7.18–7.17 (m, 3 H), 7.01–7.00 (m, 2 H), 6.51 (br s, 1 H), 5.43 (br s, 1 H), 4.97 (t, J = 7.3 Hz, 1 H), 3.73 (s, 3 H), 3.71–3.69 (m, 1 H), 3.42 (d, J = 13.2 Hz, 1 H), 2.34 (dd, J = 14.4, 7.9 Hz, 1 H), 2.26 (dd, J = 14.3, 6.8 Hz, 1 H), 2.02–1.96 (m, 1 H), 1.69–1.59 (m, 4 H), 1.59 (s, 3 H), 1.54–1.50 (m, 2 H), 1.41 (s, 9 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.84 (d, J = 5.9 Hz, 3 H), 0.80 (d, J = 6.7 Hz, 3 H), 0.76 (d, J = 5.7 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 203.79, 201.03, 172.77, 163.80, 160.69, 154.22, 136.19, 135.93, 130.16 (2 C), 127.87 (2 C), 126.66, 117.23, 110.48, 108.21, 78.89, 71.38, 71.25, 60.45, 52.43, 44.91, 39.89, 37.82, 35.62, 28.39 (3 C), 25.88, 24.63, 24.16, 23.63, 18.12, 16.97, 15.98; high-resolution mass spectrum (CI, methane) m/z 608.3701 [(M + H)$^+$], calcd for $C_{35}H_{50}N_3O_6$ 608.3699.

Aldehyde (–)-44. Procedure A. A solution of the prenylbispyrrolinone (–)-**43** (750 mg, 1.23 mmol) in acetone and H_2O (8:1, 45 mL) was treated with *N*-methylmorpholine *N*-oxide (289 mg, 2.47 mmol) and a few crystals of OsO_4 (ca. 5 mg). The mixture was stirred for 24 h and then partitioned between 10% aqueous $NaHSO_3$ (25 mL) and EtOAc (50 mL). The organic layer was washed with 10% aqueous $NaHSO_3$ and brine (2 × 25 mL each), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (50% → 100% EtOAc/hexanes, gradient elution) gave the corresponding diol as a yellow glass. This material was dissolved in benzene (10 mL) and treated with K_2CO_3 (750 mg) and lead tetraacetate (684 mg, 1.54 mmol). The resultant mixture was stirred for 10 min and then partitioned between H_2O and EtOAc (50 mL each). The organic phase was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), dried over $MgSO_4$, and concentrated in vacuo. Crystallization from Et_2O at 5 °C afforded (–)-**44** (457 mg, 64% yield) as colorless needles. Concentration of the filtrate followed by flash chromatography (50% EtOAc/hexanes) provided additional product (95 mg, 13% yield, 77% overall yield from the olefin) which was crystallized from ether at 0 °C.

