Design and Synthesis of a Protein β-Turn Mimetic

Gary L. Olson,* Matthew E. Voss, David E. Hill, Michael Kahn, Vincent S. Madison, and Charles M. Cook

Contribution from the Chemistry Research Department, Hoffmann-La Roche Inc., Roche Research Center, Nutley, New Jersey 07110. *Received June 20, 1989*

Abstract: A nine-membered-ring lactam system (**1**) has been chosen as a framework for the development of non-peptide molecules to mimic structural features of peptide and protein β-turns. The synthesis of model di- and tetrapeptide mimetics starting from 1,5-cyclooctadiene derivatives is reported. In the model dipeptide mimetic (**9**), the amide linkage is trans (NMR, X-ray) and functional groups at positions adjacent to the lactam amide bond correspond closely to the side-chain positions of residues $i + 1$ and $i + 2$ of classical type II′ β-turns. In the model tetrapeptide mimetic (**30**), all four side chains of low-energy trans amide conformers of the mimetic are well matched to their peptide counterparts.

Advances in the fields of molecular biology and peptide synthesis, coupled with improved techniques of structure elucidation and molecular modeling, have provided dramatic new insight into the structure, three-dimensional architecture, and biological function of peptides and proteins. The increased availability of peptide substances for biological characterization has led to greater appreciation of their pharmacological and biochemical properties, and the need for detailed structural information about them has mushroomed. Peptides and proteins are no longer mysterious curiosities. As hormones and inhibitors, they have become valuable as therapeutic agents. As enzymes and receptors, they are the center of mechanisms to control and modulate biological functions.

Efforts to improve upon natural peptides using the tools of peptide synthesis and site-directed mutagenesis have met with some success. Peptide and protein analogues are widely employed in elucidating structure–activity relationships,[1] and some long-acting derivatives that resist enzymatic degradation[2] have been developed. Enzyme inhibitors, with structures designed on the basis of peptide substrates, are major success stories for the pharmaceutical industry.[3] Some areas have been slower to progress, notably, the search for general approaches to make peptides and proteins more bioavailable and orally active.[4] In recognition of the difficulties of this problem, attention has turned to organic synthesis, with the hope that peptides could serve as leads for drug discovery in the same way that plant natural products and leads from random screening inspired the current generation of therapeutic agents.[5] In this effort, it is anticipated that structural insights from protein crystallography and molecular modeling will reveal principles that could lead to molecules with chemical properties resembling traditional drugs, but with their biological characteristics derived from a peptide lead. While it has been possible to design replacements for the peptide bond (peptide surrogates)[6] and to optimize peptide–receptor interactions via conformational constraints,[7] the development of small, organic molecules that could mimic the structure and biological activity of peptides remains an elusive goal.

Table I. Conformations of Classical β-Turns[11]

	turn type					
angle	I	I′	II	II′	III	III′
ϕ_1	−60	60	−60	60	−60	60
Ψ_1	−30	30	120	−120	−30	30
ϕ_2	−90	90	80	−80	−60	60
Ψ_2	0	0	0	0	−30	−30

Nevertheless, the feasibility of peptide mimetics can be demonstrated through two well-known cases derived from natural products. Synthetic opiate analgesics and opiate antagonists,[8] as well as the cholecystokinin (CCK) antagonists of the benzodiazepine class,[9] have been imaginatively fashioned from natural product leads identified through screening. In these cases, the non-peptide, organic molecules function to mimic or antagonize a native peptide (β-endorphin or CCK), despite the fact that they lack peptide bonds and have little or no conformational mobility. While these examples are encouraging for the overall concept of peptide mimetics, their structures are so distantly related to their parent peptides that the principles of the relationship are obscure. A more rational approach is needed.

Peptide Mimetics Approach. The information obtained from peptide analogues, surrogates, and conformationally constrained peptides provides a foundation for the design of peptide mimetics. The approach that we have adopted[10] involves replacement of the peptide backbone by a non-peptide framework that can carry the amino acid side-chain groups of the peptide in a conformation that mimics their orientation on the peptide. Assuming that recognition of the peptide involves binding of the side-chain substituents to the receptor, then backbone replacement could alter the physical and transport properties of the mimetic without compromising the receptor interaction. The concept we are following is to make significant changes in the peptide backbone,

(1) (a) Hruby, V. J.; Krstenansky, J. L.; Cody, W. L. In *Annu. Rep. Med. Chem.* **1984**, *19*, 303–312, and references therein. (b) See the series of the American Peptide Symposium, e.g.: *Peptides, Chemistry and Biology*, Marshall, G. R., Ed. ESCOM Science Publishers B. V.: Leiden, The Netherlands, 1988.

(2) (a) Metcalf, G. *Brain Res. Rev.* **1982**, *4*, 389–408. (b) Veber, D. F. et al. *Nature* **1979**, *280*, 512–514. (c) Freidinger, R. M.; Veber, D. F. In *Conformationally Directed Drug Design: Peptides and Nucleic Acids as Templates or Targets*; Vida, J. A., Gordon, M., Eds.; ACS Symposium Series 251; American Chemical Society: Washington, DC, 1984; pp 169–187. (d) Hruby, V. J.; Cody, W. L.; Wilkes, B. C.; Hadley, M. E. *Peptides* **1984**, 505–508.

(3) (a) Ondetti, M. A.; Cushman, D. W. *Annu. Rev. Biochem.* **1982**, *52*, 283. (b) Boger, J. *Annu. Rep. Med. Chem.* **1985**, *20*, 257–266. (c) Wyvratt, M. J.; Patchett, A. A. *Med. Chem. Rev.* **1985**, *5*, 483–531.

(4) (a) Stenerson, L. A. *Biological Approaches to the Controlled Delivery of Drugs. Ann. N.Y. Acad. Sci.* **1987**, *507*, 19–21. (b) Almquist, R. G.; Chao, W.-R.; Judd, A. K.; Mitoma, C.; Rossi, D. J.; Panasevich, R. E.; Matthews, R. J. *J. Med. Chem.* **1988**, *31*, 561–567.

(5) Burger, A. In *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; Wiley: New York, 1980; Part 1, pp 1–54.

(6) (a) Spatola, A. *Chem. Biochem. Amino Acids, Pept., Proteins* **1983**, *7*, 267–357. (b) Goodman, M.; Chorev, M. In *Prospectives in Peptide Chemistry*; Eberle, A., Geiger, R., Wieland, T., Eds.; Karger: Basle, 1981; pp 283–294. (c) Salvadori, S.; Marastoni, M.; Balboni, G.; Sarto, G. P.; Tomatis, R. *J. Med. Chem.* **1985**, *28*, 769–774.

(7) (a) Hruby, V. J. *Trends Pharmacol. Sci.* **1985**, *6*, 259–262. (b) Veber, D. F.; Freidinger, R. M.; Perlow, D. S.; Paleveda, W. J., Jr.; Holly, F. W.; Strachan, R. G.; Nutt, R. F.; Arison, B. H.; Homnick, C.; Randall, W. C.; Slitzer, M. S.; Saperstein, R.; Hirschmann, R. *Nature* **1981**, *292*, 55–58.

(8) Johnson, M. R.; Milne, G. M. In *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; Wiley, New York, 1980; Part III, pp 699–758.

(9) (a) Evans, B. E.; Bock, M. G.; Rittle, K. E.; DiPardo, R. M.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4918–4922. (b) Bock, M. G.; DiPardo, R. M.; Rittle, K. E.; Evans, B. E.; Freidinger, R. M.; Veber, D. F.; Chang, R. S. L.; Chen, T. B.; Keegan, M. E.; Lotti, V. J. *J. Med. Chem.* **1986**, *29*, 1941–1945. (c) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L. Gould, N. P.; Lundell, G. F.; Homnick, C. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; King, P. J.; Kunkel, K. A.; Springer, J. P.; Hirschfield, J. *J. Med. Chem.* **1987**, *30*, 1229–1239.

(10) The best conceptual exposition of these principles is due to: Farmer, P. S. In *Drug Design*; Ariëns, E. J., Ed.; Academic: New York, 1980; Vol. X, pp 119–143.

0002-7863/90/1512-323$02.50/0

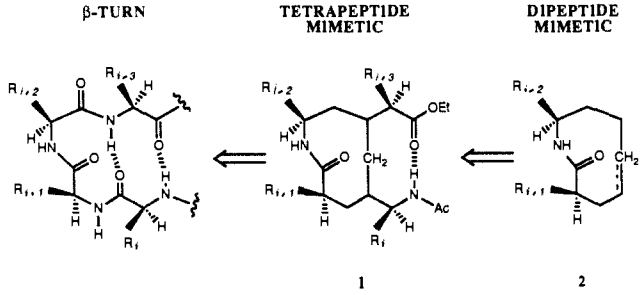


Figure 1. Peptide/protein β-turn and design of nine-membered-ring lactam mimetics.

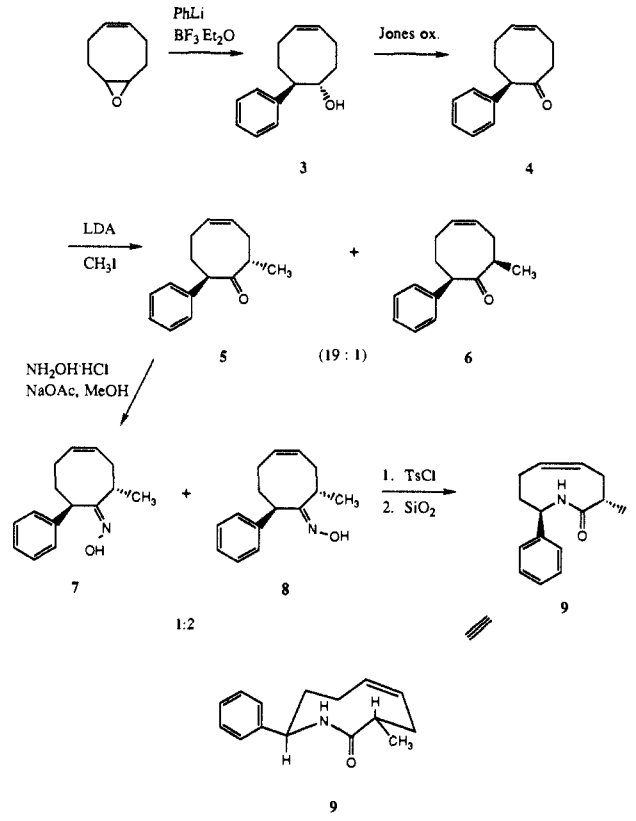
while permitting only conservative alterations to the amino acid side-chain substituents.

Our approach to peptide mimetics is being applied to several targets, each selected because there are well-founded hypotheses concerning the orientation and role of the pharmacophoric side-chain substituents and the bioactive conformations of the peptide. This information is known for only a few small, relatively constrained peptides. It would seem at first glance that our mimetics approach would be limited to such conformationally constrained targets.

Application to β-Turns in Proteins. However, well-defined conformational features are also characteristic of larger polypeptides, and particularly of proteins. Their architectural elements of sheets and helices are interconnected with loops and turns that often have well-ordered structures. In this paper, attention is focused on the β-turn, a segment of four amino acids (Figure 1; residues i to $i + 3$) that occurs where the peptide chain reverses direction.[11] Since many β-turns in proteins are located on the surface, they are likely recognition and antigenic sites. Furthermore, exposure to the hydrophilic interface is most probable for amino acids with polar side chains capable of interacting with hydrogen bond donors and acceptors from solvent, or from a recognition site on a receptor. β-Turns are also common conformations for biologically active cyclic peptides and have been hypothesized to be bioactive conformations for several linear peptides.[12] In the β-turn structure, the carbonyl of the i residue is aligned to form an intrachain hydrogen bond with the amide hydrogen at residue $i + 3$. This generates a pseudocyclic ring with different puckered conformations depending upon the orientation of the amide bonds and side chains of the residues making up the turn. β-Turns have been classified as types I, II, and III, according to the torsion angles of the "corner" residues at positions $i + 1$ and $i + 2$ for frequently observed ring conformations (Table I).[13]

There have been several non-peptide systems devised to span the i and $i + 3$ residues of the turn.[14] These compounds are effective spacers, successfully reproducing the change in direction of the peptide chain, and are being exploited in the synthesis of hybrid peptides where the dipeptide mimetic is substituted to induce a β-turn at a desired position. However, these compounds are devoid of functionality at the key corner residues $i + 1$ and $i + 2$ involved in binding to a macromolecular receptor. We set

Scheme I



out to design a non-peptide molecule that could carry the side-chain residues at the corner positions in an orientation analogous to that of the β-turn.[15] Such a compound would have the potential not only to mimic the change in chain direction of a peptide turn, but also could elicit a response from a receptor that might recognize the side-chain groups of the exposed corner residues. Furthermore, if the small molecule mimetic should reorient or fit tightly into the pocket occupied by the peptide turn on its receptor, it could exhibit antagonist properties.

