Dipeptide Surrogates Containing Asparagine-Derived Tetrahydropyrimidinones: Structure and Amide Rotomer Stereochemistry of a Proline Mimic

Joseph P. Konopelski,*[,1a,b] Yunyang Wei,[1a,2] and Marilyn M. Olmstead[1c,3]

Department of Chemistry and Biochemistry, University of California, Santa Cruz, California 95064, and Department of Chemistry, University of California, Davis, California 95616

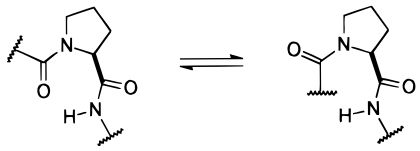
Received February 1, 1999

Novel dipeptide surrogates Fmoc-Xaa-(cyclo)Asn-OBu^t are prepared from asparagine, aromatic aldehydes, and Fmoc-protected amino acid chlorides. Previous studies have focused on basic approaches to key synthetic intermediates containing the (cyclo)Asn fragment for polypeptide preparation. The synthesis of these systems has now been extended to electron-rich aromatic aldehydes, exemplified by *p*-anisaldehyde. One-dimensional nuclear Overhauser effect experiments confirm the *trans* configuration around the central secondary amide bond and the boat conformation of the pyrimidinone ring. Variable-temperature NMR at 500 MHz was employed both to obtain thermodynamic data on the *cis*−*trans* amide bond interconversion barrier and to probe for the presence of hydrogen bonding. Single-crystal X-ray analysis of Ac-D-Ala-(cyclo)Asn-NHMe shows a high degree of structural similarity to a known proline-containing dipeptide.

Introduction

One of the attractions of the chemical approach to biological molecules is the ability to prepare derivatives with novel properties. In recent years there has been considerable interest in the synthesis of unnatural and/or conformationally constrained amino acids, peptidomimetics,[4] and small peptide fragments encompassing these residues. This interest has been fueled by the desire for synthetic polypeptides with increased hydrolytic stability, enzyme inhibition properties, and/or unique conformational restrictions in comparison to the all-natural counterpart. In addition, these unusual amino acids can be used to elucidate the relevant conformation(s) of their biologically active natural counterparts, thereby providing information concerning the three-dimensional requirements for various recognition events.[5] The preparation of such compounds requires sophisticated, versatile, and generally applicable synthetic approaches to the desired structural features.

Of all the common α-amino acids, proline plays a particular role in peptide secondary structure formation. Because the pyrrolidine ring of the Pro residue forces the Φ angle to be centered on −60° (±15°), proline presents a ready opportunity to change the direction of the polypeptide chain. Indeed, it has long been recognized that type I and type II *β*-turns most often have proline in the $i + 1$ position. The lack of a hydrogen on the amide bond in Xaa-Pro segments significantly lowers the energy difference between the *cis* and *trans* rotomers, while the activation barrier for isomerization remains significant. These two unique characteristics (ring and secondary amide structure) combine to give proline an important place in the recognition, reactivity, and stability of polypeptides and proteins. The presence of specific prolyl-peptidyl *cis*−*trans* isomerases[6] in living systems also attests to the importance of the geometry around this secondary amino acid. It is not surprising, then, that numerous mimetics and substituted proline analogues have been prepared in an effort to both understand and manipulate the topology of reverse turns and *cis*−*trans* isomer ratios in peptides.



Xaa-Pro amide isomerization

We have recently prepared a series of dipeptide surrogates of the type Fmoc-Xaa-(cyclo)Asn-OBu^t, where "(cyclo)Asn" is a novel cyclic derivative of the common amino acid asparagine.[7] In our initial studies, we outlined a substantial amount of basic chemistry of these systems and have demonstrated methods for their incorporation into polypeptide units. In addition, the deprotection of the (cyclo)Asn residue to the native amino acid could be readily achieved by mild acid treatment at aqueous reflux temperature. During the course of this work, we discovered that the Φ angle of the pyrimidinone ring in these systems was within the range expected for a proline dipeptide. Herein, we outline additional experiments designed to explore the structure of this proline mimic.

(1) (a) University of California, Santa Cruz. (b) Phone 831-459-4676; FAX 831-459-2935; email joek@chemistry.ucsc.edu. (c) University of California, Davis.

(2) On leave from the Institute of Chemical Engineering, Nanjing University of Science and Technology, PRC.

(3) To whom correspondence concerning X-ray crystallography should be addressed.

(4) (a) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699−1720. (b) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244−67.

(5) For a recent example, see: Smith, A. B., III; Keenan, T. P.; Holcomb, R. C.; Sprengeler, P. A.; Guzman, M. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1992**, *114*, 10672−4.