Procedure B. A solution of (–)-**43** (1.94 g, 3.19 mmol) and *N*-methylmorpholine *N*-oxide (0.748 g, 6.38 mmol) in acetone and H_2O (8:1, 90 mL) was treated with a few crystals of OsO_4 (ca. 5 mg) and stirred for 24 h. The reaction mixture was quenched with 10% aqueous $NaHSO_3$ solution and extracted with EtOAc (75 mL each), and the organic phase was then washed with 10% aqueous $NaHSO_3$ (2 × 75 mL) and brine (75 mL), dried over $MgSO_4$, concentrated in vacuo, and exposed to high vacuum for 15–20 min. Flash chromatography (50% → 85% EtOAc/hexanes, gradient elution) afforded the diol (2.06 g, 100% yield) as a yellow glass. The product was taken up in THF and H_2O (1:1, 16 mL), and $NaIO_4$ (1.03 g, 4.79 mmol) was slowly added portionwise. After 1 h, the reaction mixture was partitioned between H_2O and ether (50 mL each), the aqueous phase was extracted with ether (2 × 50 mL), and the combined organic solutions were washed with brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude aldehyde (1.55 g, 83% yield), a light yellow solid, was utilized without purification. An analytical sample was crystallized from ether: mp 197–200 °C; $[\alpha]^{21}_D$ –169° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3450 (w), 2975 (m), 1730 (m), 1705 (s), 1650 (s), 1575 (s), 1490 (s), 1450 (m), 1165 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (d, J = 1.6 Hz, 1 H), 8.27–8.26 (m, 2 H), 7.38 (br s, 1 H), 7.20–7.19 (m, 3 H), 7.02–7.00 (m, 2 H), 6.36 (br s, 1 H), 6.21 (br s, 1 H), 3.77–3.73 (m, 4 H), 3.38 (d, J = 13.1 Hz, 1 H), 2.87 (dd, J = 17.5, 1.8 Hz, 1 H), 2.55 (d, J = 17.5 Hz, 1 H), 2.04–1.98 (m, 1 H), 1.76 (dd, J = 14.0, 4.7 Hz, 1 H), 1.56 (dd, J = 14.0, 7.7 Hz, 1 H), 1.41 (s, 9 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.83 (d, J = 6.6 Hz, 3 H), 0.80 (d, J = 6.7 Hz, 3 H), 0.72 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 202.33, 200.80, 199.67, 172.65, 164.13, 161.04, 154.14, 136.02, 130.08 (2 C), 127.96 (2 C), 126.78, 110.97, 107.70, 78.94, 70.97, 68.00,

60.21, 52.52, 49.57, 44.10, 39.77, 38.15, 28.39 (3 C), 24.42, 24.12, 23.56, 17.39, 15.93; high-resolution mass spectrum (CI, methane) m/z 582.2195 [(M + H)$^+$], calcd for $C_{32}H_{44}N_3O_7$ 582.3179. Anal. Calcd for $C_{32}H_{43}N_3O_7$: C, 66.07; H, 7.45; N, 7.22. Found: C, 65.92; H, 7.47; N, 6.99.

Trispyrrolinone (–)-45. A suspension of aldehyde (–)-**44** (0.9472 g, 1.68 mmol) in toluene (6.1 mL) was diluted with the minimum volume of chloroform required to achieve homogeneity (ca. 20 mL), and amine (+)-**12b** (0.325 g, 1.52 mmol) was then added neat. After 15 min the solution was concentrated in vacuo, the residue azeotropically dehydrated with toluene (5 × 6 mL), and the crude imine exposed to high vacuum for 45 min. The resultant solid was dissolved in THF (15 mL) and treated with 0.5 M KHMDS in toluene (18.5 mL, 9.14 mmol). The reaction mixture was stirred for 15 min and quenched with EtOAc and 10% aqueous $NaHSO_4$ (50 mL each). The aqueous phase was extracted with EtOAc (50 mL), and the combined organic solutions were washed with saturated aqueous $NaHCO_3$ and brine (50 mL each), dried over $MgSO_4$, and concentrated in vacuo, affording an orange solid. Flash chromatography (30% EtOAc/hexanes) provided (–)-**45** (0.804 g, 71% yield) as a white solid which was crystallized from ether by slow evaporation: mp 194–196 °C; $[\alpha]^{24}_D$ –284° (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3450 (w), 3420 (w), 3350 (w), 2960 (m), 1740 (m), 1705 (s), 1645 (s), 1575 (s), 1490 (m), 1450 (m), 1365 (m), 1165 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 3.1 Hz, 1 H), 8.20 (d, J = 4.2 Hz, 1 H), 8.15 (d, J = 3.8 Hz, 1 H), 7.51–7.49 (m, 2 H), 7.19–7.17 (m, 3 H), 7.01–6.99 (m, 2 H), 6.57 (br s, 1 H), 5.34 (d, J = 4.1 Hz, 1 H), 4.97 (t, J = 7.3 Hz, 1 H), 3.73 (s, 3 H), 3.66 (d, J = 13.0 Hz, 1 H), 3.44 (d, J = 13.1 Hz, 1 H), 2.34 (dd, J = 14.6, 8.0 Hz, 1 H), 2.24 (dd, J = 14.2, 7.1 Hz, 1 H), 1.97–1.92 (m, 1 H), 1.80 (dd, J = 14.1, 4.0 Hz, 1 H), 1.68 (s, 3 H), 1.64–1.60 (m, 8 H), 1.41 (s, 9 H), 0.85 (d, J = 6.8 Hz, 6 H), 0.82 (d, J = 6.5 Hz, 3 H), 0.79 (d, J = 6.7 Hz, 3 H), 0.74 (d, J = 6.7 Hz, 3 H), 0.67 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 203.36, 202.67, 201.09, 172.66, 163.91, 161.70, 159.96, 154.27, 136.19, 136.08, 130.17 (2 C), 127.90 (2 C), 126.70, 116.87, 110.68, 109.79, 107.02, 78.97, 71.40, 71.24, 68.80, 60.56, 52.46, 47.57, 44.89, 40.07, 37.84, 36.23, 28.37 (3 C), 25.92, 24.69 (2 C), 24.33, 24.28, 23.54 (2 C), 18.10, 17.08, 15.89; high-resolution mass spectrum (CI, methane) m/z 744.4433 [M$^+$], calcd for $C_{43}H_{60}N_4O_7$ 744.4462. Anal. Calcd for $C_{43}H_{60}N_4O_7$: C, 69.33; H, 8.11; N, 7.52. Found: C, 69.28; H, 8.19; N, 7.43.

