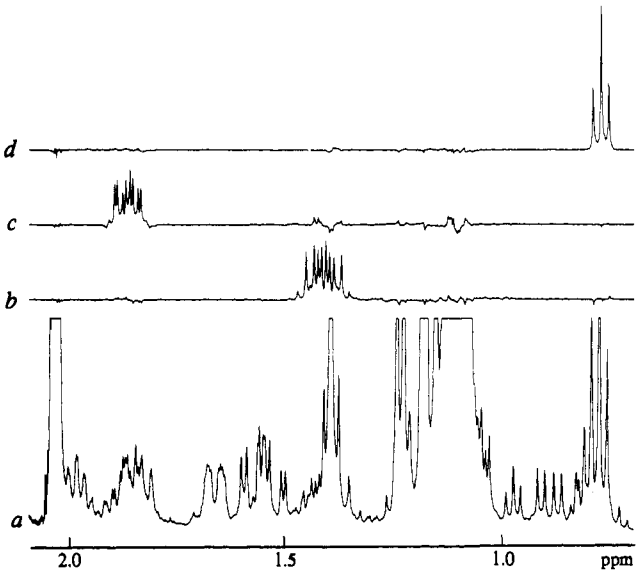

Figure 2. (a) A crowded region of the erythromycin spectrum. (b) Hartmann–Hahn coherence transfer from a methine proton to one of the adjacent (inequivalent) methylene protons. (c) A two-step transfer to the other methylene proton. (d) A three-step transfer to the adjacent methyl group. All three multiplets are obscured by overlap in the conventional spectrum a.

and the two inequivalent methylene protons may be salvaged from an overcrowded region of the erythromycin spectrum.

Several useful elaborations of this technique are possible. Chain branching or ring formation can be identified by suitably directing the flow of coherence. A nonselective "INEPT" transfer[9] from protons to carbon-13 at the end of the sequence enables an analogous step-by-step assignment of the carbon-13 spectrum.[10]

† On leave from the Institute of Organic Synthesis, Riga, Latvia.

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Design, Synthesis, and Crystal Structure of a Pyrrolinone-Based Peptidomimetic Possessing the Conformation of a β-Strand: Potential Application to the Design of Novel Inhibitors of Proteolytic Enzymes

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The design and synthesis of nonpeptidal peptidomimetics have emerged as a synergistic enterprise spanning organic, bioorganic, and medicinal chemistry,[1] driven by the quest for improved pharmacodynamic properties such as oral bioavailability and biological half-life.[2] There is mounting evidence that hydrogen bonding involving the amide backbones of peptide hormones and their receptors is not required for receptor binding or activation,[3] as demonstrated by the classic peptidomimetic morphine[4] and other ligand mimetics[5] lacking the amide scaffolding.[6] In contrast, convincing crystallographic evidence indicates that H-bonding involving the amide backbones plays a critical role in the binding of peptidal inhibitors to proteolytic enzymes.[1c,7] Because they must mimic both the β-strand conformations and, at least in part, the H-bonding capabilities of their peptide counterparts, the design of nonpeptidal enzyme inhibitors is considerably more challenging than the creation of mimetics of peptidal hormone-receptor ligands.

Interactive computer modeling[8a] suggested that a series of 3,5-linked pyrrolin-4-ones (e.g., **1**) would adopt a backbone conformation mimicking a β-strand (Figure 1). Moreover, a conformational search[8b] indicated that the peptidal side chains appended to the 5-positions could assume an orientation axial to the heterocyclic ring (Figure 2). In the calculated low-energy conformers, the pyrrolinone rings fix the dihedral angles analogous to ψ and ω in a peptide, and gauche steric interactions of the side chains with the neighboring pyrrolinone rings constrain rotations corresponding to φ. The crystalline methyl ester of an equine angiotensinogen fragment [i.e., H-Leu-Leu-Val-Tyr-OMe (**2**)] exists as a parallel β-pleated sheet.[9] Comparison with our model

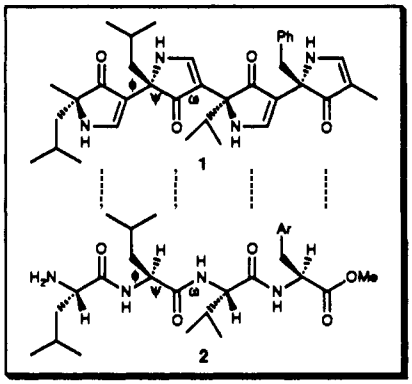

Figure 1. Correlation of the pyrrolinone backbone and side chains in **1** with tetrapeptide **2**. Dotted lines show the alignment of the carbonyl groups.

