Design, Synthesis, and Solution Structure of a Pyrrolinone-Based β-Turn Peptidomimetic

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The design and synthesis of privileged nonpeptide scaffolds[1] that can adopt the three principal secondary structures analogous to peptides and proteins constitutes a significant advance in molecular mimicry. Such scaffolds hold considerable promise for the development of selective, low-molecular weight nonpeptide ligands for biomedically important receptors. Ideally, conformational control of the privileged nonpeptide scaffold would be effected via simple structural modifications of the individual monomers. To date, however, most designed scaffolds can adopt only a single conformation;[2] exceptions include the Schreiber vinylogous amides,[3] the Hamilton oligoanthranilamides[4] and the β-peptides of Gellman[5] and Seebach.[6]

Having established the 3,5-linked (nitrogen displaced) homochiral polypyrrolinone motif as an excellent β-sheet/β-strand peptidomimetic both in the solid state[7a,b] and in solution,[7c] including the design and synthesis of a potent, orally bioavailable HIV-1 protease inhibitor[7d] and a competent ligand for the class II MHC protein HLA-DR1,[7e] we sought to extend the diversity of conformational space available to the polypyrrolinone structure motif. The observation of Ghadiri et al.[8,9] that alternating D- and L-cyclic peptides assemble into nanotubes, in conjunction with the recollection that D-amino acids stabilize β-turns[10] suggested that D,L-alternating (i.e., heterochiral) polypyrrolinones might also preferentially adopt a turn conformation. Indeed, a Monte Carlo conformational search performed on the simple D,L,D,L-tetrapyrrolinone **1** indicated that the low-energy conformations do in fact adopt a β-turn conformation (Figure 1).

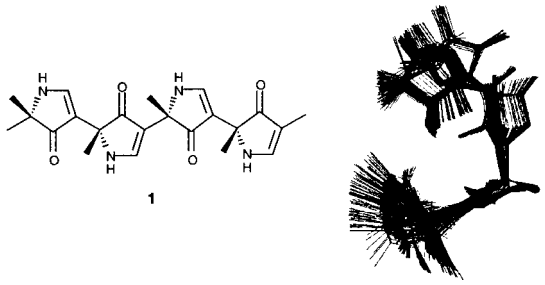
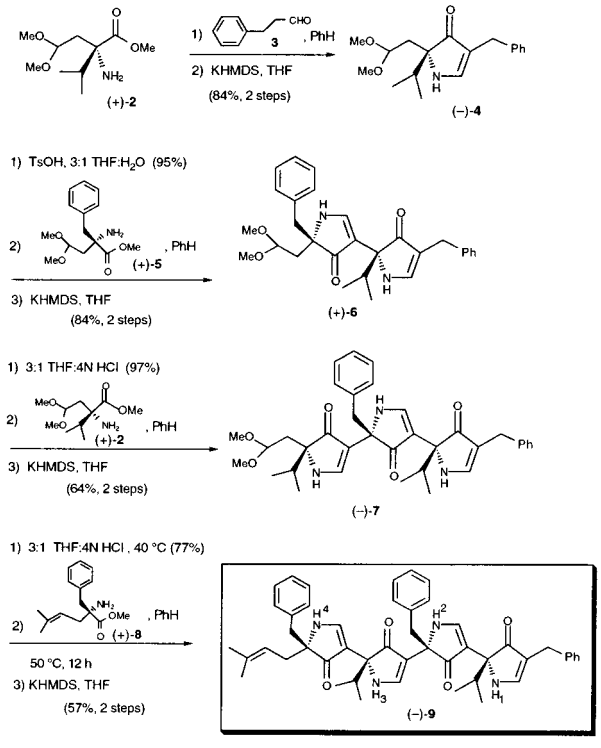


Figure 1. Tetrapyrrolinone **1** and Monte Carlo conformational search.

However, since previous studies[7b] have demonstrated that the use of methyl side-chain substituents is an oversimplification, we set (−)-**9** as our initial target. Additional conformational searches supported this choice.

The requisite α,α-disubstituted amino esters (i.e., **2**, **5**, and **8**; Scheme 1) required for the synthesis of the D,L-mixed polypyrrolinones exploiting our polypyrrolinone synthetic protocol,[7b] were prepared via the enantioretentive alkylation tactic developed by Kadary[11a] and Seebach.[11b] Construction of the D,L-mixed tetrapyrrolinone (−)-**9** was prepared as illustrated in Scheme 1; the overall

Scheme 1



yield was 18%. The structure of (−)-**9** was confirmed by a series of ^{1}H, ^{13}C, COSY, TOCSY, and NOESY NMR experiments.

To assign the solution structure of (−)-**9**, we first performed ^{1}H NMR analysis to determine the lowest concentration at which

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intermolecular hydrogen bonding occurs.[12] The chemical shift at δ 5.41 ppm (Figure 2) corresponds to the N-terminal pyrrolinone N−H (i.e., hydrogen 4). The large concentration dependence of this chemical shift clearly indicates exposure to the solvent. In contrast, the chemical shifts of hydrogens 1, 2, and 3 (i.e., δ 7.05, 7.38, and 7.34 ppm) were invariant over the concentration range studied ($\sim 5 \times 10^{-4}$ to 0.05 M), indicative of intramolecular hydrogen bonding. Taken together these results indicate that the lowest concentration at which intermolecular hydrogen bonding occurs is $\sim 10^{-3}$ M. FT-IR analysis of compound (−)-**9** over a range of concentrations from 0.001 to 0.05 M revealed both a non-hydrogen-bonded N−H band at 3440 cm^{-1}, and a hydrogen-bonded N−H band at 3350 cm^{-1}, in agreement with the ^{1}H NMR results.[12]