Aldehyde (–)-46. Procedure A. A solution of trispyrrolinone (–)-**45** (340 mg, 0.456 mmol) in acetone and H_2O (8:1, 20 mL) was treated with *N*-methylmorpholine *N*-oxide (107 mg, 0.913 mmol) and a few crystals of OsO_4 (ca. 5 mg) and stirred for 48 h. The reaction mixture was quenched with 10% aqueous $NaHSO_3$ (20 mL) and extracted with EtOAc (20 mL), and the organic layer was washed with 10% aqueous $NaHSO_3$ and brine (2 × 10 mL each), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (50% → 100% EtOAc/hexanes, gradient elution) provided the corresponding diol as a gray solid.

The diol was dissolved in benzene (10 mL) and treated with K_2CO_3 (350 mg) and lead tetraacetate (253 mg, 0.571 mmol). The reaction mixture was stirred for 10 min and then partitioned between H_2O (20 mL) and EtOAc (20 mL). The organic layer was then washed with saturated aqueous $NaHCO_3$ (3 × 20 mL), dried over $MgSO_4$, and concentrated in vacuo. The resultant oil was crystallized from Et_2O at 0 °C, affording (–)-**46** (122 mg, 37% yield) as a colorless crystalline solid. Concentration of the filtrate followed by flash chromatography (EtOAc) provided additional product (42 mg, 50% total yield overall from (–)-**45**) which was crystallized from ether at 0 °C.

Procedure B. A solution of trispyrrolinone (–)-**45** (0.200 g, 0.269 mmol) in acetone and H_2O (8:1, 7.7 mL) was treated with *N*-methylmorpholine *N*-oxide (63 mg, 0.54 mmol) and a few crystals of OsO_4 (ca. 5 mg) and stirred for 24 h. The reaction mixture was quenched with 10% aqueous $NaHSO_3$ and extracted with EtOAc (10 mL each), and the organic phase was then washed with 10% aqueous $NaHSO_3$ (10 mL). The combined aqueous layers were extracted with EtOAc (10 mL), and the combined organic solutions were washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (1:4:6 EtOH/EtOAc/hexanes) gave the corresponding diol (0.169 g, 81% yield) as a gray solid.