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(2) 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), whereas cyclosporin contains mostly N-methylated amide bonds and is orally bioavailable (Yoshimura, N.; Matsui, S.; Hamashima, T.; Oka, T. *Transplantation* **1989**, *47*, 351). These results suggested to us that the C(O)NH bond itself may contribute to the poor oral bioavailability of nearly all peptides.
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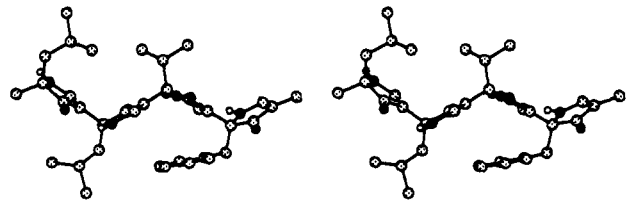
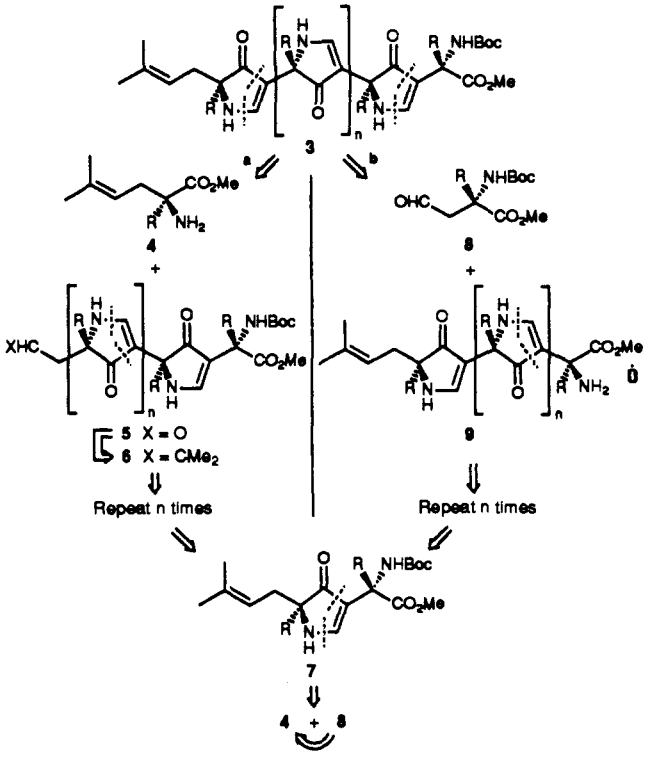


Figure 2. Stereoview of the predicted backbone conformation and side-chain orientations for four 3,5-linked pyrrolin-4-one rings.

(1) suggested that the disposition of the vinylogous amide carbonyls in **1** should closely correspond with the orientation of the peptide carbonyls in **2**, maintaining the hydrogen-bond-acceptor capabilities of the native β-strand. The pyrrolinone NH groups, though vinylogously displaced from the backbone, are comparable to amide nitrogens in basicity[10] and may further stabilize the requisite β-strand and β-pleated sheet conformations through intra- and intermolecular H-bonding, respectively.

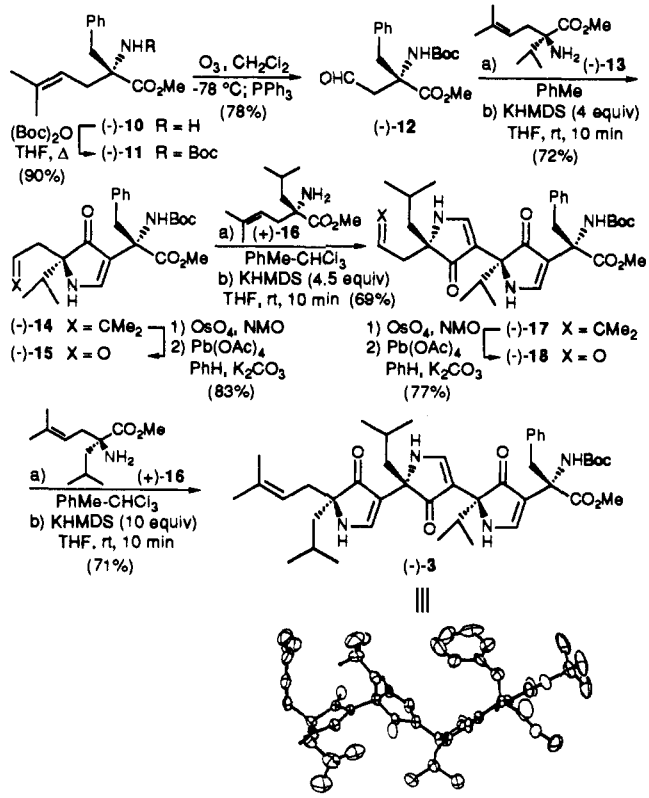
To test these predictions we synthesized tetrapeptide mimic **3**, exploiting our efficient, two-step construction of scalemic 3,5,5-trisubstituted pyrrolin-4-ones.[11] Extension of this protocol to the *iterative* formation of linked pyrrolinones could furnish **3** by either "C-terminal" or "N-terminal" elaboration (Scheme I). Retro-