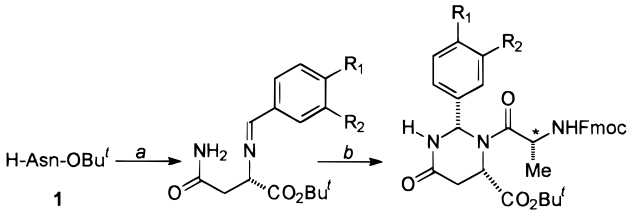
(6) Chen, J. K.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 953−69.

(7) Konopelski, J. P.; Filonova, L. K.; Olmstead, M. M. *J. Am. Chem. Soc.* **1997**, *119*, 4305−6.

10.1021/jo9901790 CCC: $18.00
Published on Web 06/17/1999

Results and Discussion

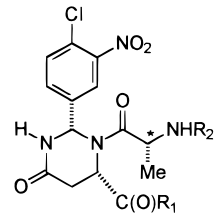
The synthesis of the key compounds in this study follows the route outlined below and in our initial publication. Asparagine *tert*-butyl ester (**1**) is employed as the starting material. This ester is commercially available or easily prepared by a three-step literature procedure from asparagine.[8] By the latter method both enantiomers are readily available. Imine **2**, prepared by the condensation of **1** with the requisite aldehyde in the presence of trimethylorthoformate,[9] is extremely clean and forms in quantitative yield. Formation of the desired dipeptide surrogate evolves from the coupling of **2** with the acid chloride derivative of the desired *N*-terminal amino acid. These amino acid chlorides, which are protected as Fmoc derivatives, are crystalline compounds as described by Carpino.[10]



a R_1 = Cl, R_2 = NO_2, **b** R_1 = OMe, R_2 = H

a) ArCHO, $(MeO)_3CH$, 98%; *b*) Fmoc-D-Ala-Cl, C_5H_5N, 51-58%

Compound **3a** had been synthesized for our initial report and shown to exist as a single isomer in solution. By contrast, the compound with the L-Ala residue at the *N*-terminus (**3a** with (*S*)-Me) was a mixture of amide isomers at room temperature in $CDCl_3$. To identify which amide isomer corresponded to **3a** and to explore in detail the conformation of the pyrimidinone ring in comparison with previous structural studies on proline dipeptides, we prepared the corresponding acetamide/methylamide derivative **5**. To this end, **3a** was treated with $HNMe_2$,



a **3a** R_1 = OBu^t, R_2 = Fmoc
b **4** R_1 = OBu^t, R_2 = Ac
5 R_1 = NHMe, R_2 = Ac

a) $HNMe_2$, then Ac_2O;
b) 1) TFA; 2) $ClCO_2Et$, H_2NMe

followed by direct acetylation with Ac_2O/pyridine to afford **4** in 80% yield. Reaction of **4** with TFA followed by coupling with $MeNH_2$ using a mixed anhydride protocol gave **5** in 74% yield.

It was of interest to extend the substitution pattern at C2 to include electron-rich aromatic rings. Previous work in our laboratory[11] and in others[12] had firmly established the utility of aliphatic aldehydes as important components in this cyclization reaction, and our own work with electron-poor aromatic aldehydes had been quite successful.[7] However, earlier work on our one-pot cyclization procedure[13] with benzaldehyde or electron-rich aromatic aldehydes gave poor yields of initial material and/or poor stability of the isolate products. Coupling of the asparagine imine derived from benzaldehyde with Fmoc-Ala-Cl afforded a 61% yield of desired product, essentially identical with the yield of **3a** formation. A more modest 51% yield of **3b** was obtained when imine **2b** was employed in the two-step protocol. Use of the imine formed from 3,4-dimethoxybenzaldehyde led to low yields of desired product. Thus, this two-step approach to the heterocycle is somewhat more tolerant of electron-rich aromatic rings than is the one-step approach and extends the limits of the substitution pattern at C2.

Origin of Isomers. As mentioned previously, **3a** exists as a single isomer at room temperature in $CDCl_3$. Conversely, **3b** and the majority of the dipeptide surrogates prepared in our initial investigation display peaks in the ^1H NMR indicative of multiple isomers that do not interconvert on the time scale of the instrument at room temperature. We briefly investigated Fmoc-Tyr-(cyclo)-Asn-OBu^t by variable-temperature NMR in our initial studies and observed a coalescence temperature of approximately 75 °C.[7] These results were interpreted as evidence of *cis*−*trans* isomerization about the secondary amide bond. A similar compound was investigated by Snieckus and displayed overall coalescence at 100 °C,[14] while the corresponding bond in a Xaa-Pro dipeptide has been characterized with a barrier to rotation of approximately 20 kcal/mol,[15] displaying an even higher coalescence temperature.