The diol was dissolved in THF and H_2O (1:1, 1.1 mL), and $NaIO_4$ (0.0718 g, 0.336 mmol) was added portionwise. After 2 h, the reaction mixture was partitioned between H_2O and Et_2O (10 mL each) and the aqueous phase extracted with Et_2O (2 × 10 mL). The combined organic solutions were washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (60% EtOAc/hexanes) afforded (–)-**46** (0.113 g, 58% yield) as a white solid which was crystallized from ether by slow evaporation: mp 203–205 °C; $[\alpha]^{26}_D$ –219° (c 1.65, $CHCl_3$); IR ($CHCl_3$) 3450 (w), 3420 (w), 3350 (w), 2970 (m), 1730 (s), 1710 (s), 1650 (s) 1580 (s), 1490 (m), 1450 (m), 1165 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (d, J = 1.6 Hz, 1 H), 8.24 (apparent d, J = 4.1 Hz, 2 H), 8.17 (d, J = 3.9 Hz, 1 H), 7.50 (br d, J = 2.7 Hz, 1 H), 7.33 (br s, 1 H), 7.19–7.18 (m, 3 H), 7.01–6.98 (m, 2 H), 6.54 (br s, 1 H), 6.27 (d, J = 4.0 Hz, 1 H), 3.73 (s, 3 H), 3.67 (d, J = 13.1 Hz, 1 H), 3.43 (d, J = 13.1 Hz, 1 H), 2.89 (dd, J = 17.8, 1.7 Hz, 1 H), 2.54 (d, J = 17.7 Hz, 1 H), 1.98–1.93 (m, 1 H), 1.82 (dd, J = 13.6, 3.9 Hz, 1 H), 1.78 (dd, J = 14.1, 5.0 Hz, 1 H), 1.62 (d, J = 14.1, 7.4 Hz, 1 H), 1.57–1.49 (m, 2 H), 1.39–1.35 (m, 10 H), 0.87–0.84 (m, 6 H), 0.82–0.79 (m, 6 H), 0.75 (d, J = 6.7 Hz, 1 H), 0.66 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 202.32, 201.83, 200.90, 199.63, 172.66, 163.92, 161.73, 160.49, 154.21, 136.02, 130.12 (2 C), 127.89 (2 C), 126.69, 110.55, 108.96, 107.06, 78.96, 71.09, 68.33, 68.09, 60.48, 52.44, 49.80, 47.41, 44.03, 39.99, 37.76, 28.34 (3 C), 24.67, 24.54, 24.12 (2 C), 23.59, 23.49, 17.04, 15.84; high-resolution mass spectrum (CI, NH_3) m/z 718.3906 [M$^+$], calcd for $C_{40}H_{54}N_4O_8$ 718.3941.