The pseudocyclic 10-membered ring formed by the β-turn backbone and hydrogen bond initially suggested the design of an analogous 10-membered covalently bonded ring system with a central amide bond. However, space-filling models of such compounds showed that they occupied some additional molecular volume outside that of a peptide turn. Consequently, the smaller nine-membered-ring system (**1**; Figure 1) was selected as our initial mimetic. In **1**, a methylene group replaces the intrachain hydrogen bond of the peptide turn, and all of the amide bonds except for the central one are replaced by methylenes. This amide was retained since its peptide counterpart is relatively exposed in a turn and could be involved in hydrogen-bonding interactions with a receptor. The functionality of **1** and the synthetic schemes we have employed permit the introduction of substituents flanking the amide group. These groups represent the side chains of the $i + 1$ and $i + 2$ residues at the corner positions. Using this approach, we have designed simple dipeptide mimetics lacking the amino and carboxy residues at positions i and $i + 3$ and model tetrapeptide mimetics with these amino and carboxy groups. We now report the synthesis of these model systems and describe their three-dimensional structure and relationship to model peptide β-turns.

Dipeptide Mimetic. A. Synthesis of a Nine-Membered-Ring Lactam Dipeptide Mimetic (2; Figure 1). The system chosen to model the spatial relationships of the corner positions of a β-turn was a nine-membered-ring lactam (**2**; Figure 1). Our first target molecule was the simplified disubstituted lactam **9**, chosen for

(11) (a) Rose, G. D.; Gierasch, L. M.; Smith, J. A. *Adv. Protein Chem.* **1985**, *110*, 1–109. (b) Richardson, J. S. *Adv. Protein Chem.* **1981**, *34*, 167–339.

(12) (a) Schiller, P. W. In *The Peptides: Conformation in Biology and Drug Design*; Hruby, V., Ed.; Academic Press: New York, 1985; Vol. 7, pp 115–164. (b) Siemon, I. Z.; Lisowski, M.; Konopinska, D.; Nawrocka, E. *Eur. J. Biochem.* **1980**, *112*, 339–343.

(13) (a) Pavone, V. *Int. J. Biol. Macromol.* **1988**, *10*, 238–240. (b) Milner-White, E. J.; Poet, R. *Trends Biochem. Sci.* **1987**, *12*, 189.

(14) (a) Feigel, M. *J. Am. Chem. Soc.* **1986**, *108*, 181–182. (b) Sato, K.; Nagai, U. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1231–1234. (c) Kemp, D. S.; McNamara, P. E. *J. Org. Chem.* **1984**, *49*, 2286–2288. (d) Wyvratt, M. J.; Ikeler, T. J.; Tischler, M. H.; Springer, J. P.; Tristram, E. W.; Patchett,A. A. *Peptides—Structure and Function, Proceedings of the Eighth American Peptide Symposium*; **1983**, 551–554. (e) Krstenansky, J.; Baranowsky, R. L.; Currie, B. L. *Biochem. Biophys. Res. Commun.* **1982**, *109*, 1368–1374. (f) Kemp, D. S.; Stites, W. E. *Tetrahedron Lett.* **1988**, *29*, 5057–5060. (g) Kahn, M.; Bertenshaw, S. *Tetrahedron Lett.* **1989**, *30*, 2317, and references therein.

(15) Preliminary accounts of an application of this approach have been published by M.K.: Kahn, M.; Chen, B. *Tetrahedron Lett.* **1987**, *28*, 1623–1626.

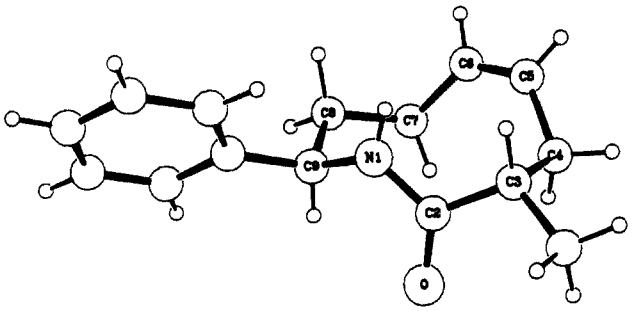


Figure 2. X-ray crystal structure of lactam 9.

its ability to mimic the side-chain orientations at the corner residue positions. Compound 9 was synthesized by modification of a route to nine-membered-ring lactams published by Wilson and Sawicki[16] (Scheme I). Starting with the readily available monoepoxide of 1,5-cyclooctadiene,[17] oxirane opening with phenyllithium/BF_3·Et_2O[18] gave the trans phenyl alcohol 3, which was oxidized with Jones' reagent to give ketone 4 in 62% yield for two steps. Kinetic deprotonation of 4 (LDA, −78 °C) followed by alkylation with excess methyl iodide gave a mixture of methyl epimers 5 and 6 (19:1 ratio, 95% yield), where the expected axial addition product 5 predominates. Pure 5 was obtained by recrystallization from ethyl acetate/hexanes and was treated with an excess of NH_2-OH·HCl and NaOAc (methanol reflux, 48 h) to form oximes 7 and 8 (1:2 ratio) in 75% yield. Separation by flash chromatography afforded the pure anti (hydroxyl positioned away from the phenyl group) oxime 8. Resubjecting 7 to the oximation conditions reestablished the equilibrium mixture, allowing an efficient overall conversion to the desired anti oxime 8. Beckmann rearrangement of 8 occurred upon exposure of the derived tosyl oxime to silica gel[19] to afford the target lactam 9 in 69% overall yield.

B. **Modeling and Structure of Dipeptide Mimetic 9.** The ring conformations and side-chain orientations of lactam 9 were studied by molecular modeling, ^{1}H NMR, and X-ray crystallography. The X-ray structure is depicted in Figure 2. Low-energy conformations of the ring were explored systematically by both the conformational search option of SYBYL[20] and an algebraic cyclization procedure,[21] yielding equivalent results. In both procedures, some flexibility of the amide bond (up to 30°) and the ethylenic bond (up to 20°) was required in order to scan torsional space adequately.

In the algebraic procedure, the bonds between N1 and C9, N1 and C2, and C5 and C6 (see Figure 2) were allowed to vary independently and the torsional angles required to cyclize the ring were computed. The ethylenic bond was varied in 20° increments; the other two bonds were varied in 10° increments. The resulting 756 combinations of these variables were explored and a total of 122 cyclic conformations were found. The energy of the backbone was minimized for each conformation with the consistent force field program developed by Lifson.[22] The minimized conformers were found to fall into four conformational families with a root-mean-square deviation of ring atoms within a family of less than 0.32 Å.

As a test of methodology and to provide a common basis for comparison with later studies, the conformational analysis was repeated using SYBYL. In this procedure, the bond between C9 and C10 was removed and the remaining bonds were varied by fixed increments of 2° for the amide and ethylenic bonds and 10° for the other bonds. Those conformations satisfying both a ring closure and a van der Waals contact constraint were tabulated. The ring closure constraint required that acceptable conformations close the bond between atoms 9 and 10 to within 0.15 Å of the original bond length and that the resulting bond angles be within 15° of their original values. The acceptable van der Waals contact distance was set to 90% of the sum of atomic van der Waals radii. To simplify the problem, all hydrogens except for the amide hydrogen were omitted at this stage. Two starting conformations were generated by model building: one with the amide proton anti to the C10 proton; the other with these protons syn. A total of 284 conformations were generated from these two runs. These were grouped by root-mean-square differences of the ring atom positions with a cutoff of 0.1 Å. The hydrogens were added to the remaining conformations and the structures were minimized by using the Tripos force field MAXIMIN[23] with an 1-fold torsional energy term of 1.35 kcal replacing the default 2-fold term for the H–N–C–O amide bond.[24] The minimized structures were again

Table II. Conformations of Lactam 9 and Relative Energies

conformer	energy, kcal/mol SYBYL	energy, kcal/mol MM2	orientation[a] O	orientation[a] C=C	orientation[a] phenyl
1	0.00	0.00	down	up	eq
2	2.76	4.18	down	up	ax
3	2.28	3.52	down	down	eq
4	2.02	3.43	down	down	ax
5	3.30	2.31	up	down	ax
6	1.97	3.53	up	down	eq
7	2.39	3.67	up	up	ax
8	0.40	2.03	up	up	eq

[a] Orientations are with respect to the mean plane of the ring with the C9–C12 (phenyl ring) vector defined as up.

Table III. Root-Mean-Square Fit of Conformations of Lactam 9 to Model β-Turn Types

conformer	I	I′	II	II′	III	III′
1	0.41	0.45	0.28	0.29	0.57	0.61
2	0.26	0.72	0.44	0.48	0.37	0.86
3	0.42	0.43	0.33	0.33	0.59	0.60
4	0.27	0.76	0.47	0.52	0.35	0.90
5	0.42	0.44	0.28	0.28	0.58	0.60
6	0.69	0.26	0.46	0.41	0.84	0.38
7	0.41	0.45	0.34	0.35	0.57	0.62
8	0.73	0.26	0.50	0.45	0.87	0.36

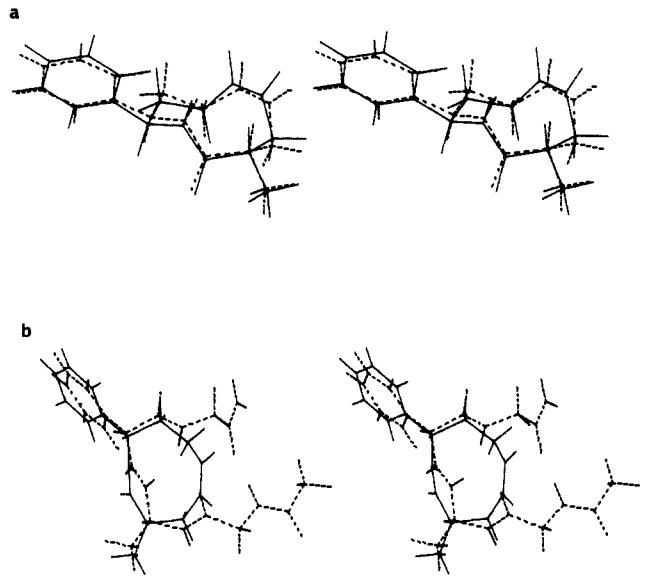
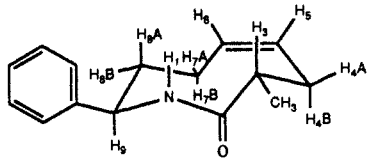


Figure 3. (a) Superposition of X-ray structure (···) and lowest energy conformer (—) of lactam 9. (b) Superposition of X-ray structure of lactam 9 (···) and model type II′ β-turn (AcGly-D-Ala-Phe-GlyNH_2) (—).

(16) Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 330–336.
(17) Davies, S. G.; Polywka, M. E. C.; Thomas, S. E. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1277–1282.
(18) Ganem, B.; Eis, M. J.; Wrobel, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 3693–3694.
(19) Costa, A.; Mestres, R.; Riego, J. M. *Synth. Commun.* **1982**, *12*, 1003–1006.
(20) SYBYL Version 5.2, Tripos Associates Inc., St. Louis, MO.
(21) Madison, V. *Biopolymers* **1973**, *12*, 1837–1852.
(22) Warshel, A.; Levitt, M.; Lifson, S. *J. Mol. Spectrosc.* **1970**, *33*, 84–89.
(23) Labonowski, J.; Motoc, I.; Naylor, C. B.; Mayer, D.; Dammkoehler, R. A. *Quant. Struct.-Act. Relat. Pharmacol. Chem. Biol.* **1986**, *5*, 138–152.

