ORGANIC LETTERS

2010
Vol. 12, No. 13
2990−2993

Design, Synthesis, and Structural Analysis of D,L-Mixed Polypyrrolinones. 1. From Nonpeptide Peptidomimetics to Nanotubes

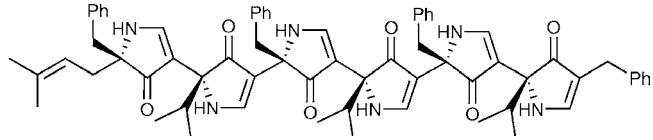
Amos B. Smith, III,* Wenyong Wang, Adam K. Charnley, Patrick J. Carroll, Craig S. Kenesky, and Ralph Hirschmann*,‡

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

smithab@sas.upenn.edu

Received May 2, 2010

ABSTRACT



To expand the potential conformational space available to the polypyrroline structural motif, an open chain, D,L-alternating hexapyrrolinone was designed and synthesized. Structural studies, including solution NMR and X-ray crystallographic analysis, revealed that the hexapyrrolinone adopts a turn conformation both in solution and in the solid state, with aggregation in solution and a nanotube-like quaternary structure in the crystal.

A major achievement in the field of nonpeptide peptidomimetics would comprise the design and synthesis of biologically relevant mimics, capable of adopting conformations similar to the three principal secondary structures accessible to peptides and proteins (e.g., β-turns, β-strands, or α-helices), with conformational control manifested simply via structural modification of the side-chains and/or the stereogenicity of the constituent monomers. To date, only a limited number of conformationally versatile nonpeptide peptidomimetics have been reported.[1]

In 1992, the Hirschmann−Smith collaboration reported the design and synthesis of a new class of peptidomimetics based on the pyrrolinone scaffold (Figure 1).[2] Computational studies suggested that oligomers based on this repeating vinylogous amide motif held the promise of adopting structures similar, but not identical, to the three secondary structures of peptides and proteins.[2,3] As such, the polypyrrolinones constituted early examples of foldamers as defined by Gellman[4,1a,b] and elegantly demonstrated for β-peptides by both Seebach[5,1c] and Gellman.[4b,1a,b] Pleasingly, initial studies demonstrated that homochiral polypyrrolinones (e.g., all D),[6] such as (−)-**1**, can adopt extended parallel (**1a**, Figure 1) or antiparallel (**1b**) β-strand/β-sheet mimics, depending on the presence or absence of a Boc C-terminus.[2,3,7] This observation led to the design and synthesis of a series of potent pyrrolinone-based enzyme inhibitors,[8] requiring the

‡ May 6, 1922−June 20, 2009.

(1) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (b) Horne, S. W.; Gellman, S. H. *Acc. Chem. Res.* **2008**, *41*, 1399. (c) Seebach, D.; Hook, D. F.; Glattli, A. *Biopolymers (Pept. Sci.)* **2006**, *84*, 23. (d) Stigers, K. D.; Soth, M. J.; Nowick, J. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 714. (e) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893. (f) *Foldamers: Structure, Properties and Applications*; Hecht, S., Huc, I., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2007. (g) Angelo, N. G.; Arora, P. S. *J. Am. Chem. Soc.* **2005**, *127*, 17134. (h) Goodman, C. M.; Choi, S.; Shandler, S.; DeGrado, W. F. *Nat. Chem. Biol.* **2007**, *3*, 252, and references cited therein.

(2) Smith, A. B., III; Keenan, T. P.; Holcomb, R. C.; Sprengler, P. A.; Guzman, M. C.; Wood, J. L.; Carrol, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1992**, *114*, 10672.

(3) (a) Smith, A. B., III; Guzman, M. C.; Sprengler, P. A.; Keenan, T. P.; Holcomb, R. C.; Wood, J. L.; Carrol, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1994**, *116*, 9947. (b) Smith, A. B., III; Favor, D. A.; Sprengler, P. A.; Guzman, M. C.; Carrol, P. J.; Furst, G. T.; Hirschmann, R. *Bioorg. Med. Chem.* **1999**, *7*, 9. (c) Smith, A. B., III; Wang, W.; Sprengler, P. A.; Hirschmann, R. *J. Am. Chem. Soc.* **2000**, *122*, 11037.