Tetrapyrrolinone (–)-47. A solution of aldehyde (–)-**46** (1.15 g, 1.60 mmol) in benzene (6.4 mL) and chloroform (9.2 mL) was treated with amine (–)-**12a** (0.433 g, 1.76 mmol) and concentrated in vacuo. The residue was azeotropically dehydrated with benzene (5 × 6 mL), and the resultant oil was exposed to high vacuum and dissolved in THF (16 mL). Following the addition of 0.5 M KHMDS in toluene (26.5 mL, 13.25 mmol), the mixture was stirred for 15 min and then partitioned between EtOAc and 10% aqueous $NaHSO_4$ (100 mL each). The aqueous phase was extracted with EtOAc (2 × 100 mL), and the combined organic solutions were washed with saturated aqueous $NaHCO_3$ and brine (200 mL each), dried over $MgSO_4$, concentrated in vacuo, and exposed to high vacuum. Flash chromatography (50% EtOAc/hexanes) provided (–)-**47** (0.978 g, 66% yield) as a yellow solid which was crystallized from CH_2Cl_2/hexanes: mp 186–188 °C dec; $[\alpha]^{26}_D$ –327° (c 1.05, $CHCl_3$); IR ($CHCl_3$) 3420 (m), 3360 (m), 3010 (m), 2970 (m), 1745 (m), 1705 (s), 1650 (s) 1580 (s), 1490 (s), 1450 (s), 1365 (m), 1170 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (br s, 1 H), 8.12 (d, J = 3.6 Hz, 1 H), 8.04 (d, J = 3.8 Hz, 1 H), 7.86 (d, J = 3.27 Hz, 1 H), 7.52 (br s, 1 H), 7.34 (br s, 1 H), 7.20 (br d, J = 3.4 Hz, 1 H), 7.14 (m, 6 H), 6.98 (m, 4 H), 6.53 (br s, 1 H), 5.50 (br s, 1 H), 4.96 (t, J = 7.3 Hz, 1 H), 3.70 (s, 3 H), 3.65 (d, J = 12.6 Hz, 1 H), 3.42 (d, J = 13.1 Hz, 1 H), 2.90 (d, J = 13.4 Hz, 1 H), 2.79 (d, J = 13.4 Hz, 1 H), 2.46 (dd, J = 14.4, 7.8 Hz, 1 H), 2.30 (dd, J = 14.2, 6.9 Hz, 1 H), 1.92 (heptet, J = 6.7 Hz, 1 H), 1.75 (m, 1 H), 1.65 (s, 3 H), 1.59 (s, 3 H), 1.58 (m, 1 H), 1.41 (m, 4 H), 1.39 (s, 9 H), 0.84 (d, J = 6.7 Hz, 3 H), 0.81 (d, J = 6.3 Hz, 3 H), 0.78 (d, J = 6.2 Hz, 3 H), 0.75 (d, J = 5.5 Hz, 3 H), 0.72 (d, J = 6.6 Hz, 3 H), 0.64 (d, J = 5.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.73, 202.53, 201.52, 200.96, 176.42, 172.74, 163.81, 161.79, 160.57, 159.88, 154.21, 136.09, 134.84, 130.12, 129.73, 127.86, 127.66, 126.93, 126.64, 116.68, 110.46, 110.06, 108.42, 107.11, 78.91, 71.42, 71.22, 68.37, 60.51, 52.38, 47.30. 47.00, 42.11, 39.95, 38.00, 37.76, 34.37, 30.00, 29.00, 28.34, 28.00, 25.84, 24.53, 24.45, 24.30, 23.56, 23.37, 23.00, 18.11, 17.06, 15.84, 14.00; high-resolution mass spectrum (FAB, *p*-nitrobenzyl alcohol) m/z 938.5034 [(M + Na)$^+$], calcd for $C_{54}H_{69}N_5O_8Na$ 938.5044.

Aldehyde (–)-48. A solution of tetrapyrrolinone (–)-**47** (0.140 g, 0.1532 mmol) in acetone and H_2O (8:1, 4.4 mL) was treated with a few crystals of OsO_4 (ca. 5 mg) and stirred for 24 h. The reaction mixture was partitioned between 10% aqueous $NaHSO_3$ and EtOAc (10 mL each), the aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined organic solutions were washed with 10% aqueous $NaHSO_3$ solution (10 mL) and brine (30 mL), dried over $MgSO_4$, concentrated in vacuo, and exposed to high vacuum. Flash chromatography (1:3:7 EtOH/EtOAc/hexanes) gave the corresponding diol (0.105 g, 72% yield) as a gray solid.