Table IV. Vicinal ^1H–^1H Coupling Constants for Lactam **9**



protons	J_{obsd}, Hz	J_{calcd}, Hz
H3–H4A	2.5	2.9
H3–H4B	13.0	11.9
H4A–H5	7.5	8.2
H4B–H5	8.5	8.4
H6–H7A	5.0	4.0
H6–H7B	11.0	11.8
H7A–H8A	1.0	2.0
H7A–H8B	3.0	6.1
H7B–H8A	11.0	11.3
H7B–H8B	<1.0	1.8
H8A–H9	11.0	10.0
H8B–H9	5.5	7.0
H9–H1	11.0	10.9
	corr coeff, r = 0.964	

grouped into families by using a cutoff of 0.15 Å. At this cutoff, eight distinct families were found. (With a cutoff of 0.32 Å, these eight families collapse pairwise to the four families found with the algebraic search.)

The eight conformational families can be classified by the relative positions of the phenyl ring, carbonyl oxygen, and ethylenic groups with respect to the mean plane of the ring (Table II). The C6 to the phenyl ring vector is arbitrarily defined as "up". The orientation of the phenyl ring was classified by the magnitude of the torsion angle: C7–C8–C9–C12. The ring atoms in conformations 1–4 are mirror images of conformations 5–8. The lowest energy conformer (1) is shown in Figure 3a overlaid on the X-ray structure. The energy barrier between low-energy conformations was calculated by using the dihedral angle driver of MM2. A small barrier (3.9 kcal/mol) was calculated for the rotation of the amide group by 180° to convert conformer 1 to conformer 7. The barrier for reversing the orientation of the ethylenic group (i.e., conformer 1 to conformer 3) was in excess of 12 kcal/mol. On the basis of these results, at a temperature of 25 °C and above, the ring conformations of **9** should exist as a mixture containing at least 60% conformer 1. In $CDCl_3$ at room temperature, the ^1H NMR spectrum (see below and Table IV) indicated only a single conformer consistent with conformer 1.

A similar conformational search analysis of the amide bond cis isomer yields 22 unique conformational families ranging in energy from +2.89 to +23.45 kcal/mol relative to the lowest energy trans conformer. From this difference, the cis population should account for less than 1% of the total.

The 400-MHz ^1H NMR spectrum of **9** in $CDCl_3$ indicated an 11 Hz coupling constant for the ethylenic bond, confirming its cis orientation. By use of the computer-generated conformation, vicinal proton coupling constants were calculated from the Karplus equation[25] and shown to be in excellent agreement with those measured experimentally (Table IV.) In the solid phase, X-ray crystallographic analysis revealed a conformation (Figure 2) nearly identical with the lowest energy trans conformation with a ring atom root-mean-square difference of 0.17 Å as shown in Figure 3a.

The lowest energy conformer 1 of mimetic **9** was compared to model tetrapeptide β-turns of types I, I′, II, II′, III, and III′. These conformations were generated by using the standard torsional angle parameters listed in Table III for the tetrapeptide Gly-Ala-Ala-Gly. A least-squares fit was calculated between mimetic atoms C3, C4, C8, and C9 and the peptide atoms N(2), $C_\alpha(2)$, $C_\alpha(3)$ and C(3), resulting in a best fit (root mean square 0.31 Å) to the type II′ turn. This choice of atoms for the fit was made to find the turn that best matches the side-chain positions, rather than matching the amide bonds atom by atom. Nevertheless, the amide groups also fit the type II′ turn. The fit of **9** with a model type II′ turn for AcGly-D-Ala-L-PhGly-GlyNH_2 (as built and minimized in SYBYL) is shown in Figure 3b and illustrates the *excellent correspondence of the corner residue substituents of the mimetic 9 and the peptide model β-turn.*

Tetrapeptide Mimetic. A. Synthesis of a Nine-Membered-Ring Tetrapeptide Mimetic (1; Figure 1). Encouraged by the results of the model system **9**, a tetrapeptide mimetic of the type represented by **1** was designed. A model structure (**30**) was selected for synthesis. This structure incorporates amino and carboxy termini of the i and $i + 3$ residues as well as the corner substituents into the nine-membered-ring lactam template, providing an AcGly-Gly-(Phe)Gly-GlyOEt tetrapeptide mimetic. Because it proved impossible to functionalize the double bond in **9** without transannular participation of the amide nitrogen,[26] a new route was needed for the synthesis of the tetrapeptide mimetic. The starting point in the synthetic scheme was 2,6-cyclooctadien-1-one, which was available[27] *in* three steps from cyclooctadiene (Scheme II).

The amino terminus was introduced by conjugate addition of nitromethane to 2,6-cyclooctadien-1-one, with tetramethylguanidine (TMG) serving as the catalytic base,[28] to provide the 1,4 addition product **10** in 77% yield. Protection of the carbonyl as the ethylene ketal **11** (68% yield) was followed by the reduction of the nitro group with lithium aluminum hydride to the amine **12** and protection as the acetamide (65% overall) to give crystalline ketal **13** in 65% overall yield. Compound **13** could readily be prepared in 25-g lots. With the amino terminus in position, and functionality available to append the carboxy terminal chain in place, our attention turned to the introduction of the $i + 2$ side-chain substituent. The ketal group in **13** was hydrolyzed to give the β,γ-enone **14**. The olefin was functionalized via oxidation with OsO_4 to provide approximately a 1:1 ratio of hemiketals **15** and **16**, produced by spontaneous cyclization of the corresponding cis diols. Acetylation of the mixture opened the hemiketal ring system to provide a mixture of cis diacetates **17**. Exposure of **17** to Alumina in benzene effected elimination of the β-acetoxy group to give the enone **18**, which was now set up for conjugate addition chemistry to introduce a side-chain substituent at the $i + 2$ residue. To facilitate comparisons with the dipeptide turn mimetic series (e.g., **2**, **9**) it was decided to introduce a phenyl substituent at this point. Thus, the acetate was interchanged for a *tert*-butyldimethylsilyl (TBDMS) group that would be stable to phenyl cuprate. Acetate hydrolysis was accomplished in only moderate yield due to partial cyclization of the intermediate alcohol **19** to the corresponding, water-soluble hemiketal **21** during the isolation. Reaction of **19** with (TBDMS)Cl/imidazole gave the desired TBDMS ether **20**. In addition, the recovered **21** could also be converted to the TBDMS ether to provide an acceptable yield (60% overall) of **20**. Phenyl cuprate addition to **20** gave **22** as an isomeric mixture in ca. 90% yield. The carboxy terminus was introduced by a Horner–Emmons olefination to give a mixture of E and Z esters **23**. Hydrogenation, followed by treatment of the crude diastereomeric mixture with Jones' reagent removed the silyl ether and oxidized the resulting secondary alcohol to give

(24) The torsional term was chosen to reproduce the cis–trans isomerization energy (2.80 kcal/mol) found for *N*-methylacetamide with GAUSSIAN 80 and the 3-21G basis set: Binkley, J. S.; Whiteside, R.; Seeger, R.; DeFrees, D.; Schlegel, H. B.; Topiol, S.; Kahn, L. R.; Pople, J. A. *QCPE* **1981**, *No. 406*. Chandra Singh U.; Kollman, P. *QCPE* **1982**, *No. 446*.

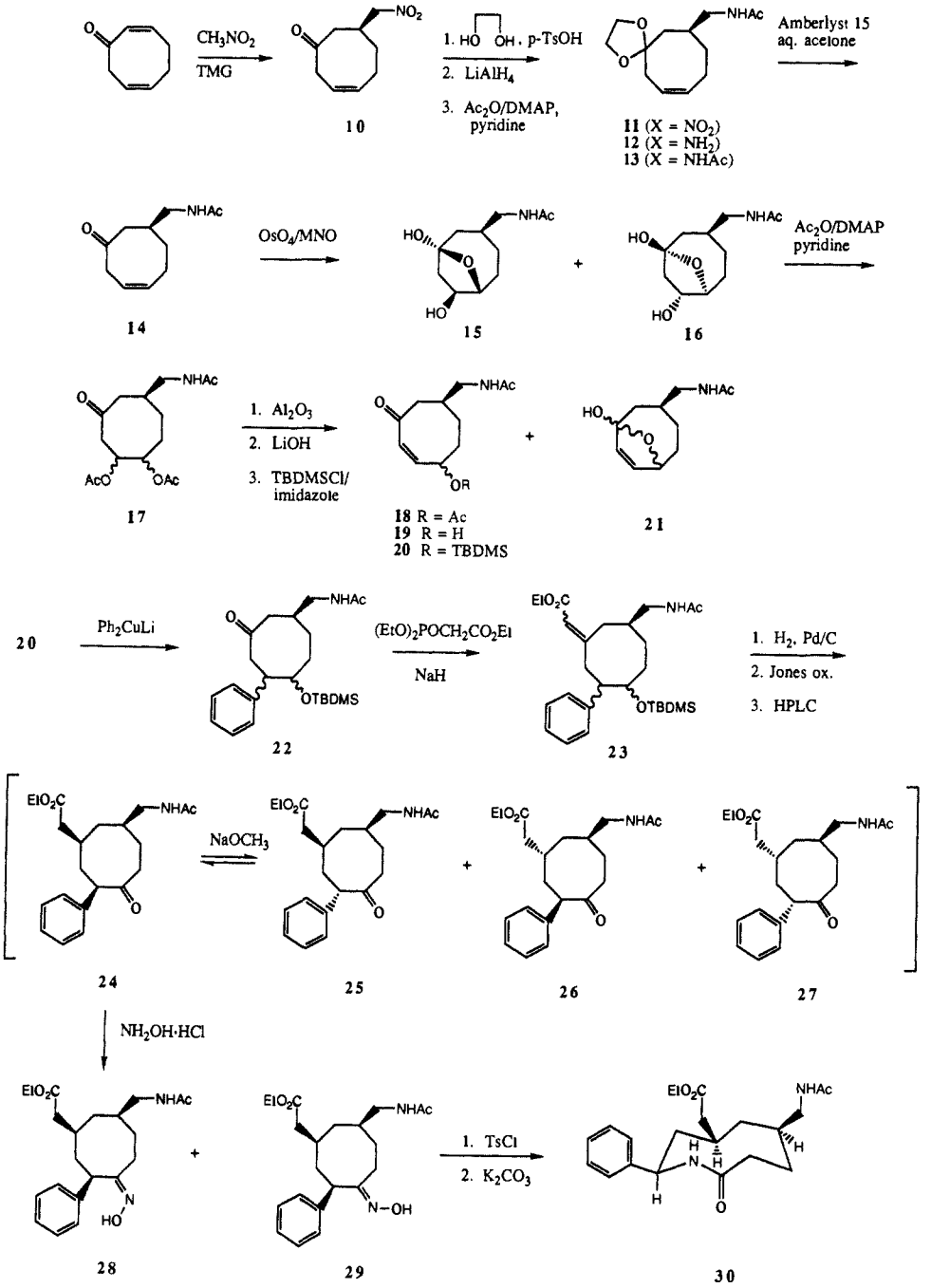
(25) (a) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11–15. (b) The form of the equation used was $J_{H,H} = A\cos^2\phi_d + 1.4$. For ϕ_d between 0 and 90°, A = 8.5; for ϕ_d between 90 and 180°, A = 10.5 for CH–CH and A = 9.5 for NH–CH.

(26) These side products differ significantly with respect to the orientation of the central amide bond, but the corner residue positions are not affected drastically. These compounds have been exploited by M.K. for the synthesis of several other mimetics. See: (a) Kahn, M.; Devens, B. *Tetrahedron Lett.* **1986**, 4841–4844. (b) Kahn, M.; Chen, B.; Zieske, P. *Heterocycles* **1987**, *25*, 29–31.

(27) (a) Echter, T.; Meier, H. *Chem. Ber.* **1985**, *118*, 182. (b) Cantrell, T. S.; Solomon, J. S. *J. Am. Chem. Soc.* **1970**, *92*, 4656.

(28) Ono, N.; Kamimura, A.; Miyake, H.; Hamamoto, I.; Kaji, A. *J. Org. Chem.* **1985**, *50*, 3692–3698.