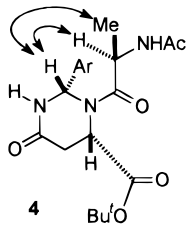
The presence of the methyl singlet for the anisole functionality in **3b** afforded the opportunity to obtain thermodynamic data on this system. At room temperature, a pair of singlets corresponding to the −OMe functionality in the two isomers of **3b** are visible at δ 3.730 and 3.649 in an approximate ratio of 1:1 in DMSO-d_6. Overall coalescence was observed at 65 °C. These data correspond to an activation energy ($\Delta G^{\ddagger}$) for *cis*−*trans* isomerization of 16.9 kcal/mol, significantly lower than that of an Xaa-Pro dipeptide.

Conformation of Triamide. Triamide **5** is unique in the synthetic series from **3a** in that it is appreciably water soluble and exhibits NMR signals indicative of two isomers at room temperature in D_2O. Although water solubility is expected for similar Xaa-Pro triamides, the presence of a minor amide isomer in this series of proline mimics was not.

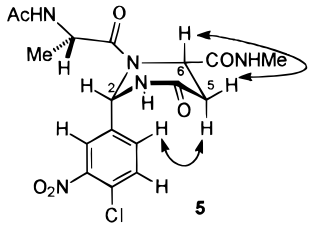
Nuclear Overhauser experiments were carried out on **4** to determine key structural features of the major isomer in solution. As shown in the diagram, the *trans* amide isomer should bring the methyl and/or asymmetric center hydrogen of the D-alanine residue in close proxim-

(8) König, W.; Kernebeck, K. *Liebigs Ann. Chem.* **1979,** 227−47.
(9) Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937−40.
(10) For a review, see: Carpino, L. A. *Acc. Chem. Res.* **1996**, *29*, 268−74.
(11) Chu, K. S.; Negrete, G. R.; Konopelski, J. P.; Lakner, F. J.; Woo, N.-T.; Olmstead, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 1800−12.
(12) Juaristi, E.; López-Ruiz, H.; Madrigal, D.; Ramírez-Quirós, Y.; Escalante, J. *J. Org. Chem.* **1998**, *63*, 4706−10.
(13) Lakner, F. J.; Chu, K. S.; Negrete, G. N.; Konopelski, J. P. *Org. Synth.* **1995**, *73*, 201−14.
(14) Beaulieu, F.; Arora, J.; Veith, U.; Taylor, N. J.; Chapell, B. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 8727−8.
(15) Creighton, T. E. *Proteins: Structures and Molecular Properties*, 2nd ed.; Freeman: New York, 1993; p 181.

ity to the C2 hydrogen of the pyrimidinone. A 1D NOE experiment on **4** indicated such a close approach of the alanine asymmetric center to the C2 proton, as depicted by the arrows in the diagram, thereby setting the major isomer as *trans* in this compound.



4



5

Nuclear Overhauser experiments were also used to determine the structure of the pyrimidinone ring. Previously, we[7,11] and others[14,16] have obtained X-ray crystallographic data to support the boat conformation of the heterocyclic ring, but to our knowledge, there has never been conclusive data on the solution conformation of these systems. Irradiation of a sample of **5** in the area of the C5 protons (δ 2.3−2.6) afforded the expected enhancement of the C6 (asymmetric) proton, as well as an enhancement of the *ortho* protons on the C2 aromatic substituent, as indicated in the diagram. This result could only arise from the boat conformation, which places the C2 axial substituent (in this case the 4-chloro-3-nitrophenyl ring) in close proximity to the axial hydrogen on C5, the other "flagpole" substituent. We had proposed a close approach of the *cis* substituents on these two centers to explain our results in the formation of dihydropyrimidinones in a palladium-catalyzed reaction we studied some time ago.[7] However, this is the first definitive evidence for the preference in solution of the boat conformation in these compounds.

The temperature dependence of the N−H proton chemical shift of amides in polypeptides has emerged as an important measure of structure brought on by hydrogen bonding.[17] The data obtained for **5** in DMSO-d_6 indicate no significant hydrogen bonding over the temperature range of 25−50 °C. These results are consistent with the *trans* geometry around the D-Ala-(cyclo)Asn amide bond.