The diol was dissolved in THF and H_2O (1:1 0.56 mL), and $NaIO_4$ (0.036 g, 0.34 mmol) was slowly added portionwise. After 2.5 h, the mixture was partitioned between H_2O and Et_2O (10 mL each), the aqueous phase was extracted with Et_2O (2 × 10 mL), and the combined organic solutions were washed with brine (30 mL), dried over $MgSO_4$, concentrated in vacuo, and exposed to high vacuum. Flash chromatography (60% EtOAc/hexanes) afforded (–)-**48** (0.0674 g, 69% yield) as a light solid which was crystallized from diisopropyl ether by slow evaporation: mp 157–162 °C dec; $[\alpha]^{26}_D$ –320° (c 0.15, $CHCl_3$); IR ($CHCl_3$) 3420 (m), 3360 (m), 3010 (m), 2960 (m), 1725 (m), 1700 (s), 1640 (s) 1575 (s), 1490 (m), 1445 (s), 1160 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (br s, 1 H), 8.24 (br s, 1 H), 8.15 (br s, 1 H), 8.06 (d, J = 3.4 Hz, 1 H), 7.86 (br s, 1 H), 7.60 (d, J = 3.4 Hz, 1 H), 7.15 (m, 3 H), 7.12 (m, 3

H), 6.98 (m, 4 H), 6.68 (br s, 1 H), 6.45 (br s, 1 H), 3.68 (s, 4 H), 3.39 (d, J = 12.6 Hz, 1 H), 2.94 (m, 2 H), 2.72 (d, J = 17.4 Hz, 1 H), 1.92 (heptet, J = 6.8 Hz, 1 H), 1.80 (br d, J = 11.1, 1 H), 1.55 (m, 1 H), 1.41 (m, 5 H), 1.38 (s, 9 H), 0.87 (m, 1 H), 0.84 (d, J = 6.7 Hz, 3 H), 0.77 (d, J = 5.8 Hz, 3 H), 0.72 (d, J = 6.4 Hz, 9 H), 0.60 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.44, 201.16, 200.95, 199.25, 172.79, 163.95, 161.90, 160.56, 154.18, 136.02, 133.76, 130.10, 129.77, 127.90, 127.74, 127.28, 126.69, 110.58, 109.65, 108.62, 107.00, 78.95, 71.20, 68.35, 68.08, 67.92, 60.42, 60.34, 52.44, 48.00, 47.34, 47.02, 41.77, 39.90, 37.76, 28.35, 24.58, 24.53, 24.40, 24.24, 23.55, 23.45, 17.04, 15.84, 14.13; high-resolution mass spectrum (CI, NH_3) m/z 912.4576 [M^+], calcd for $C_{51}H_{63}N_5O_9$ 912.4523.