Scheme II



the ketone mixture **24–27**. Reverse-phase HPLC separation of the mixture afforded the four diastereomeric ketones, **24–27** in an 8.5:2.3:2.1:1 mixture ratio. The dominant diastereomer **24** (isolated in 22% yield) was shown to have the all-cis geometry depicted through a difference NOE experiment, in which irradiation of each of the methine protons in turn was shown to enhance the other two, demonstrating that they were all on the same face of the ring system. The diastereomer **25** was presumed to be epimeric with **24** at the position of attachment of the phenyl ring. An attempt to establish an equilibrium mixture by exposure of this isomer to anhydrous sodium methoxide produced a change in peak ratios, but was inconclusive due to partial saponification of the ester and acetyl groups. The assignment of the minor diastereomers to structures **26** or **27** could not be made unequivocally by NMR, so their structures are assigned arbitrarily. With the stereochemical outcome of the sequence understood, the major ketone diastereomer **24** was treated with $NH_2OH/NaOAc$ to afford an 8:1 mixture of the anti:syn oximes (**29**, **28**), which were separated by chromatography. Beckmann rearrangement[16] of **29** gave the desired lactam **30**. The absence of an additional methyl group as in **5** presumably was responsible for the improved anti/syn ratio.

B. Modeling and Structure of Tetrapeptide Mimetic 30. The ^1H NMR spectrum (Figure 4) of **30** at room temperature was complex, indicating that several conformational isomers were present. This complexity is not unexpected, inasmuch as the fully reduced ring system of **30** could show both alternative puckerings and cis/trans isomerization about the amide bond, whereas **9** was constrained by the C5–C6 double bond. For example, the unsubstituted lactam 1-aza-2-cyclononanone is known to exist as a mixture of the cis and trans amide forms at room temperature.[29] At room temperature in $CDCl_3$, mimetic **30** shows multiple resonances in its ^1H NMR for the acetyl methyl group, the ethyl ester protons, and the amide proton absorptions and a general multiplicity of peaks in the envelope region of the spectrum. However, when the sample is warmed from 30 °C to 55 °C in 5 °C increments (Figure 4), coalescence of several of the proton

(29) Williamson, K. L.; Roberts, J. D. *J. Am. Chem. Soc.* **1976**, *98*, 5082–5086.

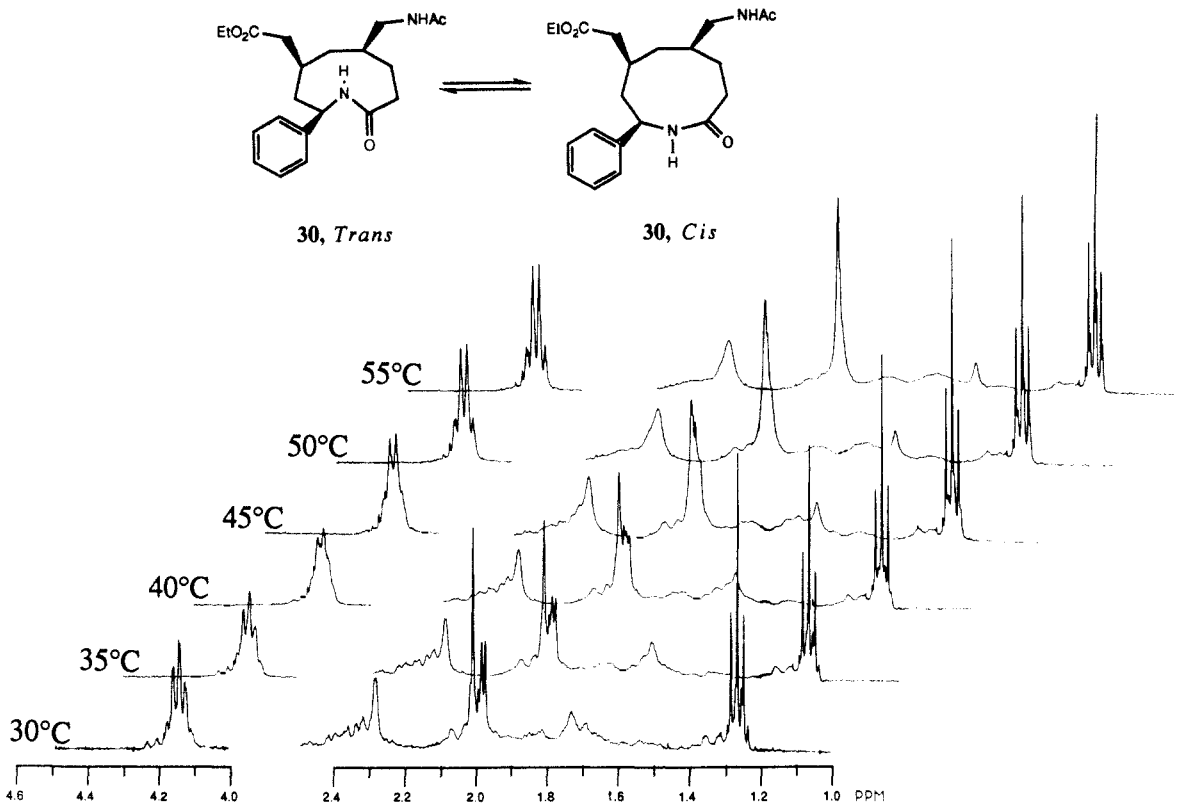


Figure 4. Temperature-dependent ^1H NMR spectrum of tetrapeptide mimetic **30** in $CDCl_3$.

resonances can be seen, especially the acetyl methyl group. This leads us to conclude that while **30** is a single chemical isomer it is a mixture of interconverting conformational isomers at room temperature in solution.

The accessible conformations of mimetic **30** were studied by using the systematic conformational search option of SYBYL. As in the analysis of the dipeptide mimetic **9**, side chains were replaced by methyl groups and methylenic hydrogens were removed. The analysis was repeated from a number of different starting conformations and with different choices for the ring closure bond: C5–C6, C6–C7, and C7–C8. The rotatable bonds were varied with 10° increments except for the amide bond, which was sampled at 0 ± 4° for the cis geometry and 180 ± 4° for the trans geometry. The analyses were run with a van der Waals scaling factor of 0.9 and with ring closure set to 0.15 Å and 15° from the starting conformation.

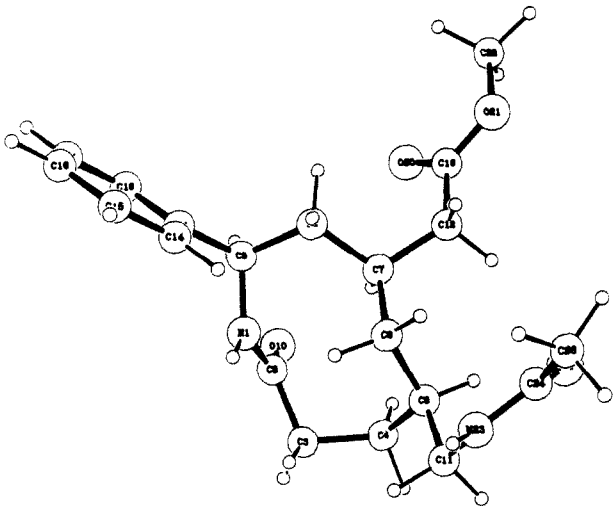
Each run of the conformational search generated a set of 50–120 conformations. After 20 cycles of minimization, the members of each set were combined and compared by using the nine ring atoms. From these, a set of 17 trans and 14 different conformations (i.e., those that differed more than 0.10 Å root mean square) were retained. The side chains were reattached to these structures and the structures reminimized. The minimized structures were again examined for uniqueness. With a cutoff of 0.15 Å, 13 trans structures and all 14 cis structures were retained. With a cutoff of 0.30 Å, 9 unique trans structures and 12 cis structures were retained. The final energies for these conformations ranged from 3.34 to 23.72 kcal/mol. The 27 independent conformations were compared to the 6 standard β-turns.[30] The comparison was made by fitting six atoms with equal weight: C12, C9, C3, and C11 of mimetic **30** were matched to the four peptide α-carbons; C5 was matched to the terminal carbonyl carbon; C7 was matched to the terminal nitrogen of the peptide. This choice selects those conformations of the mimetic in which the side chains are in the proper orientation. Since these side chains correspond to the i to $i + 3$ residues of the polypeptide chain, matching these positions gives a more realistic comparison of the mimetic and the peptide than matching the nine-membered ring to the turn backbone on an atom-by-atom basis. For the trans conformation of mimetic **30**, four conformations (Figure 5) have energies within 2.5 kcal of the lowest energy conformation. Each of these conformations fits at least one of the classical turns to within 0.5 Å (Figure 6). For the conformations of mimetic **30** with cis amide bonds, two conformations have energies within 2.5 kcal/mol of the lowest energy conformation (Figure 7). For these conformations, the fit with classical turn types is less good (Figure 8). Conformation 1 fits a type I′ turn to 0.53 Å: conformation 2 fits a type II turn to 0.63 Å. None of the low-energy conformations found for either cis or trans showed a close fit with type III or III′ turns.

The studies reported here demonstrate the feasibility of designing non-peptide mimetics of peptide and protein β-turns based on the nine-membered-ring lactam systems **1** and **2**. The dipeptide mimetic model compound **9** illustrates the excellent correspondence of the side-chain residues of the nine-membered-ring lactam with the corner positions of a type II′ β-turn in solution and in the solid state. The simple tetrapeptide mimetic, compound **30**, exhibits structural and conformational properties expected for this model structure. The low-energy trans amide conformers of **30** closely match those of model tetrapeptide β-turns of types I and II′. The nine-membered-ring lactam system should become a useful one for the study of β-turn structures, and for the design of specific mimetics of peptides and proteins of biological significance. Work on the incorporation of these systems into peptide sequences to study the initiation of β-turn geometries is in progress.

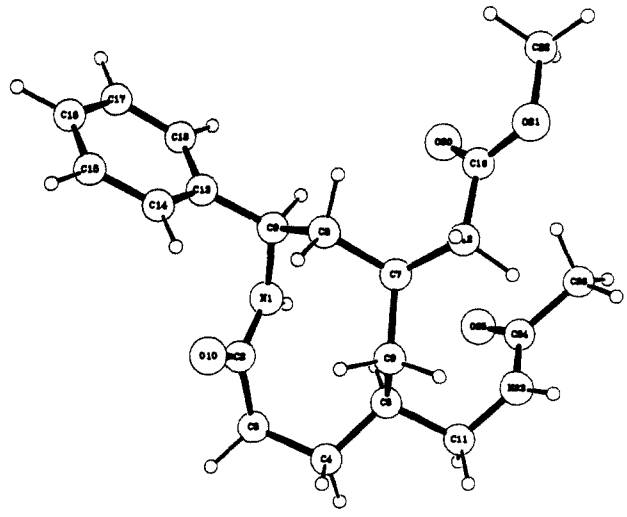
Experimental Section

General Procedures. Melting points were determined on a Büchi Meltemp apparatus and are uncorrected. ^1H NMR spectra were obtained with Varian XL-200 and XL-400 instruments. Infrared spectra were measured with a Digilab FTS-15E Fourier transform infrared spectrophotometer. FAB mass spectra were recorded on a VG-7070HF spectrometer. Thin-layer chromatography was carried out on Merck silica gel GF254 plates and column chromatography on EM reagents silica gel 60 [70–230 or 230–400 (flash) mesh]. Liquid chromatography was performed on Waters Prep 500 and Delta-Prep instruments with the columns and eluants indicated.

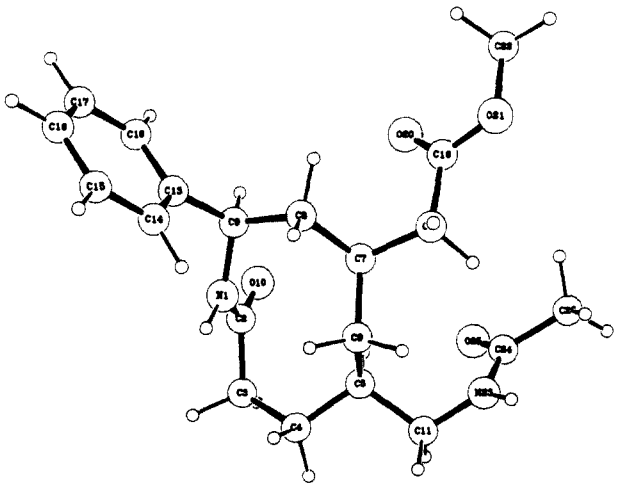
(30) A full listing of the conformational energies and root-mean-square fits to each of the β-turn types is provided in the supplementary materials.