(4) (a) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 1054. (b) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071. See also ref 1.

(5) (a) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Marinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913. (b) Seebach, D.; Ciceri, P. E.; Overhand, M.; Jaun, B.; Rigo, D.; Oberer, L.; Hommel, U.; Amstutz, R.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 2043. (c) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015. See also ref 1.

(6) While D,L descriptors are not directly applicable to the pyrrolinone units, their use simplifies comparison with peptidal structures.

10.1021/ol101007n
Published on Web 06/02/2010

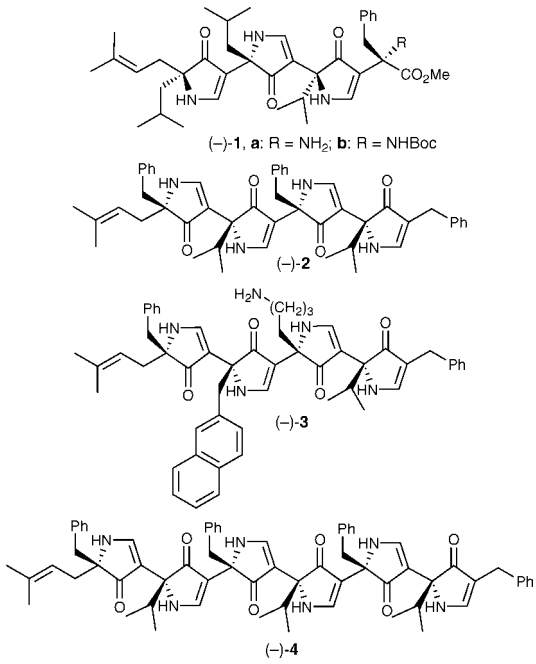


Figure 1. Designed β-strand/β-sheet trispyrrolinones (−)-**1a**,**b**; β-turn tetrapyrrolinones (−)-**2** and (−)-**3**; and hexapyrrolinone (−)-**4**.

β-strand/β-sheet motif, including metalloproteases,[9] and orally bioavailable HIV-1 protease inhibitors,[10] as well as a peptide−pyrrolinone hybrid ligand for the class II MHC protein HLA-DR1.[11]

With these initial achievements, a central theme of the pyrrolinone-based peptidomimetic program became the expansion, by design, of the diverse conformational space accessible to the polypyrrolinone structural motif for peptide/protein mimicry. We recognized that the ability to control the various possible conformations, via simple modulation of the side-chain structure and/or α-stereogenicity, would significantly enhance the opportunities for the polypyrrolinone construct in biologically relevant mimics.

The well-recognized principle that D-amino acids stabilize β-turns,[12] in conjunction with the pioneering reports by Karle[13] and De Santis,[14] later extended by the Lorenzi,[15] Ghadiri,[16] and Ciufolini[17] laboratories, demonstrating that peptides embodying alternating D- and L-amino acids can adopt turn conformations, and in some cases assemble into nanotubes, suggested that a sequence of alternating D,L-linked pyrrolinones might also preferentially adopt a turn structure. That this scenario proved correct was demonstrated by the synthesis of the alternating D,L-*tetra*-pyrrolinone (−)-**2**, shown by NMR studies, in conjunction with molecular modeling, to adopt a low-energy turn conformation in solution.[3c] Importantly, control over the conformation of (−)-**2** was achieved by alternating the building block configuration along the sequence. An equally important issue concerned the biological relevance of such polypyrrolinone turn mimics. Toward this end, we designed and synthesized several mimics [cf. (−)-**3**] of the neuropeptide hormone somatostatin-14 (SRIF), known to incorporate a β-turn as the pharmacophore structural element.[18] Importantly, a heterochiral tetrapyrrolinone proved to be a functional mimic of SRIF.[19]

Having achieved both bioactive β-strand and β-turn mimics with designed polypyrrolinones, we turned to larger congeners, with an eye toward the possibility of helix mimics.[3b] We first selected alternating D,L-hexapyrrolinone (−)-**4** (Figure 1) and carried out a 10 000-step Monte Carlo conformational search[20] employing the MMFFS force field.[21] The calculations rendered a set of low energy conformations, typified by a turn motif with four intramolecular hydrogen bonds among neighboring residues and one hydrogen bond spanning the cleft between the terminal residues (Figure 2a).