Pentapyrrolinone (–)-49. A solution of aldehyde (–)-**48** (0.266 g, 0.299 mmol) in benzene (1.2 mL) was treated with amine (–)-**12c** (0.0652 g, 0.329 mmol) and concentrated in vacuo. The residue was azeotropically dehydrated with benzene (5 × 1.2 mL) and the resultant oil exposed to high vacuum for 30 min. The crude imine was dissolved in THF (3.4 mL), and 0.5 M KHMDS in toluene (5.20 mL, 2.60 mmol) was added. The solution was stirred for 1.5 h and then partitioned between EtOAc and 10% aqueous $NaHSO_4$ (25 mL each). The aqueous phase was extracted with EtOAc (2 × 25 mL), and the combined organic solutions were washed with saturated aqueous $NaHCO_3$ and brine (15 mL each), dried over $MgSO_4$, concentrated in vacuo, and exposed to high vacuum. Flash chromatography (60% EtOAc/hexanes) provided (–)-**49** (0.148 g, 48% yield) as a yellow solid: mp 207–208 °C dec; $[\alpha]^{26}_D$ –415° (c 0.58, $CHCl_3$); IR ($CHCl_3$) 3420 (m), 3350 (w), 3010 (m), 2970 (m), 1735 (m), 1710 (m), 1645 (s) 1575 (s), 1445 (s), 1160 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 4.2 Hz, 1 H), 8.22 (br s, 1 H), 8.12 (br s, 1 H), 8.01 (d, J = 3.5 Hz, 1 H), 7.78 (br s, 1 H), 7.64 (br s, 1 H), 7.53 (br s, 1 H), 7.37 (br s, 1 H), 7.23 (d, J = 3.3 Hz, 1 H), 7.15 (m, 3 H), 7.09 (m, 3 H), 7.03 (m, 2 H), 6.97 (m, 2 H), 6.58 (br s, 1 H), 5.64 (d, J = 3.6 Hz, 1 H), 4.96 (t, J = 6.7 Hz, 1 H), 3.69 (s, 3 H), 3.65 (d, J = 13.0 Hz, 1 H), 3.43 (d, J = 12.9 Hz, 1 H), 3.09 (d, J = 13.2 Hz, 1 H), 2.88 (d, J = 13.2 Hz, 1 H), 2.40 (m, 2 H), 1.95 (m, 1 H), 1.75 (q, J = 9.11 Hz, 1 H), 1.63 (s, 3 H), 1.60 (s, 3 H), 1.56 (m, 1 H), 1.51 (m, 1 H), 1.38 (s, 9 H), 1.38 (m, 3 H), 0.90 (d, J = 6.9 Hz, 3 H), 0.84 (d, J = 6.8 Hz, 3 H), 0.76 (d, J = 6.2 Hz, 3 H), 0.74–0.69 (m, 12 H), 0.61 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.04, 202.60, 201.32, 201.20, 201.02, 177.00, 175.00, 172.76, 163.79, 161.75, 160.48, 160.30, 154.29, 136.14, 135.40, 134.50, 130.17, 129.99, 127.87, 127.35, 126.93, 126.64, 116.75, 110.29, 109.45, 108.84, 108.46, 107.12, 78.94, 73.80, 71.23, 68.43, 68.37, 68.07, 60.66, 52.40, 47.40, 46.65, 44.45, 40.08, 37.77, 33.52, 33.11, 29.00, 28.37, 25.88, 24.58, 24.42, 24.28, 23.56, 18.09, 17.10, 16.92, 16.22, 15.89; high-resolution mass spectrum (FAB, p-nitrobenzyl alcohol) m/z 1061.5641 [(M + Na)$^+$], calcd for $C_{61}H_{78}N_6O_9Na$ 1061.5629.

Amino Ester (–)-50. At 0 °C a solution of trispyrrolinone (–)-**45** (63.4 mg, 0.0851 mmol) in CH_2Cl_2 (0.34 mL) was treated with TMSOTf (0.041 mL, 0.213 mmol) and stirred for 10 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (90% EtOAc/hexanes) afforded (–)-**50** (53.3 mg, 97% yield) as a light yellow solid which was crystallized from hexanes/Et_2O: mp 88–91 °C; $[\alpha]^{24}_D$ –257° (c 1.76, $CHCl_3$); IR ($CHCl_3$) 3940 (w), 3855 (w), 3000 (m), 2960 (m), 1735 (m), 1645 (s), 1575 (s), 1560 (m), 1445 (m), 1220 (m), 1170 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 4.09 Hz, 1 H), 8.18 (d, J = 4.2 Hz, 1 H), 8.07 (d, J = 3.9 Hz, 1 H), 7.65 (d, J = 4.0 Hz, 1 H), 7.53 (d, J = 3.8 Hz, 1 H), 7.20 (m, 3 H), 7.11 (m, 2 H), 5.86 (d, J = 4.0 Hz, 1 H), 4.93 (t, J = 7.4 Hz, 1 H), 3.61 (s, 3 H), 3.33 (d, J = 12.8 Hz, 1 H), 3.06 (d, J = 12.8 Hz, 1 H), 2.55 (dd, J = 14.3, 7.8 Hz, 1 H), 2.41 (br s, 2 H), 2.20 (dd, J = 14.2, 6.9 Hz, 1 H), 1.93 (heptet, J = 6.8 Hz, 1 H), 1.74 (dd, J = 14.0, 4.0 Hz, 1 H), 1.62 (s, 3 H), 1.57 (m, 1 H), 1.55 (s, 3 H), 1.41 (dd, J = 14.0, 8.5 Hz, 1 H), 1.36 (heptet, J = 6.32 Hz, 1 H), 0.85 (m, 2 H), 0.83 (d, J = 7.0 Hz, 3 H), 0.81 (d, J = 6.8 Hz, 3 H), 0.78 (d, J = 6.5 Hz, 3 H), 0.74 (d, J = 6.7 Hz, 3 H), 0.71 (d, J = 6.7 Hz, 3 H), 0.64 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 203.21, 202.71, 202.08, 175.01, 162.22, 161.84, 160.18, 135.90, 135.47, 130.06, 128.25, 127.00, 116.95, 114.25, 109.29, 106.89, 71.36, 71.22, 68.92, 59.46, 52.03, 47.56, 44.91, 44.14, 37.82, 36.26, 25.84, 25.59, 24.71, 24.33, 24.20, 23.59, 23.43, 18.05, 17.08, 15.96; high-resolution mass spectrum (CI, methane) m/z 643.3860 [(M + H)$^+$], calcd for $C_{38}H_{52}N_4O_5$ 643.3848.