The evidence given above supports a structure for **5** in which the ring is in a boat conformation with *trans* geometry around the secondary amide bond and no secondary structure due to hydrogen bonding. Nonetheless, we sought to confirm these data and obtain direct comparison with other structures in the literature by single-crystal X-ray analysis. The results are shown in Figure 1, accompanied by a comparison of structural data between **5** and Ac-Tyr-Pro-NHMe as obtained by Scheraga (Table 1).[18] The stereoview in Figure 1 highlights the central *trans* amide bond. As can be seen in the Table, the dihedral angles about the *N*-terminal amino acids are equal in magnitude but opposite in rotation, as would

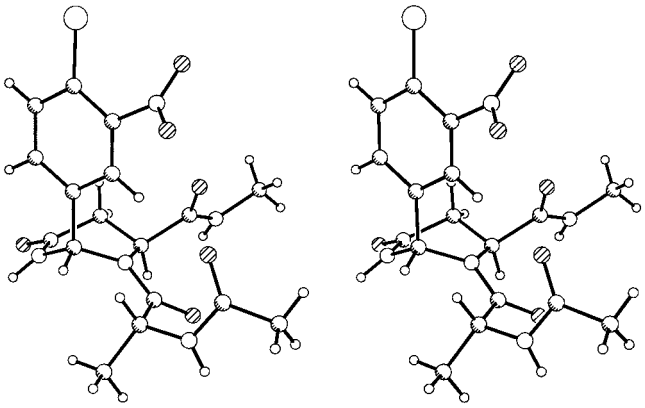


Figure 1. Stereoview of Ac-D-Ala-(cyclo)Asn-NHMe·2H_2O. The water molecules have been removed for clarity.

Table 1. Comparison of Structural Data between 5 and Ac-Tyr-Pro-NHMe[18]

Ac-D-Ala-(cyclo)Asn-NHMe·2(H_2O)			Ac-Tyr-Pro-NHMe·2(H_2O)		
D-Ala	Φ	73	Tyr	Φ	−71
	Ψ	−147		Ψ	149
	Ω	−177		Ω	−178
(cyclo)Asn	Φ	−71	Pro	Φ	−75
	Ψ	150		Ψ	144
	Ω	174		Ω	−178
% *cis* in H_2O	24		% *cis* in H_2O	35	

be expected for these residues from opposite enantiomeric series. *However, the structural data for the two cyclic amino acids are nearly identical in both sign and magnitude, indicating a high degree of similarity.* Likewise, the percent *cis* content in D_2O is quite similar.

In conclusion, the initial suggestion that the (cyclo)-Asn residue functions as a proline mimic has been validated. Amide bond isomer distribution and ring conformation are supported by both solution- and solid-phase data. In addition, we have documented the $\Delta G^{\ddagger}$ of amide bond isomerization, which is lower than the corresponding value for proline itself. Extensions of this work to tripeptides and tetrapeptides is currently underway in our laboratory and will be reported in due course.

Experimental Section[19]

Imine 2b. To a solution of H-Asn-OBu^t (**1**, 0.150 g, 0.80 mmol) in 4.0 mL of trimethylorthoformate was added the *p*-anisaldehyde (0.80 mmol). The resulting mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo. Methylene chloride (3 × 2 mL) was added and removed in vacuo to remove trimethylorthoformate completely. The residue (0.240 g, 98%) was used directly in the next reaction. ^{1}H NMR (DMSO-d_6) δ 1.37 (s, 9 H), 2.68 (dd, J = 15.1, 5.9 Hz, 2 H), 3.79 (s, 3 H), 4.20 (t, J = 6.7 Hz, 1 H), 6.82 (s, 1 H), 6.99 (d, J = 8.5 Hz, 2 H), 7.36 (s, 1 H), 7.67 (d, J = 8.4 Hz, 2 H), 8.24 (s, 1 H).

Fmoc-D-Ala-(cyclo-MeOC$_6$H$_4$CH)-Asn-OBu^t (3b). To imine **2b** (0.201 g, from 0.122 g, 0.65 mmol of H-Asn-OBu^t) in 10 mL of benzene was added pyridine (0.08 mL, 1.0 mmol), followed by Fmoc-D-Ala-Cl (0.283 g, 0.86 mmol). The mixture was stirred at 65 °C for 5 h. Solid byproducts were removed by filtration and washing with benzene. The solvent was then removed in vacuo, and the residue was purified by column

(16) Seebach, D.; Lamatsch, B.; Amstutz, R.; Beck, A. K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradón, B.; Hidber, P. C.; Irwin, J. J.; Locher, R.; Maestro, M.; Maetzke, T.; Mouriño, A.; Pfammatter, E.; Plattner, D. A.; Schickli, C.; Schweizer, W. B.; Seiler, P.; Stucky, G.; Petter, W.; Escalant, J.; Juaristi, E.; Quintana, D.; Miravitlles, C.; Molins, E. *Helv. Chim. Acta* **1992**, *75*, 913−34.