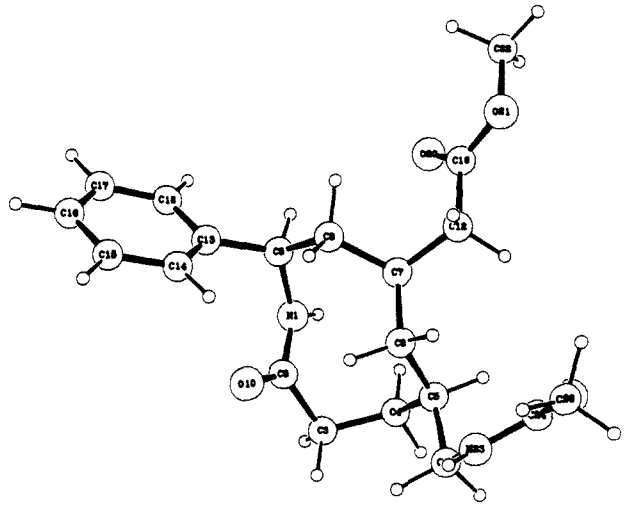
Trans Conformation 1, Energy = 3.34 kcal/mol



Trans Conformation 2, Energy = 3.76 kcal/mol



Trans Conformation 3, Energy = 4.04 kcal/mol



Trans Conformation 4, Energy = 5.37 kcal/mol

Figure 5. Lowest energy trans conformations of tetrapeptide mimetic **30**.

(±)-*trans*-8-Phenyl-4-cyclooctene-1-ol (3). Phenyllithium (60 mL, 2 M in 70:30 cyclohexane/ether) was precooled to −70 °C (addition funnel was jacketed with dry ice/acetone bath) and was added dropwise to freshly distilled boron trifluoride etherate (14.9 mL, 121 mmol) in anhydrous tetrahydrofuran (120 mL) at −78 °C. The internal temperature was monitored, and the addition rate was adjusted so that the internal temperature did not exceed −65 °C. Immediately after the addition was completed, the monoepoxide of 1,5-cyclooctadiene[17] (5.0 g, 40.3 mmol) was added in a slow stream. After 10 min at −78 °C, the reaction was quenched with saturated $NaHCO_3$ (25 mL) and the dry ice bath was removed. When the mixture reached room temperature, brine (75 mL) was added, and the mixture was extracted with ether (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated. Purification was effected by HPLC (Waters Prep 500, 10% ethyl acetate/hexanes) to provide **3** (3.5 g, 43% yield) as a yellow liquid: R_f 0.36 (1:7, ether/hexanes); IR ($CHCl_3$) 3585, 3040, 2880, 1060, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.21 (m, 5 H), 5.73 (m, 1 H), 5.60 (m, 1 H), 4.05 (m, 1 H), 3.03 (m, 1 H), 2.68–2.22 (m, 4 H), 2.11 (m, 1 H), 1.93–1.74 (m, 1 H), 1.23 (s, 1 H); MS (70 eV) *m/e* (relative intensity) 202 (M^+, 15), 184 (17), 104 (100), 91 (32), 80 (12).

(±)-8-Phenyl-4-cyclooctene-1-one (4). Jones' reagent (5.7 mL of a solution prepared by dissolving 26.72 g of chromium trioxide in 23 mL of concentrated sulfuric acid and diluting to 100 mL) was added dropwise to **3** (2.30 g, 11.4 mmol) in acetone (30 mL) at 0 °C. After the addition was completed, stirring was continued for an additional 15 min at 0 °C and then excess oxidizing reagent was quenched with 2-propanol (2 mL). The solids were removed by filtration through Celite, washing with ether (50 mL). The solvent was evaporated and the residue taken up in ether (75 mL) and washed with water (25 mL), saturated $NaHCO_3$ (25 mL), and brine (25 mL). After drying over $MgSO_4$, the solvent was removed to leave a waxy solid. The product was evaporatively distilled [bp 115 °C (0.3 Torr)] to afford **4** (1.73 g, 76% yield) as a low-melting solid: mp 46 °C; R_f 0.42 (1:7, ether/hexanes); IR ($CHCl_3$) 3040, 2890, 1710, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.20 (m, 5 H), 5.89–5.71 (m, 2 H), 4.00 (dd, J_1 = 12 Hz, J_2 = 3.5 Hz, 1 H), 2.77–2.10 (m, 6 H), 1.96 (m, 1 H), 1.63 (m, 1 H); MS (70 eV) *m/e* (relative intensity) 200 (M^+, 26), 161 (24), 104 (100), 91 (33), 77 (30).

[(±)-*trans*]-2-Methyl-8-phenyl-4-cyclooctene-1-one (5). *n*-Butyllithium (5.2 mL, 13.0 mmol, 2.5 M in hexanes) was added dropwise to diisopropylamine (1.31 g, 13.0 mmol) in anhydrous tetrahydrofuran (20 mL) at −78 °C. After the addition was completed, the reaction was allowed to come to room temperature over 30 min. The solution was recooled to −78 °C, followed by the dropwise addition of ketone **4** (1.13 g, 8.65 mmol) in anhydrous tetrahydrofuran (10 mL). The reaction was stirred at −78 °C for 30 min, and then methyl iodide (2.45 g, 17.3 mmol) was added dropwise over 5 min. The temperature was maintained at −78 °C for 1 h and then the reaction was allowed to warm to room temperature over 1 h. The reaction was poured into a separatory funnel containing a saturated ammonium chloride solution (50 mL) and then extracted with ether (3 × 40 mL). The combined extracts were washed with cold 5% HCl (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). Drying over $MgSO_4$ was followed by evaporation of the solvent to afford a mixture of methyl epimers **5** and **6** (1.84 g 99% yield, 19:1, trans/cis) as a waxy solid. A single recrystallization (ether/hexanes) provided pure trans epimer **5** (1.29 g, 70% yield) as a white, crystalline solid: mp 94 °C; R_f 0.45 (1:7 ether/hexanes); IR ($CHCl_3$) 2940, 1708, 1455, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.18 (m, 5 H), 5.76 (m, 2 H), 4.08 (dd, J_1 = 11.53 Hz, J_2 = 2.90 Hz, 1 H), 2.58 (m, 2 H), 2.34 (m, 1 H), 2.21 (m, 2 H), 1.95 (m, 1 H), 1.74 (m, 1 H), 1.24 (d, J = 6.54 Hz, 3 H); MS (70 eV) *m/e* (relative intensity) 214 (M^+, 37), 186 (12),

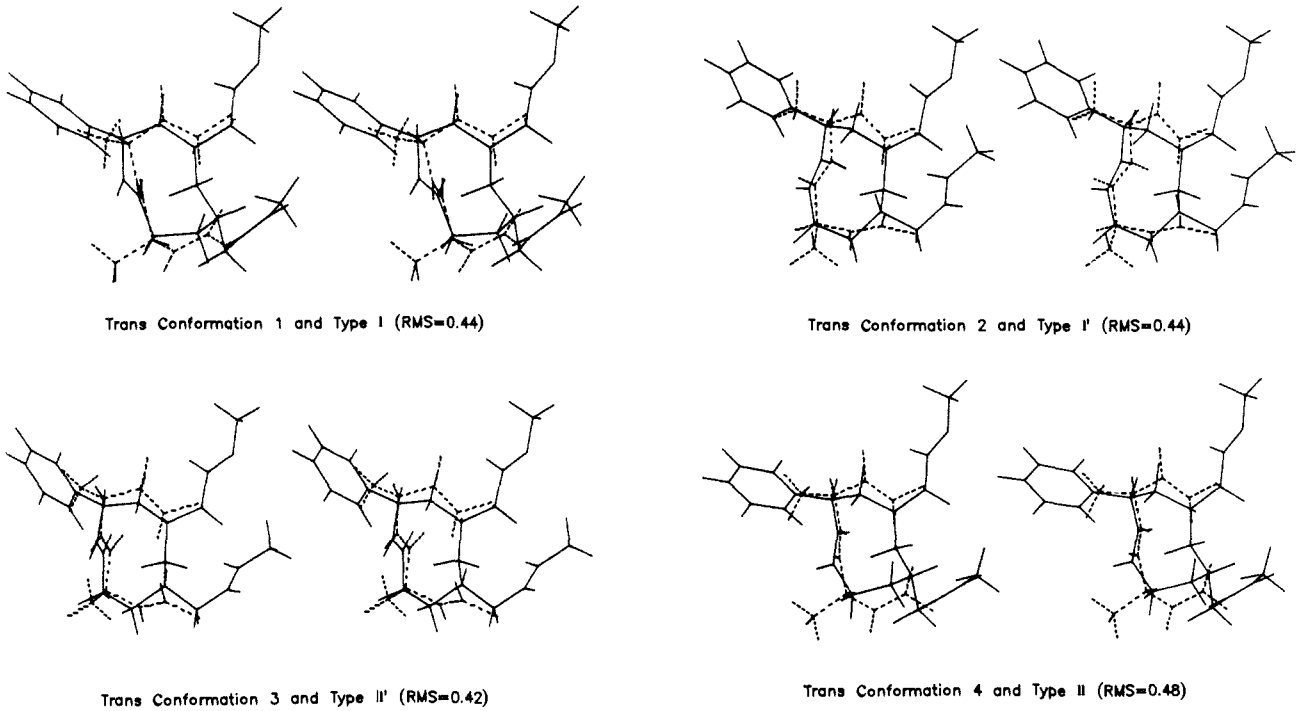


Figure 6. Fit of trans conformations of mimetic **30** (—) to model β-turn types.

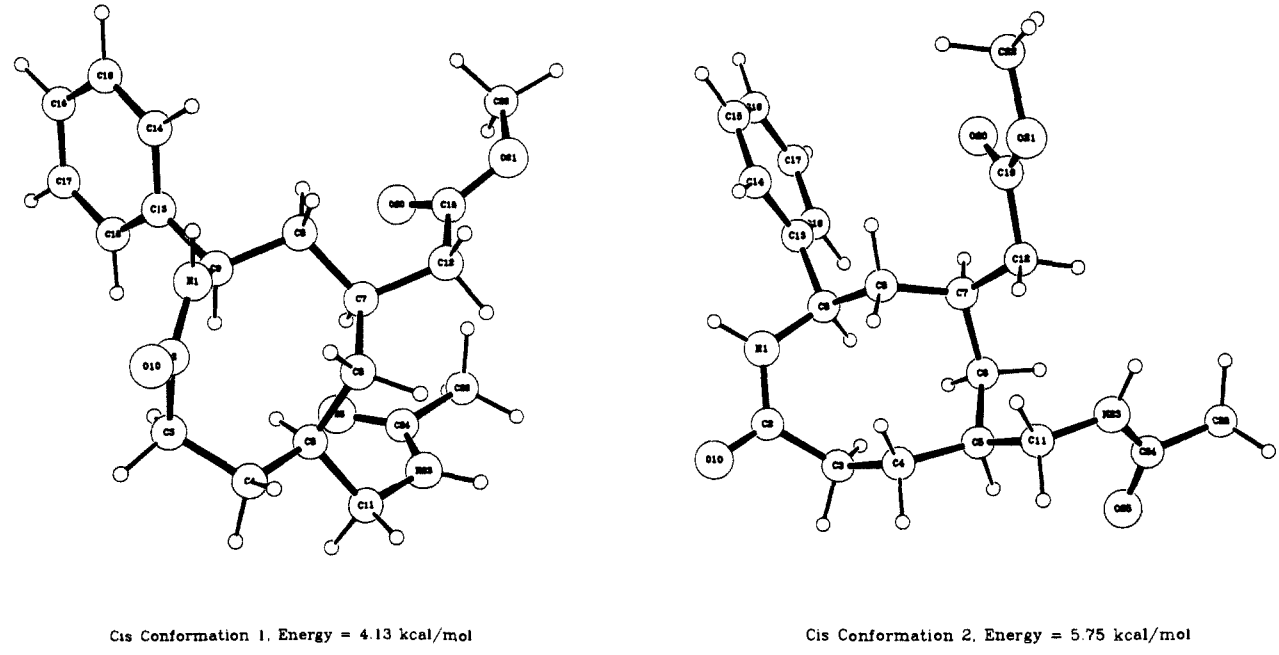


Figure 7. Lowest energy cis conformations of tetrapeptide mimetic **30**.