Molecular Modeling. All calculations were performed on a Silicon Graphics Iris 4D/440VGX, VAX 750, or Personal Iris 35GL (Unix operating system). The MacroModel program [versions 1.5–2.5 (VAX) and 3.1x (Iris)] was used for construction and analysis of all modeled structures.[23] Minimizations and Monte Carlo calculations were performed using the Batchmin accessory of MacroModel. Comparisons of various conformations of the calculated structures were accomplished using the root mean square (RMS) minimization algorithm[42] for the selected atoms included with the MacroModel program.

To calculate the energy profile for rotation about the ϕ and ψ angles of bispyrrolinone **2**, the backbone torsional angles were incrementally constrained at 10° intervals with a force constant of 1000 kJ/(mol rad) and minimizations were performed for each step. The resulting geometries were stored, and the energy associated with each was normalized to the lowest energy conformer. Graphs of the energy vs dihedral angle were then generated.

The Monte Carlo conformational searches performed on structures **3** and **5** used both random (**3** and **5**) or systematic, unbounded (**5**) multiple minimum algorithms.[25] The total number of conformers to be generated was set to a large value (either 5000 or 10 000) and the calculation run until either no new conformations were found or the targeted number of conformations had been generated. Each newly generated structure was minimized by between 300 and 500 minimization steps or until the gradient was <0.05 kJ/(Å mol). The energy window for acceptance of a particular conformation was 25 kJ/mol, although if the energy was 40–50 kJ/mol higher than the lowest energy structure after ca. 100–200 iterations of minimization, the conformer was rejected. To be classified as unique and subsequently stored, a structure had to differ from all previously stored conformations by an RMS comparison of all non-hydrogen atoms of >0.25 Å. The total number of conformations generated for **3** was 2584, and 1278 initial conformations met both the energy and conformational uniqueness criteria. This number was reduced by performing further minimizations to a total of 41 unique conformations. Figure 9 was generated by overlaying the 12 linear, 10 turned, and 14 twisted conformers; 5 structures were not included since they did not fit any of the 3 backbone classes. For the systematic search on **5**, 10 000 conformations were generated and 2799 stored. In this case, further minimization did not reduce the number of unique conformations. Figure 13 was constructed by overlaying the first 53 conformers, 27 linear and 23 turned, that had an energy range of ca. 8 kJ/mol; 3 structures fit the twisted backbone class, but were not included in the figure.

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(42) (a) Kabsch, W. *Acta Crystallogr.* **1976**, *A32*, 922. (b) Kabsch, W. *Acta Crystallogr.* **1978**, *A34*, 827.