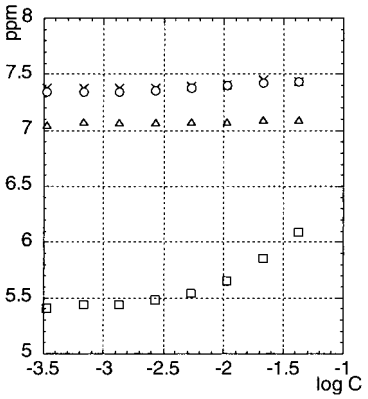

Figure 2. Concentration dependence of the N−H chemical shifts of tetrapyrrolione (−)-**9** in $CDCl_3$: H1 (△); H2 (×); H3 (○); H4 (□).

To define the secondary structure of tetrapyrrolinone (−)-**9**, we performed a series of 2D NOESY NMR studies[13] (10^{-3} M, $CDCl_3$). The nuclear Overhauser effect (NOE) time-dependence intensity profile of (−)-**9** indicated that for most cross-peaks the intensities were in the linear range up to 500 ms. A total of 35 NOE cross-peaks were observed with 450 ms as the mixing time. Among them, 5 long range sequential NOEs (Figure 3) clearly established that the prenyl side chain was in close contact with the pyrrolinone ring at the C terminus of the molecule, consistent with a turn conformation.

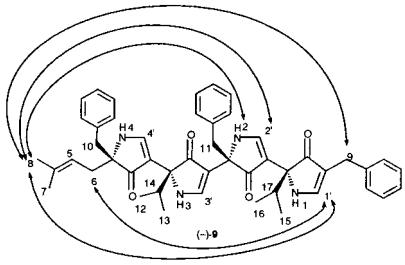

Figure 3. Long-range NOEs in tetrapyrrolinone (−)-**9** using 450 ms as mixing time.

The solution structure of tetrapyrrolinone (−)-**9** was then generated using the NOE constraints as imputs to a 5000-step Monte Carlo conformational search employing the MM2*[14] force field in MacroModel, with the GB/SA solvation continuum model

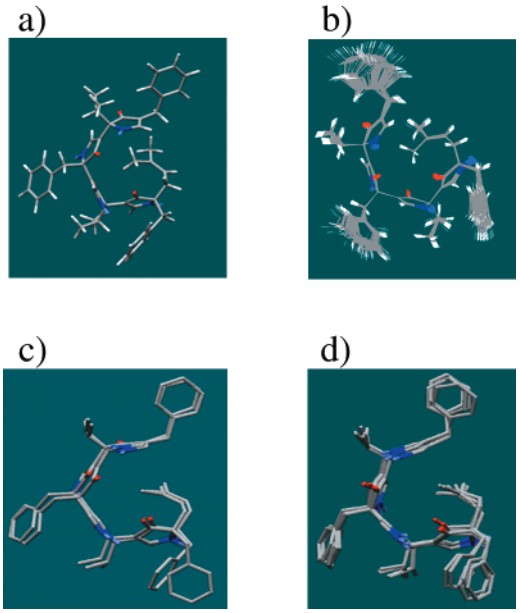

Figure 4. (a) Lowest-energy conformer of tetrapyrrolinone (−)-**9** in $CHCl_3$; (b) superimposition of all 34 low-energy conformers within 2 kcal/mol; (c) overlay of representative structures of two major clusters; (d) overlay of the lowest-energy conformers generated from five force fields.

($CHCl_3$).[15] The lowest-energy conformer of (−)-**9** is shown in Figure 4a. The structure is consistent with the NOE data except for one violation in the distance between hydrogen 1′ and 8 (5.6 Å versus the 1.8−5.0 Å range), presumably due to the flexibility of the prenyl side chain. The hydrogen bonding pattern in the lowest-energy conformer of (−)-**9** is consistent with the NMR and FT-IR dilution studies.[16] The overlay of all 34 low-energy conformers within 2 kcal/mol indicates high conformational homology (Figure 4b). Among 560 conformers generated in the 5000-step Monte Carlo conformational search, 530 conformers were grouped into two major clusters using Xcluster analysis,[17] with 217 and 303 members respectively at cluster level 545. An overlay of a representative structure from each cluster revealed excellent agreement (Figure 4c). Since the accuracy of the molecular dynamic calculations relies on the ability of the parameters to mimic the potential energy of the molecule, we evaluated the suitability of the MM2* force field for (−)-**9**, by comparing the derived conformations obtained employing the other force fields available in MacroModel. Although Amber94 was not suitable for the pyrrolinone functionality, MM3*, MMFF, Amber*, and OPLS* gave excellent atom-for-atom correlation for the lowest-energy conformations (Figure 4d).

In summary, these studies demonstrate the feasibility of designing a turn structure utilizing D,L-mixed polypyrrolinones. Efforts to crystallize (−)-**9** and to design a somatostatin mimic exploiting the D,L-mixed polypyrrolinone scaffold are in progress.

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Supporting Information Available: Spectroscopic, analytical data for **2**, **4**−**7**, **9** and selected experimental procedures, NOESY spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Three intramolecular hydrogen bonds exist in (−)-**9** with distances of 2.45, 2.67, 2.36 Å. Hydrogen bonding angles for N−H···O are 109°, 100°, and 94°, respectively. As expected, the N-terminal hydrogen 4 is exposed to the solvent.
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