The computationally predicted ability of the pyrrolinone-derived turn to draw the termini of the hexapyrrolinone oligomer close together confirmed our interest in **4** as a

(7) (a) Smith, A. B., III; Holcomb, R. C.; Guzman, M. C.; Keenan, T. P.; Sprengeler, P. A.; Hirschmann, R. *Tetrahedron Lett.* **1993**, *34*, 63. Guzman, M. C. *Ph.D. Thesis*, University of Pennsylvania, 1995.

(8) Smith, A. B., III; Akaishi, R.; Jones, D. R.; Keenan, T. P.; Guzman, M. C.; Holcomb, R. C.; Sprengeler, P. A.; Wood, J.; Hirschmann, R.; Holloway, M. K. *Biopolymers (Pept. Sci.)* **1995**, *37*, 29.

(9) Smith, A. B., III; Nittoli, T.; Sprengeler, P. A.; Duan, J. W.; Liu, R.-Q.; Hirschmann, R. *Org. Lett.* **2000**, *2*, 3809.

(10) (a) Smith, A. B., III; Cantin, L.-D.; Pasternak, A.; Guise-Zawacki, L.; Yao, W. Q.; Charnley, A. K.; Barbosa, J.; Sprengeler, P. A.; Hirschmann, R.; Munshi, S.; Olsen, D. B.; Schleif, W. A.; Kuo, L. C. *J. Med. Chem.* **2003**, *46*, 1831, and references cited therein. (b) Smith, A. B., III; Charnley, A. K.; Harada, H.; Beiger, J. J.; Cantin, L.-D.; Kenesky, C. S.; Hirschmann, R.; Munshi, S.; Olsen, D. B.; Stahlhut, M. W.; Schleif, W. A.; Kuo, L. C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 859.

(11) Lee, K. H.; Olson, G. L.; Bolin, D. R.; Benowitz, A. B.; Sprengeler, P. A.; Smith, A. B., III; Hirschmann, R. F.; Wiley, D. C. *J. Am. Chem. Soc.* **2000**, *122*, 8370, and references cited therein. .

(12) Nutt, R. F.; Veber, D. F.; Saperstein, R.; Hirschmann, R. *Int. J. Pept. Protein Res.* **1983**, *21*, 66.

(13) (a) Karle, I. L.; Handa, B. K.; Hassall, C. H. *Acta Crystallogr.* **1975**, *B31*, 555. (b) Chiang, C. C.; Karle, I. L. *Int. J. Pept. Protein Res.* **1982**, *20*, 133.

(14) De Santis, P.; Morosetti, S.; Rizzo, R. *Macromolecules* **1974**, *7*, 52.

(15) (a) Tomasic, L.; Lorenzi, G. P. *Helv. Chim. Acta* **1987**, *70*, 1012. (b) Pavone, V.; Benedetti, E.; Di Blasio, B.; Lombardi, A.; Pedone, C.; Tomasich, L.; Lorenzi, G. P. *Biopolymers* **1989**, *28*, 215. (c) Saviano, M.; Zaccaro, L.; Lombardi, A.; Pedone, C.; Di Blasio, B.; Sun, X.; Lorenzi, G. P. *J. Inclusion Phenom.* **1994**, *18*, 27. (d) Sun, X.; Lorenzi, G. P. *Helv. Chim. Acta* **1994**, *77*, 1520.