Scheme I



synthetic N-terminal disconnection (path a) leads to α-alkylated amino ester **4** and aldehyde **5**, the latter derived from olefin **6**. Repetition of the sequence furnishes monopyrrolinone **7**, whereupon similar disconnection generates **4** as well as aldehyde **8**, the latter again available from **4** via protection and ozonolysis. Alternatively, C-terminal disconnection (path b) would afford **8** and amino ester **9**; iteration would then lead to **7** as before. The N-terminal approach proved exceptionally well suited to the assembly of β-strand mimetic (−)-**3**, as shown in Scheme II.[12]

Scheme II



Least-squares comparison of the X-ray structures of **3** and **2** confirmed the expected overlap of the side chains and carbonyl groups (Figure 3). Moreover, examination of the unit cell established that **3** adopts an antiparallel β-pleated-sheet organization in the crystal (Figure 4), demonstrating convincingly that the pyrrolinone nitrogens do serve as interstrand hydrogen-bond donors in the desired β-strand conformation. As we had predicted, re-

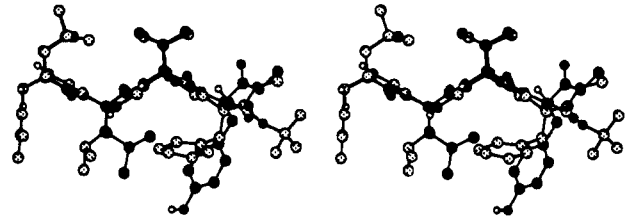


Figure 3. Stereoview of the RMS overlay of the backbone atoms in the X-ray structures of **3** (gray) and **2** (black).

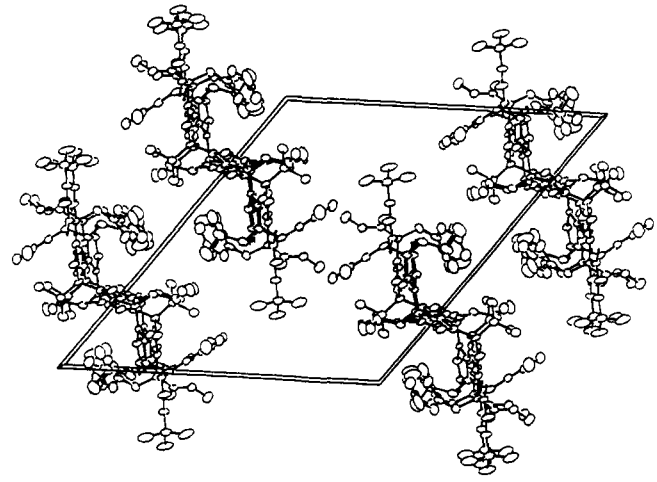


Figure 4. ORTEP view down the antiparallel sheet axis of the unit cell of **3**.

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(12) All new compounds gave satisfactory IR, 500-MHz ^{1}H NMR, and 125-MHz ^{13}C NMR spectra as well as appropriate parent ion identification by high-resolution mass spectrometry.

moval of the Boc moiety in **3** furnished a species which assumed the parallel sheet arrangement in the solid state. We note parenthetically that, in peptide **2**, H-bonding between the phenolic hydroxyl and the N-terminus of a neighboring strand causes deviation from the ideal β-strand conformation at the C-terminus. Our mimic **3**, lacking the phenolic hydroxyl, shows no such deviation.

The importance of β-pleated sheets in peptides and proteins is well established. Martin,[13a] Clardy and Schreiber,[13b] and Simon and Bartlett[13c] have recently described novel molecules which can adopt extended or sheetlike structures. None of these however share our objectives to mimic native β-strands and sheets with regard to side-chain orientations and interstrand H-bond donating capabilities. We believe that the design and synthesis of **3** open up a new approach to novel, nonpeptidal mimics of β-pleated strands and sheets.[14] Efforts to determine the solution structures of **3** and related compounds and to design pyrrolinone-based inhibitors of human renin and the HIV1 protease will be reported in due course.

Acknowledgments. We acknowledge support of this investigation by Bachem, Inc. (Torrance, CA), the National Institutes of Health (Institute of General Medical Sciences) through grant GM-41821, Merck Research Laboratories, and Sterling Winthrop Inc. In addition, we thank Dr. George Furst, and Mr. John M. Dykins of the University of Pennsylvania Spectroscopic Service Centers for assistance in securing and interpreting high-field NMR and mass spectra, respectively.