156 (40), 104 (100), 82 (36), 67 (51). Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.10; H 8.35.

[(±)-2*S*-*trans*-*anti*]-2-Methyl-8-phenyl-4-cycloocten-1-one Oxime (8). Sodium acetate (0.84 g, 10.3 mmol), hydroxylamine hydrochloride (0.71 g, 10.3 mmol), **5** (1.10 g, 5.14 mmol), and anhydrous methanol (20 mL) were combined in a resealable glass pressure flask and then heated to 80 °C overnight. The reaction was cooled to room temperature, and a second portion of sodium bicarbonate and hydroxylamine hydrochloride was added. The flask was resealed then heated to 80 °C for an additional 36 h. After cooling to room temperature, the methanol was evaporated and the residue was taken up in chloroform (75 mL) and washed with cold 5% HCl (25 mL), saturated $NaHCO_3$ (25 mL), and brine (25 mL). The organic layer was dried over $MgSO_4$ and then evaporated to provide oximes **8** and **7** (2:1 mixture, anti/syn) as a waxy solid. Flash chromatography (35 g of SiO_2, 250 mL of 2% ether/hexanes, 250 mL of 5% ether/hexanes, 250 mL of 20% ether/hexanes) provided **8** (672 mg, 57% yield, anti) and **7** (312 mg, 27% yield, syn) as white, crystalline solids. For compound **8**: mp 121 °C; R_f 0.31 (1:7, ether/hexane); IR ($CHCl_3$) 3585, 3280, 2940, 1190, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.53 (s, 1 H), 7.33–7.16 (7, 5 H), 5.77 (m, 2 H), 3.80 (m, 1 H), 3.62 (dd, J_1 = 3.32 Hz, J_2 = 11.96 Hz, 1 H), 2.25 (m, 4 H), 2.04 (m, 1 H), 1.91 (m, 1 H), 1.14 (d, J = 6.93 Hz, 3 H); MS (70 eV) *m/e* (relative intensity) 229 (M^+, 60), 212 (65), 156 (17), 129 (27), 104 (58), 91 (100), 67 (23), 41 (40). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.23; H, 8.53; N, 6.10. For compound **7**: mp 136-7 °C; R_f 0.12 (1:7, ether/hexane); IR ($CHCl_3$) 3695, 3250, 3025, 2985, 1605, 1505, 1470, 1455, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (s, 1 H), 7.34–7.15 (m, 5 H), 5.77 (m, 2 H), 3.70 (br d, J = 9.73 Hz, 1 H), 2.71 (m, 1 H), 2.59 (m, 1 H), 2.28 (m, 4 H), 1.98 (m, 1 H), 1.24 (d, J = 6.98 Hz, 3 H); MS (70 eV) *m/e* (relative intensity) 229 (M^+, 23), 212 (100), 201 (42), 129 (27), 104 (30), 91 (54). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.56; H, 8.24; N, 6.06.

Resubjecting the unwanted syn isomer to the oximation conditions afforded the thermodynamic 2:1 mixture for an efficient utilization of the starting material.

[(±)-(*Z*)]-1,3,4,7,8,9-Hexahydro-3-methyl-9-phenyl-2*H*-azonin-2-one

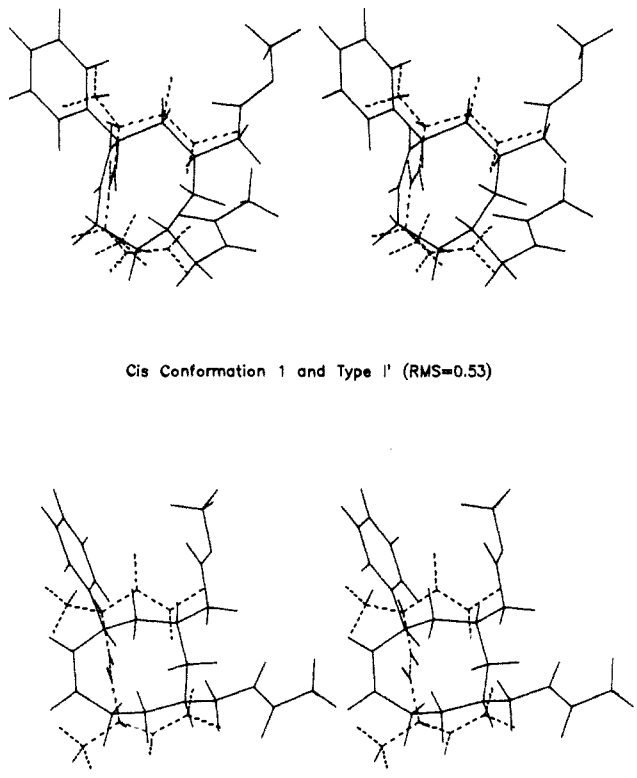


Figure 8. Fit of cis conformations of mimetic **30** (—) to model β-turn types.

(**9**). *p*-Toluenesulfonyl chloride (661 mg, 3.47 mmol) in anhydrous methylene chloride (5 mL) was added dropwise over a 20-min period to **8** (662 mg, 2.89 mmol) and pyridine (0.47 mL, 5.78 mmol) in anhydrous methylene chloride (20 mL) at −10 °C. The mixture was allowed to warm to room temperature and then was stirred overnight. The Beckmann rearrangement was effected by first evaporating the solvent and then eluting the crude tosyl oxime down a silica gel flash column (40 g of SiO_2, 250 mL of 50% ether/hexanes, 500 mL of ether). Evaporation of the product fractions provided analytically pure **9** (441 mg, 67% yield) as a fluffy white, crystalline solid: mp 179 °C; R_f 0.30 (1:1, ether/hexanes); IR ($CHCl_3$) 3320, 2920, 1645, 1525, 1235, 695 cm^{-1}; ^1H NMR (see Table IV); MS (70 eV) *m/e* (relative intensity) 229 (M^+, 16), 214 (19), 156 (24), 104 (100), 91 (35), 67 (49). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.85; H, 8.37; N, 6.13. A sample for X-ray analysis was recrystallized from CH_2Cl_2/hexanes.

X-ray Crystallography of Compound 9. The crystal data and tables of final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles are provided in supplementary materials. The structure of **9** depicted in the Figure 2 is based on the crystal data determined at 295 K. The structure had a final discrepancy index of R = 0.052 and R_w = 0.060.

(±)-(7-Nitromethyl)-3-cycloocten-1-one (10). Tetramethylguanidine (5.66 g, 49.2 mmol) was added to dry nitromethane (350 mL) at 0 °C and stirred for 10 min. 2,6-Cyclooctadien-1-one (30 g, 246 mmol) in anhydrous nitromethane (50 mL) was then added dropwise over 1 h. The temperature was maintained at 0 °C for 1 h, followed by removal of the ice bath and allowing the reaction to warm to room temperature over a 2-h period. The light yellow solution was poured into a separatory funnel (2 L) containing ether (1 L) and washed with cold 5% HCl (200 mL), saturated $NaHCO_3$ (200 mL), and brine (200 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by HPLC (Waters Prep 500, 20% ethyl acetate/hexanes) to provide **10** (34.8 g, 77% yield) as a yellow liquid: R_f 0.28 (50% ether/hexanes); IR ($CHCl_3$) 3040, 2940, 1700, 1552, 1378 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78–5.62 (m, 2 H), 4.34 (d, J = 6.93 Hz, 2 H), 3.23 (m, 1 H), 3.08 (dd, J_1 = 5.98 Hz, J_2 = 17.51 Hz, 1 H), 2.94 (m, 1 H), 2.63 (m, 1 H), 2.42 (dd, J_1 = 2.19 Hz, J_2 = 13.34 Hz, 1 H), 2.19 (m, 1 H), 2.06 (m, 1 H), 1.76 (m, 1 H), 1.38 (m, 1 H); MS (70 eV), *m/e* (relative intensity) 183 (M^+, 4), 147 (4), 136 (9), 93 (56), 79 (43), 67 (100), 55 (72). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.92; H, 7.32;, N, 7.68.

(±)-11-(Nitromethyl)-1,4-dioxaspiro[4.7]dodec-7-ene (11). Ethylene glycol (33.4 g, 538 mmol), *p*-toluenesulfonic acid monohydrate (2.0 g, 10.6 mmol), and **10** (49.2 g, 269 mmol) were combined in benzene (500 mL) and then heated to reflux in a Dean–Stark apparatus. After 5 h no further water collection was noted and the TLC analysis showed complete consumption of **10**. The reaction was cooled to room temperature and transferred to a separatory funnel (2 L) containing ethyl acetate (600 mL). The organic layer was washed with water (200 mL), saturated $NaHCO_3$ (200 mL), and brine (200 mL) and then dried over $MgSO_4$. Evaporation of the solvent gave a yellow oil that was purified by HPLC (Waters Prep 500, 15% ethyl acetate/hexanes) to provide **11** (41.8 g, 68% yield) as a white, waxy solid. An analytical sample was obtained by recrystallization (ethyl acetate/hexanes) to afford **11** as white crystals: mp 46 °C; R_f 0.41 (50% ether/hexanes); IR ($CHCl_3$) 2880, 1551, 1378 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (m, 2 H), 4.26 (m, 2 H), 4.01–3.78 (m, 4 H), 2.59–2.18 (m, 5 H), 1.93 (dd, J_1 = 7.3 Hz, J_2 = 14.7 Hz, 1 H), 1.60 (m, 2 H), 1.37 (m, I H); MS (70 eV) *m/e* (relative intensity) 227 (M^+, 1), 181 (11), 167 (14), 158 (12), 125 (23), 112 (45), 101 (38), 86 (100), 67 (25), 55 (23). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.29; H, 7.48; N, 6.27.

(±)-11-(Aminomethyl)-1,4-dioxaspiro[4.7]dodec-7-ene (12). The nitro ketal **11** (41.8 g, 184 mmol) in anhydrous tetrahydrofuran (200 mL) was added dropwise to a suspension of lithium aluminum hydride (14.0 g, 368 mmol) in anhydrous tetrahydrofuran (800 mL) at room temperature. The reaction flask was equipped with a mechanical stirrer, an internal thermometer, and a water bath to maintain the reaction between 16 and 22 °C. The addition rate was adjusted so the internal temperature was maintained in this range (addition takes ~2.5 h). *Caution: If the addition is done blow 10 °C, **11** does not react. However, upon subsequent warming to room temperature after the addition is complete, the reaction will initiate and proceed out of control!* After the addition was completed, the water bath was removed and the reaction stirred overnight at room temperature. The mixture was cooled to 5 °C and excess hydride reagent was quenched by the dropwise addition of a saturated $MgSO_4$ solution. The precipitated salts were removed by filtration through Celite, washing with chloroform (400 mL). The filter cake was allowed to dry and was triturated with chloroform (2 × 500 mL); the salts were again removed by filtration through Celite. The combined organic solutions were evaporated to afford **12** (34.1 g, 94% yield) as a clear oil. The crude product was subsequently carried forward to the next reaction without further purification: R_f 0.56 (lower phase of a mixture prepared by shaking chloroform/methanol/water/acetic acid, 90:30:10:6); IR ($CHCl_3$) 3665, 3580, 2880, 1648, 1455, 1070, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (m, 1 H), 5.66 (m, 1 H), 3.98 (m, 4 H), 2.66–2.17 (m, 6 H), 1.89–1.41 (m, 4 H), 1.21 (m, 1 H); MS (70 eV) *m/e* (relative intensity) 197 (M^+, 9), 167 (100), 142 (12), 125 (68), 112 (21), 99 (71), 86 (96), 41 (55); HRMS (EI) calcd for $C_{11}H_{20}NO_2$ (M^+) 198.1494, found 198.1540.