(16) (a) Ghadiri, M. R.; Granja, J. R.; Milligan, R. A.; McRee, D. E.; Khazanovich, N. *Nature* **1993**, *366*, 324. (b) Ghadiri, M. R.; Kobayashi, K.; Granja, J. R.; Chadha, R. K.; McRee, D. E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 93. (c) Hartgerink, J. D.; Granja, J. R.; Milligan, R. A.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 43. (d) Clark, T. D.; Buriak, J. M.; Kobayashi, K.; Isler, M. P.; McRee, D. E.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 8949.

(17) Xi, N.; Alemany, L. B.; Ciufolini, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 80.

(18) (a) Nutt, R. F.; Colton, C. D.; Saperstein, R.; Veber, D. F. *Somatostatin*; Reichlin, S., Ed.; Plenum: New York, NY, 1987; p 83. (b) Veber, D. F. *Peptides-Chemistry and Biology: Proceedings of the 12th American Peptide Symposium*; Smith, J. A., Rivier, J. E., Eds.; ESCOM: Leiden, 1992; p 3.

(19) Smith, A. B., III; Charnley, A. K.; Mesaros, E. F.; Kikuchi, O.; Wang, W.; Benowitz, A.; Chu, C.-L.; Feng, J.-J.; Chen, K.-H.; Lin, A.; Cheng, F.-C.; Taylor, L.; Hirschmann, R. *Org. Lett.* **2005**, *7*, 399.

(20) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

(21) (a) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490. (b) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 520. (c) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 553. (d) Halgren, T. A.; Nachbar, R. B. *J. Comput. Chem.* **1996**, *17*, 587. (e) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 615. (f) Halgren, T. A. *J. Comput. Chem.* **1999**, *20*, 720. (g) Halgren, T. A. *J. Comput. Chem.* **1999**, *20*, 730.

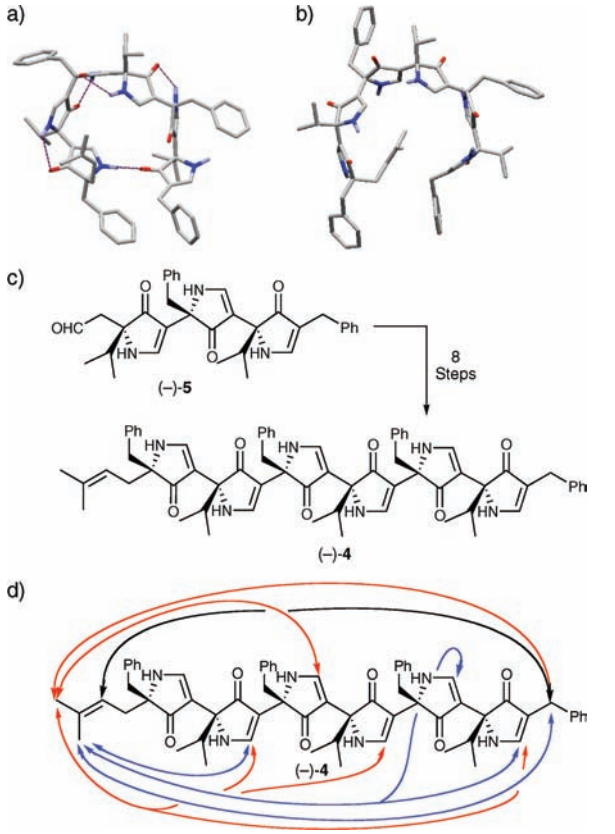


Figure 2. (a) Computational model of (−)-**4** in $CHCl_3$ arising from a 10 000-step Monte Carlo conformational search. (b) The solution structure of the alternating D,L-hexapyrrolinone (−)-**4**. (c) Synthesis of hexapyrrolinone (−)-**4**. (d) Ten critical long-range NOEs, color coded by their interactions with the prenyl side chain.

synthetic target. To access **4**, we turned to our iterative pyrrolinone synthetic protocol, beginning with aldehyde (−)-**5** (Figure 2c) and building the pyrrolinone chain in the C to N direction (see Supporting Information). Yields for the two-step iterative sequences were in general good.