Supplementary Material Available: Listings of complete spectral data for **3** and **10-18** and tables of experimental details, positional parameters, and thermal parameters for the X-ray analyses of **3** and **18** (28 pages). Ordering information is given on any current masthead page.

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Electrophilic Activation of the Horner-Wadsworth-Emmons-Wittig Reaction: Highly Selective Synthesis of Dissymmetric Olefins

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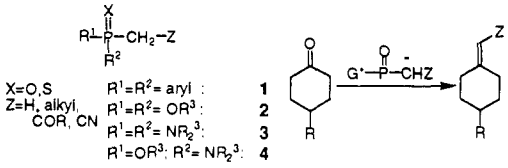
The carbonyl olefination reaction employing phosphoryl-stabilized carbanions (Horner-Wadsworth-Emmons (HWE)) reaction[1] is now a well-established and useful alternative to the Wittig olefination.[2] The HWE reaction of anions derived from phosphine oxides (**1**), phosphonates (**2**), phosphonamides (**3**), and their thiono counterparts (X = S) have well-documented advantages in many situations. One class of reagents, the (intrinsically chiral) phosphonamidates (**4**), has rarely been employed. As part of our general program of the structure[3] and utility[4] of auxiliary-based, chiral P=O stabilized anions, we have examined the potential of scalemic phosphonamidates for the synthesis of dissymmetric alkylidenes, Scheme I. The syntheses of chiral

Scheme I



Scheme II

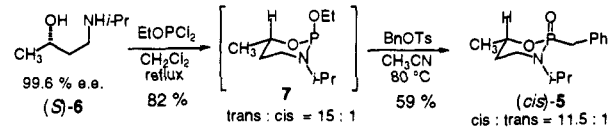
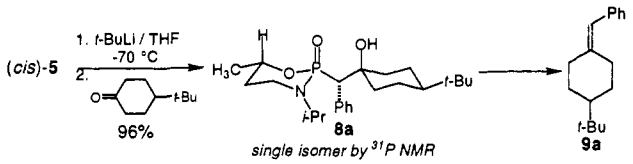


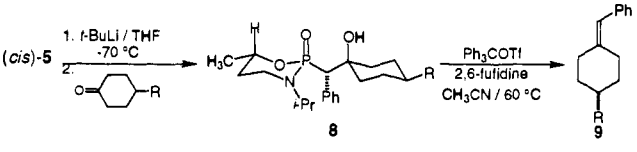
Table I. Optimization of Electrophile-Activated Olefination of **8a**



reagent (equiv)	base[a] (equiv)	temp, °C (time, h)	solvent	yield,[b] %	ee,[c] % (config)
	A (1.5)	−78 → 65 (24)	THF	72	11 (*R*)
	A (1.5)	−78 (0.25)	THF	8[d]	3 (*R*)
MeOTf (5)	B (5)	rt[f] (13)	CH_2Cl_2	27[e]	>99 (*S*)
Et_3OBF_4 (1)	B (2)	rt (6)	CH_2Cl_2	46[e]	>99 (*S*)
Ph_3CClO_4 (1.6)	B (2)	rt (1.25)	CH_2Cl_2	59[e]	>99 (*S*)
Ph_3CClO_4 (1.6)	B (2)	60 (3)	CH_3CN	60	>99 (*S*)
Ph_3CBF_4 (1.6)	B (2)	60 (1.75)	CH_3CN	69	>99 (*S*)
Ph_3COTf (1.6)	B (2)	60 (2.5)	CH_3CN	68-80	>99 (*S*)
Ph_3COTf (2.3)	B (2)	rt (22)	HCO_2Me	61	nd[g]
Ph_3COTf (2.1)	B (2)	rt (28)	CH_3NO_2	51	nd

[a] A: KHMDS. B: 2,6-Lutidine. [b] Yield of isolated, purified product. [c] Footnote 16. [d] (*cis*)-**5** was recovered in 77% yield. [e] Starting material remained. [f] Room temperature. [g] Not determined.

Table II. Asymmetric Olefination of 4-Substituted Cyclohexanones



R	product	de	yield,[a] %	product	ee,[b] %	ee,[b] % (config)
$C(CH_3)_3$	**8a**	>98[c]	96	**9a**	68	>99 (*S*)
CH_3	**8b**	88[c]	99	**9b**	73	86 (*S*)
C_6H_5	**8c**	98[d]	94	**9c**	76	>99 (*S*)
$CO_2C(CH_3)_3$	**8d**	98[d]	98	**9d**	77	95 (*S*)

[a] Yield of isolated, purified product. [b] Footnote 16. [c] ^{31}P NMR analysis. [d] HPLC analysis.

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