(±)-*N*-[(1,4-Dioxaspiro[4.7]dodec-10-en-7-yl)methyl]acetamide (13). Acetic anhydride (23.7 g, 232 mmol) was added in a slow stream to **12** (30.5 g, 155 mmol) and (dimethylamino)pyridine (1.89 g, 15.5 mmol) in anhydrous pyridine (200 mL) at 0 °C. After the addition was completed the reaction was stirred 1 h at 0 °C and then allowed to warm to room temperature over a 2-h period. The pyridine was removed by evaporation and the residue was taken up in chloroform (500 mL). The chloroform solution was washed with cold 5% HCl (100 mL), water (100 mL), and brine (100 mL). Drying over $MgSO_4$ was followed by evaporation of the solvent to give an off-white solid that was purified by HPLC (Waters Prep 500, 2% methanol/ethyl acetate) to provide **13** (25.52 g, 69% yield) as a white crystalline solid: mp 94 °C; R_f 0.24 (5% methanol/ethyl acetate); IR ($CHCl_3$) 3440, 2870, 1662, 1520, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (m, 1 H), 5.61 (m, 2 H), 4.02–3.83 (m, 4 H), 3.08 (m, 2 H), 2.45 (dd, J_1 = 8.71 Hz, J_2 = 13.69 Hz, 1 H), 2.36–2.14 (m, 3 H), 1.98 (s, 3 H), 1.87 (dd, J_1 = 6.73 Hz, J_2 = 13.93 Hz, 1 H), 1.46 (d, J = 13.28 Hz), 1.28 (m, 1 H); MS (70 eV) *m/e* (relative intensity) 239 (M^+, 2.5), 180 (11), 167 (100), 152 (13), 125, (20) 99 (21), 86 (32), 43 (29). Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.13; H, 9.02; N, 5.82.

(±)-*N*-[(1-Oxo-3-cycloocten-7-yl)methyl]acetamide (14). Amberlyst 15 resin (20 g, 20–50 mesh beads) was added to **13** (25.52 g, 107 mmol) in 2% aqueous acetone (700 mL) at room temperature. After 48 h, the resin was removed by filtration through Celite washing with acetone. The solvent was evaporated and the residue purified by HPLC (Waters Prep 500, 2% methanol/ethylacetate) to afford **14** (16.12 g, 77% yield) as a colorless oil: R_f 0.24 (5% methanol/ethyl acetate). A less polar fraction, 3.01 g (14% yield) was identified as the isomer where the olefin moved into conjugation with the ketone: R_f 0.3 (5% methanol/ethyl acetate). For **14**: IR ($CHCl_3$) 3450, 1692, 1672, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (m, 1 H), 1.73 (m, 1 H), 2.00 (s, 3 H), 2.1–2.25 (m, 2 H), 2.4–2.55 (m, 2 H), 3.0–3.4 (m, 4 H), 5.55–5.70 (2 m, 2 H), 6.06 (br

s, 1 H); MS (70 eV) *m/e* (relative intensity) 195 (M^+, 1), 153 (39), 136 (32): HRMS (EI) calcd for $C_{11}H_{17}NO_2$ (M^+) 195.1250, found 195.1259.

(±)-*N*-[(1,7-Dihydroxy-9-oxabicyclo[4.2.1]nonan-3-yl)methyl]acetamide (15, 16). A solution of osmium tetraoxide (39 mL, 0.01 M in ether, 0.39 mmol) was added in one portion to a solution of the enone **14** (15.42 g, 79.1 mmol) and *N*-methylmorpholine *N*-oxide (9.73 g, 83.0 mmol) in THF/water (4:1, 350 mL) at room temperature. The solution was stirred for 24 h and was quenched by the addition of 10 mL of saturated sodium bisulfite solution. The mixture was stirred for 30 min and filtered through Florisil, washing with THF, water, and THF. The filtrate was concentrated on a rotary evaporator and then dried at 25 °C/1.0 Torr overnight. The residue was slurried with hot ether, the ether was decanted (discarded), and methanol (200 mL) was added. The suspension was heated to reflux, cooled, and filtered to remove residual salts. Evaporation of the solvent gave 16.2 g (89% yield) of the crude hemiketal mixture of **15** and **16**: R_f 0.45 (lower phase of mixture prepared by shaking 90:30:10:6 chloroform/methanol/water/acetic acid); IR ($CHCl_3$) 3310, 1652, 1558 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.2–2.0 (m, 8 H), 1.80 (s, 3 H), 2.83 (m, 2 H), 3.75–4.10 (m, 2 H), 4.73 (d, J = 4.7 Hz, 0.5 H), 4.89 (d, J = 4.7 Hz, 0.5 H), 5.78 (s, 0.5 H), 5.95 (s, 0.5 H); MS (FAB) 230 (M^+ + H), 212, 170; HRMS (FAB): Calcd for $C_{11}H_{19}NO_4$ 230.1392, found 230.1411.

[(±)-1α]-*N*-[[6-(Acetyloxy)-3-oxo-4-cyloocten-1-yl]methyl]acetamide (18). To the mixture of hemiketals **15** and **16** (5.90 g, 25.8 mmol) in pyridine (150 mL) containing (dimethylamino)pyridine (0.5 g, 4.1 mmol) was added acetic anhydride (7.9 g, 77.3 mmol). The mixture was stirred at room temperature overnight and was concentrated in vacuo. The residue was chromatographed (silica gel, 175 g, 2% methanol/ethyl acetate) to give 6.07 g (75% yield) of the diacetoxy ketone mixture **17** as an oil: R_f 0.36 (5% methanol/ethyl acetate. Alumina (60 g) was added in one portion to the mixture **17** (2.07 g, 19.4 mmol) in benzene (150 mL) at room temperature under a calcium sulfate drying tube. The reaction was stirred vigorously for 48 h and then the alumina was removed by filtration through a pad of Celite. Drying over $MgSO_4$ was followed by evaporation of the solvent to provide crude **18** (4.76 g, 97% yield) as approximately a 1:1 mixture of inseparable diastereomers: R_f 0.52 (10% methanol/ethyl acetate); IR ($CHCl_3$) 3445, 1732, 1672, 1519 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.28–6.08 (m, 3 H), 5.97 (br t, 0.5 H), 5.69 (br, t, 0.5 H), 3.52–2.88 (m, 2 H), 2.61 (m, 1 H), 2.52 (m, 1 H), 2.13 (m, 1 H), 2.11 (s, 3 H), 2.01 (s, 1.5 H), 1.98 (s, 1.5 H), 1.74–1.53 (m, 2 H), 1.41–1.22 (m, 2 H); MS (70 eV) *m/e* (relative intensity) 254 (M^+ + 1, 2.4), 253 (M^+, 0.4), 211 (13), 169 (8), 152 (11), 134 (27), 122 (23), 72 (22), 43 (100); HRMS (FAB) calcd for $C_{13}H_{20}NO_4$ (M^+ + 1) 254.1392 found 254.1413.

[(±)-1α]-*N*-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-oxo-4-cyclooctene-1-yl]methyl]acetamide (20). Lithium hydroxide monohydrate (2.37 g, 56.4 mmol) in 10 mL of water was added in one portion to **18** (4.76 g, 18.8 mmol) stirring in tetrahydrofuran at room temperature. After 2 h, brine (50 mL) and additional sodium chloride (to saturate the aqueous layer) were added to the reaction, followed by adjusting the pH to 6.5 with cold 10% HCl. The neutralized reaction mixture was transferred to a separatory funnel and quickly extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried by filtration through a pad of $MgSO_4$. The solvent was then removed by evaporation and the residue was immediately dissolved in dimethylformamide (25 mL) followed by addition of imidazole (2.04 g, 30.0 mmol) and *tert*-butyldimethylchlorosilane (4.52 g, 30.0 mmol). After stirring overnight at room temperature under argon, excess reagent was quenched by the addition of saturated NH_4Cl (3 mL), followed by extraction with ethyl acetate (5 × 30 mL). The combined organic layers were washed with brine and then dried over $MgSO_4$. After removal of the solvent by evaporation (high vacuum for DMF), the residue was purified by preparative HPLC (Waters Prep 500, single column, ethyl acetate) to provide **20** (1.23 g, 13% overall yield over five steps from enone **14**) as approximately a 1:1 mixture of diastereomers: R_f 0.70 (10% methanol/ethyl acetate); IR ($CHCl_3$) 3445, 2935, 1660, 1255, 1080, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.36 (m, 1 H), 6.01 (m, 1.5 H), 5.63 (br t, 0.5 H), 5.23 (m, 0.5 H), 5.14 (m, 0.5 H), 3.41–3.23 (m, 2 H), 2.87 (m, 0.5 H), 2.61–2.44 (m, 1.5 H), 2.16–1.91 (m, 2 H), 2.00 (s, 1.5 H), 1.98 (s, 1.5 H), 1.69–1.47 (m, 1.5 H), 1.22 (m, 0.5 H), 0.91 (br s, 9 H), 0.12 (s, 3 H), 0.09 (s, 3 H); MS (70 eV) *m/e* (relative intensity) 325 (M^+, 2.5), 310 (3), 307 (5), 268 (73), 209 (26), 134 (22), 116 (14), 75 (100), 73 (53), 43 (25); HRMS (FAB) calcd for $C_{17}H_{32}NO_3Si$ (M^+ + 1) 326.2151, found 326.2141.

(±)-*N*-[[6-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-oxo-5-phenylcyclooctyl]methyl]acetamide (22). Phenyllithium (19 mL, 2.0 M, 37.8 mmol) was added dropwise to copper(I) bromide–dimethyl sulfide complex (3.89 g, 18.9 mmol) suspended in ether (30 mL) at 0 °C. The reaction mixture was a dark green color upon completion of the addition. Stirring was continued for 5 min and then **20** (1.23 g, 3.78 mmol) was added dropwise in ether (10 mL) over 5 min. After 0.5 h the reaction was quenched by the slow addition of saturated NH_4Cl/NH_4OH (9:1, 30 mL). The reaction mixture was stirred vigorously until the organic layer was clear and the aqueous layer was dark blue. The mixture was transferred into a separatory funnel and extracted with ether (2 × 100 mL). The combined organic extracts were washed with saturated NH_4Cl/NH_4OH (9:1, 30 mL), water (30 mL), and brine (30 mL) and then dried over $MgSO_4$. Evaporation of the solvent gave a dark oil, which was purified by flash chromatography (50 g of SiO_2, eluting with 10–50% ethyl acetate/hexanes) to afford **22** (1.17 g, 77% yield) as approximately a 1:1 mixture of isomers: R_f 0.60 (10% methanol/ethyl acetate); IR ($CHCl_3$) 3445, 2880, 1680, 1668, 1520, 838, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.20 (m, 5 H), 6.07 (br t, 1 H), 3.81 (m, 1 H), 3.57 (m, 1 H), 3.41 (m, 1 H), 3.01 (dd, J_1 = 4.27 Hz, J_2 = 11.3 Hz, 1 H), 2.85 (m, 1 H), 2.72 (m, 1 H), 2.46 (m, 2 H), 2.33 (dd, J_1 = 5.55 Hz, J_2 = 11.63 Hz, 1 H), 2.18 (m, 1 H), 2.02 (s, 3 H), 1.71 (m, 1 H), 1.53 (m, 1 H), 1.38 (m, 1 H), 0.68 (br s, 9 H), –0.20 (s, 3 H), –0.69 (s, 3 H); MS (70 eV) *m/e* (relative intensity) 388 (M^+ – 15, 2), 346 (94), 268 (66), 209 (24), 152 (24), 91 (23), 75 (89), 73 (100), 43 (46); HRMS (FAB) calcd for $C_{23}H_{38}NO_3Si$ (M^+ + 1) 404.2621, found 404.2625.

[(±)-7α]-7-[(Acetylamino)methyl]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-phenylcyclooctylideneacetic Acid Ethyl Ester (23). Triethylphosphonoacetate (2.47 g, 11.0 mmol) was added to sodium hydride (0.441 g, 11.0 mmol, 60% in mineral oil, washed 2 × hexanes) in anhydrous benzene (20 mL) at 0 °C, with the evolution of hydrogen. Stirring was continued for 10 min at 0 °C, and then the ice bath was removed and the reaction mixture was allowed to stir at room temperature. Then ketone **22** (1.11 g, 2.75 mmol) in anhydrous benzene (10 mL) was added dropwise to the reaction over 10 min. The reaction was stirred for 1 h at room temperature, refluxed for 5 h, cooled to room temperature, quenched with brine (50 mL) and saturated NH_4Cl (10 mL), and extracted with ethyl acetate (4 × 40 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the mixture of diastereomers was flash chromatographed (50 g of silica gel, 90% hexane/ethyl acetate) to afford 1.03 g (79% yield) of **23** as a light yellow oil: IR ($CHCl_3$) 3440, 3360, 1722, 1698, 1660, 1525, 1250, 832, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.13 (m, 5 H), 6.91 (br s, 1 H), 5.80 (s, 1 H), 4.27–4.10 (m, 2 H), 3.78 (m, 1 H), 3.42 (m, 1 H), 3.22 (m, 1 H), 2.90 (m, 2 H), 2.61 (m, 2 H), 2.41 (m, 1 H), 2.08–1.96 (m, 2 H), 2.03 (s, 3 H), 1.72 (m, 1 H), 1.41–1.21 (m, 5 H), 0.65 (s, 9 H), –0.19 (s, 3 H), –0.66 (s, 3 H); MS (FAB) *m/e* 474 (M^+ + 1), 416, 370, 342, 296, 254, 209, 117.