To establish the solution conformation of (−)-**4**, a series of ROESY NMR experiments in $CDCl_3$ [1 mM in (−)-**4**], similar to those exploited with (−)-**2**,[3c] were conducted. Ten critical long-range NOEs were observed (Figure 2d). The ROE NMR data were then employed as a constraint file in a 10 000-step Monte Carlo conformational search; the result revealed (−)-**4** to exist in solution in a flat, G-shaped turn conformation similar to that previously reported for (−)-**2** (Figure 2b).[3c]

Crystallization of (−)-**4** from $CHCl_3$ via vapor-phase equilibration with hexane furnished single crystals (mp 195−197 °C) suitable for X-ray analysis.[22] Pleasingly, the derived ORTEP diagram (Figure 3a) reveals a flat G-shaped structure similar to the low energy conformation observed in solution. Importantly, overlay of the solution structure with the crystal structure provided excellent atom-to-atom correspondence (Figure 3b; root-mean-square value of 0.508 Å). Of equal importance, the unit cell structure possesses four (−)-**4** monomers that self-assemble into a nanotube-like quaternary structure (Figure 3c−e), with the monomers arrayed in an antiparallel fashion.

A crystallographic 3-fold rotation axis, parallel to the *c* axis, passes through the center of the best molecular plane. The tubular structure is best revealed by removing the internal and external side-chains (Figure 3e). In this way, the intermolecular hydrogen bonds, which stabilize the molecular assembly, are more clearly visible. To ascertain the possibility of self-assembly of (−)-**4** in solution, we

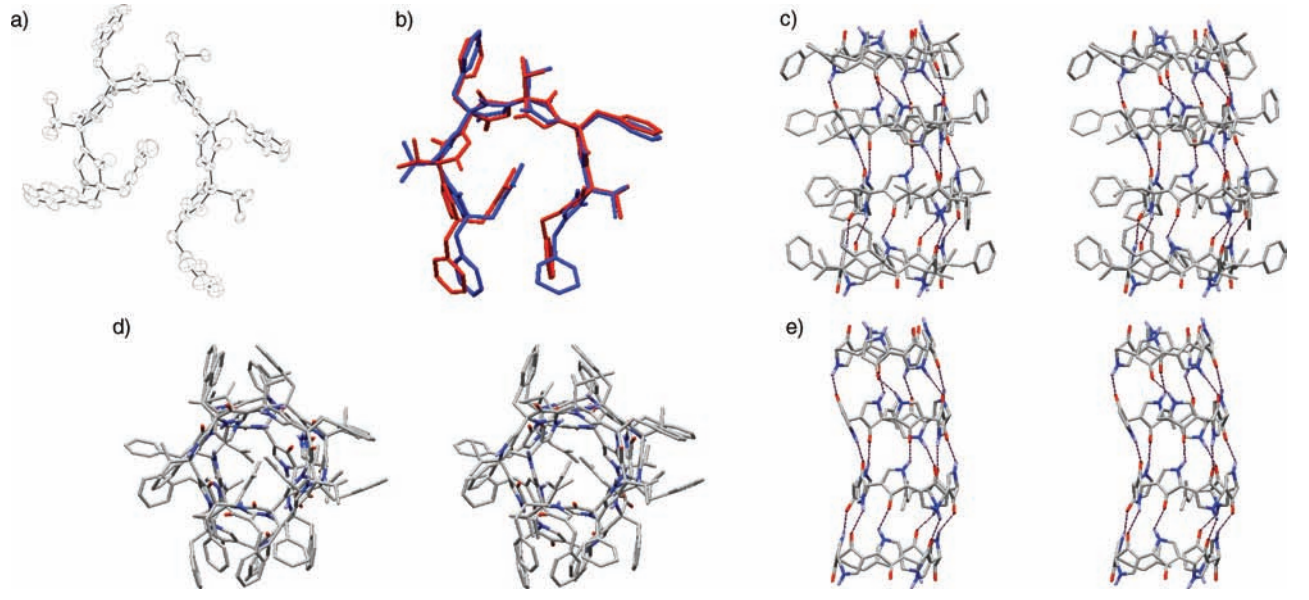


Figure 3. (a) ORTEP diagram of the D,L-mixed hexapyrrolinone (−)-**4**. (b) Overlay of the crystal structure (blue) and the solution structure (red) of (−)-**4**. (c) and (d) Stereoviews illustrating the nanotube-like assembly of (−)-**4** in the crystal packing diagram, side view and top view, respectively, with intermolecular hydrogen bonding illustrated. (e) Stereoview with side-chains removed to highlight the nanotube-like assembly.

performed a variable concentration ^{1}H NMR analysis to define the lowest concentration at which intermolecular interactions occur (Figure 4). A significant change in the proton resonance at δ 5.50 ppm (1×10^{-4} M), highly indicative of solvent exposure, was observed with increasing concentration (ca. 1×10^{-4} M to 3×10^{-2} M). We therefore assigned this resonance to the N-terminal pyrrolinone N−H(6), the only pyrrolinone N−H that cannot form an intramolecular hydrogen bond with the carbonyl oxygen of an adjacent pyrrolinone. The internal pyrrolinone N−Hs [NH(1−5)], which resonate in the hydrogen bonded N−H region (ca. δ 6.95−8.00 ppm), displayed modest shifts (0.06−0.41 ppm, 3.5×10^{-3} M to 2.6×10^{-2} M) consistent with self-assembly.

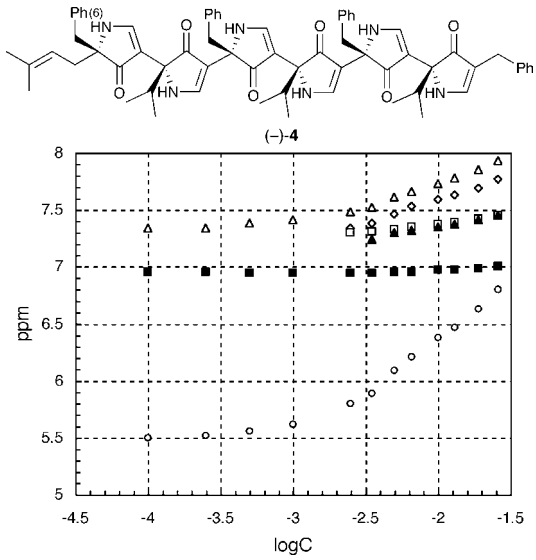


Figure 4. Concentration dependence of the N−H chemical shifts in $CDCl_3$ for the D,L-mixed hexapyrrolinone (−)-**4**. N-Terminal N−H(6) (○). Internal N−Hs (NH(1−5) (Δ◇□▲■)).

Taken together, these results suggest that the lowest concentration at which intermolecular hydrogen bonding occurs is ca. 10^{-3} M.

In summary, the design, synthesis, and structural analysis of an alternating D,L-hexapyrrolinone (−)-**4** has been achieved. Structural analysis, involving solution NMR studies and X-ray crystallography, reveals that (−)-**4** adopts a turn conformation both in solution and in the solid state, with aggregation occurring in solution and nanotube-like structures in the solid state. Further extension of the D,L-alternating pyrrolinone motif holds the promise of additional novel chemical and structural properties (e.g., helices). Studies to this end continue in our Laboratory.

Acknowledgment. Support was provided by the NIH through Grant AI-42010. Additional support was provided by Graduate Fellowships from Bristol-Myers Squibb and the University of Pennsylvania to A.K.C. We thank Dr. G. Furst at University of Pennsylvania for assistance obtaining and analyzing the 2D NMR spectra. We also thank Samuel H. Gellman, the Ralph Hirschmann Professor of Chemistry at the University of Wisconsin, for insightful discussion.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101007N

(22) For crystallographic data of hexapyrrolinone (−)-**4**, see Supporting Information.