[(±)-1α,3α,7α]-[7-[(Acetylamino)methyl]-4-oxo-3-phenylcycloocty]-acetic Acid Ethyl Ester (24–27). The unsaturated ester **23** (1.37 g, 2.89 mmol) in absolute ethanol (100 mL) was reduced over 10% Pd/C (1.0 g) in a Parr apparatus at 50 psi for 36 h at 50 °C. The catalyst was removed by filtration through Celite. The solvent was then evaporated to provide the saturated ester as a mixture of diastereomers (1.00 g). The crude mixture was carried forward without further purification. Jones' reagent [1.46 mL, prepared from 0.46 g (4.56 mmol) of chromium trioxide in 5 mL of 4 M H_2SO_4] was added dropwise to the crude TBDMS ether (1.00 g, 2.77 mmol) in acetone (20 mL) at 0 °C. After 10 min at 0 °C and 45 min at room temperature, a solution of saturated sodium sulfite (20 mL) was added in one portion. The green slurry was transferred to a separatory funnel and extracted with ethyl acetate (5 × 20 mL). The combined organic extracts were washed with brine and then dried over $MgSO_4$. The solvent was evaporated and the residue filtered through 20 g of silica gel, eluting with ethyl acetate to afford 720 mg of the mixture of diastereomeric ketones **24–27**. The diastereomers were separated by reverse-phase HPLC (Waters Delta Prep, 30 cm × 30 mm C_{18} Delta Pak column, 0% water/methanol to 100% water/methanol over 55 min) to provide an 8.5:2.3:2.1:1 mixture of diastereomers where the predominant isomer was **24** (272 mg): IR ($CHCl_3$) 3450, 3372, 1710, 1666, 1515, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.22 (m, 5 H), 6.12 (br s, 1 H), 4.13 (m, 1 H), 4.12 (q, J = 7.12 Hz, 2 H), 3.37 (m, 1 H), 2.93 (m, 1 H), 2.56 (m, 2 H), 2.28 (d, J = 5.55 Hz, 2 H), 2.24 (m, 1 H), 2.17–1.73 (m, 5 H), 2.01 (s, 3 H), 1.51 (dd, J_1 = 3.09 Hz, J_2 = 15.81 Hz, 1 H), 1.26 (t, J = 7.12 Hz, 3 H), 1.18 (m, 1 H); MS (70 eV) *m/e* (relative intensity) 359 (M^+, 28), 317 (36), 272 (26), 226 (89), 213 (30), 167 (19), 112 (51), 91 (78), 43 (100), 30 (100); HRMS (FAB) calcd for $C_{21}H_{30}NO_4$ (M^+ + 1) 360.2175 found 360.2143.

[(±)-1α,3α,7α-*anti*]-7-[(Acetylamino)methyl]-4-hydroxyimino-3-phenylcyclooctaneacetic Acid Ethyl Ester (29). Sodium acetate (58 mg, 0.70 mmol), hydroxylamine hydrochloride (58 mg, 0.84 mmol), and **24** (150 mg, 0.42 mmol) were combined in anhydrous methanol (5 mL) and then heated to reflux overnight. The reaction was allowed to cool and then sodium acetate (58 mg, 0.70 mmol) and hydroxylamine hydrochloride (58 mg, 0.84 mmol) were added, followed by refluxing the reaction an additional 24 h. After being cooled, the reaction mixture was

transferred to a separatory funnel containing brine (10 mL). The mixture was extracted with chloroform (6 × 10 mL), and then the combined extracts were dried over $MgSO_4$. The solvent was evaporated and the residue was purified by reverse-phase chromatography (Water Delta Prep, 30 cm × 30 mm C_{18} Delta Pak column, 80% water/methanol to 40% water/methanol over 10 min, 40% water/methanol to 100% methanol over 15 min) to provide syn oxime **28** (10 mg, 6% yield) and the desired anti oxime **29** (82 mg, 53% yield) as colorless oils: ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.42 (br s, 1 H), 7.30–7.18 (m, 6 H), 4.12 (m, 3 H), 3.65–2.74 (m, 6 H), 2.59–1.02 (m, 8 H), 1.69 (s, 3 H), 1.24 (t, J = 5.5 Hz, 3 H).

[(±)-2α,4α,6α]-6-[(Acetylamino)methyl]-9-oxo-2-phenyl-1*H*-perhydroazonine-4-acetic Acid Ethyl Ester (30). *p*-Toluenesulfonyl chloride (63 mg, 0.33 mmol) in anhydrous methylene chloride (1 mL) was added dropwise over 20 min to a solution of **29** (82 mg, 0.22 mmol) and pyridine (36 μL, 0.44 mmol) in 2 mL of methylene chloride at 0 °C. The mixture was stirred at 0 °C for 5 h and then poured into cold 5% HCl (5 mL). The slurry was extracted with chloroform (5 × 5 mL), and the extracts were dried over $MgSO_4$. The chloroform was evaporated, and the residue was taken up in tetrahydrofuran (3 mL). Potassium carbonate (50 mg, 0.36 mmol) in water (3 mL) was added, and the reaction was stirred overnight at room temperature. The reaction mixture was transferred to a separatory funnel and extracted with chloroform (5 × 5 mL). The extracts were dried over $MgSO_4$, and then the solvent was evaporated. The residue was purified by reverse-phase HPLC (Waters Delta Prep, 30 cm × 30 mm C_{18} Delta Pak column, 65% methanol/water) to afford **30** (25 mg, 30% yield) as a colorless oil: IR ($CHCl_3$) 3445, 3370, 1719, 1662, 1520, 700 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.41–7.20 (m, 5 H), 5.22 (d, J = 9.5 Hz, 0.25 H), 5.03 (d, J = 9.5 Hz, 0.25 H), 4.18–4.08 (m, 2 H), 3.72–3.66 (m, 0.25 H), 3.57–3.52 (m, 0.25 H), 3.10–2.90 (m, 2 H), 1.96 (s, 0.18 of CH_3), 1.95 (s, 0.5 of CH_3), 1.93 (s, 0.32 of CH_3), 1.26–1.21 (m, 3 H); MS (70 eV) m/e (relative intensity) 374 (M^+, 23), 329 (9), 287 (11), 260 (18), 198 (6), 140 (19), 106 (100), 91 (32), 43 (37); HRMS (EI) calcd for $C_{21}H_{30}N_2O_4$ (M^+) 374.2206, found 375.2185. Temperature-dependent ^{1}H NMR spectra of **30** in $CDCl_3$ are described in the text and Figure 4.

Acknowledgment. We thank members of our Physical Chemistry Department for obtaining spectral and microanalytical data, especially Mr. Louis J. Todaro and Ms. Ann-Marie Chiu for performing the X-ray crystallography analyses, and Dr. Thomas J. Williams and Mr. Gino J. Sasso for assistance with NMR studies.

Registry No. (±)-**3**, 123836-24-8; (±)-**4**, 123836-25-9; (±)-**5**, 123836-26-0; (±)-**6**, 123930-04-1; (±)-**7**, 123836-27-1; (±)-**8**, 123930-05-2; (±)-**8** (*O*-tosyl derivative), 123836-50-0; (±)-**9**, 123836-28-2; (±)-**10**, 123836-29-3; (±)-**11**, 123836-30-6; (±)-**12**, 123836-31-7; (±)-**13**, 123836-32-8; (±)-**14**, 123836-33-9; (±)-**15**, 123836-34-0; (±)-**16**, 123930-06-3; (±)-1α,5α,6α-**17**, 123836-35-1; (±)-1α,5β,6β-**17**, 123836-46-4; (±)-1α,6α-**18**, 123836-36-2; (±)-1α,6β-**18**, 123836-47-5; (±)-1α,6α-**19**, 123836-37-3; (±)-1α,6β-**19**, 123836-48-6; (±)-1α,6α-**20**, 123836-38-4; (±)-1α,6β-**20**, 123836-49-7; **21**, 123836-39-5; **22**, 123836-40-8; **23**, 123836-41-9; (±)-**24**, 123836-42-0; (±)-**25**, 123930-07-4; (±)-**26**, 123930-08-5; (±)-**27**, 123930-09-6; (±)-**28**, 123836-43-1; (±)-**29**, 123836-44-2; (±)-**30**, 123836-45-3; PhLi, 591-51-5; MeI, 74-88-4; $MeNO_2$, 75-52-5; $HOCH_2CH_2OH$, 107-21-1; $(EtO)_2P(O)CH_2COOEt$, 867-13-0; (*Z*)-*cis*-1,5-cyclooctadiene monoepoxide, 19740-90-0; (*Z*,*Z*)-2,6-cyclooctadien-1-one, 31351-00-5.

Supplementary Material Available: Tables I–XII of crystal data, experimental details, bond lengths, bond angles, torsion angles, and equivalent isotropic thermal factors for lactam **9** at 295 and 110 K and Table XIII listing conformational energies and root-mean-square fits for **30** to each of the model β-turn types (9 pages). Ordering information is given on any current masthead page.

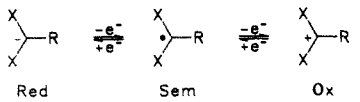
In Situ Generation of 2,3-Diaryltetrazolinylidenes: Trapping Experiments and Ring Opening to 1-Cyanoazimines†

Rainer H. Lowack and Robert Weiss*

Contribution from the Institut für Organische Chemie der Friedrich-Alexander-Universität Erlangen-Nürnberg, Henkestrasse 42, D-8520 Erlangen, Federal Republic of Germany.
Received March 21, 1989

Abstract: The redox system formazanide ion/tetrazolium ion, realized as an ECE sequence, is conceived as a general device to manipulate both electron-deficient and -surplus centers attached to the carbon atom of this system electronically. In order to introduce this redox substituent as a nucleophilic entity into organic substrates, we generated 2,3-diaryltetrazolinylidenes **16** as novel heterocyclic carbenes in solution (a) by dephosphonionation of a (triphenylphosphonio)tetrazolium salt, (b) via oxidation of a tetrazolium-5-thiolate, and (c) by deprotonation of 2,3-diaryltetrazolium salts. Carbenes **16** were trapped by protonation, deuteronation, halogenation, and oxygen transfer. Generated in the absence of electrophilic trapping agents, carbenes **16** open up to 1-cyanoazimines. The latter show promise as NCN-transfer reagents. The ring opening of carbene **16** is discussed on the basis of semiempirical calculations and compared to such reactions of isomeric tetrazolinylidenes.

The system carbenium ion/radical/carbanion **1**/**2**/**3** represents in principle the simplest two-step redox system of organic chemistry (1). The carbanion center in **1** and the corresponding carbenium



(1)

ion center in **3** exert electronically opposed effects on attached organic groups R. These effects are reversed in the course of redox reaction 1. The obvious preparative benefit to be drawn from this direct redox umpolung[1] is, however, usually thwarted by the fact that for a given set of ligands X, the redox system 1 cannot be reversibly realized due to thermodynamic and/or kinetic instability of certain oxidation levels of the redox system involved. An ideal solution to this problem would consist in coupling the very process of electron transfer with a transformation of carbanion stabilizing substituents X into carbenium ion stabilizing substituents X′ without having to resort to additional external reagents (2). Obviously this abstract postulate could be satisfied by an ECE

† Dedicated to Professor Paul v. R. Schleyer on the occasion of his 60th birthday.

(1) Seebach, D. *Angew. Chem.* **1979**, *91*, 259; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.

0002-7863/90/1512-333$02.50/0