(17) For a discussion, see: Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 512−23.

(18) Montelione, G. T.; Arnold, E.; Meinwald, Y. C.; Stimson, E. R.; Denton, J. B.; Huang, S.-G.; Clardy, J.; Scheraga, H. A. *J. Am. Chem. Soc.* **1984**, *106*, 7946−58.

(19) For generic experimental details, consult ref 11. Details of the syntheses of **3a** and Fmoc-Tyr-(cyclo)Asn-OBu^t are given in the Supporting Information to ref 7.

chromatography on silica gel using methylene chloride/ether (7:3) as eluent to afford 0.197 g (51%, based on H-Asn-OBu^t) as a white solid: mp 103−106 °C; $[\alpha]^{25}_D = +4.1$ [c = 1.18, $CHCl_3$]; ^{1}H NMR ($CDCl_3$) δ 1.34 and 1.40 (s, 9 H), 1.42−1.47 (m, 3 H), 2.46∼2.86 (m, 2 H), 3.72 and 3.77 (s, 3 H), 4.13−4.40 (m, 3 H), 4.57−4.66 (m, 1 H), 4.76 and 5.27 (t, J = 6.5 Hz, 1 H), 5.77 and 5.82 (d, J = 8.5 Hz, 1 H), 6.29 and 7.09 (br s, 1 H), 6.85 (d, J = 8.0 Hz, 2 H), 7.31−7.42 (m, 6 H), 7.58−7.61 (m, 2 H), 7.76 (d, J = 7.5 Hz, 2 H), 8.21 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.5, 19.2, 27.8, 28.0, 33.0, 47.1, 47.3, 54.0, 54.9, 55.3, 63.8, 65.9, 67.3, 82.4, 83.4, 114.0, 114.2, 120.1, 125.3, 127.2, 127.8, 127.9, 128.0, 130.1, 130.4, 136.2, 141.4, 143.8, 143.9, 144.1, 149.7, 155.6, 156.4, 159.7, 159.9, 168.4, 169.1, 170.0, 171.1, 172.3, 174.6; IR (thin film) 2977, 1650, 1512, 1450, 1205, 1148, 740 cm^{-1}. According to the ^{1}H NMR integration of the OCH_3 peaks, the conformational isomer ratio is 2:1 in $CDCl_3$ and 1:1 in DMSO-d_6. Dynamic ^{1}H NMR in DMSO-d_6 shows the coalescence of OCH_3 peaks at 65 °C, and the activation free energy ($\Delta G^{\ddagger}$) of rotation around the amide bond is 70.54 kJ/mol (16.86 kcal/mol); HRMS calcd for $[M + 1]^+$ $C_{34}H_{38}N_3O_7$ 600.2710, found 600.2712.

Ac-D-Ala-(cyclo-Cl,NO$_2$-C$_6$H$_3$CH)-Asn-OBu^t (4). Compound **3a** (0.65 g, 1.000 mmol) was dissolved in Me_2NH (25 mL, 2 M solution in THF). The resultant solution was stirred at room temperature for 20 min. Solvent was removed in vacuo. The residue was dissolved in THF (1 mL), and petroleum ether (5 mL) was added to precipitate the desired product, which was separated from the liquid, washed with additional petroleum ether, and dried.

The above product (0.407 g) was dissolved in methylene chloride (20 mL) and treated with pyridine (0.16 mL, 1.98 mmol) and acetic anhydride (0.20 mL, 2.12 mmol). The resultant solution was stirred at room temperature for 22 h. Solvent was removed in vacuo. The resultant residue was purified by column chromatography on silica gel using methylene chloride/methanol as eluent to give the desired acetate (0.375 g, 80%) as a white solid: mp 112−113 °C; $[\alpha]^{25}_D = +22.5$ [c = 1.24, MeOH]; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.43 (d, J = 6.0 Hz, 3 H), 1.98 (s, 3 H), 2.63 (dd, J = 8.0, 16.5 Hz, 1 H), 2.83 (dd, J = 7.0, 16.0 Hz, 1 H), 4.50−4.65 (m, 1 H), 5.50 (t, J = 7.5 Hz, 1 H), 6.81 (d, J = 4.5 Hz, 1 H), 7.03 (d, J = 7.5 Hz, 1 H), 7.51 (d, J = 8.5 Hz, 1 H), 7.64 (dd, J = 2.0, 8.0 Hz, 1 H), 7.95 (s, 1 H), 8.01 (d, J = 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.6, 22.5, 27.6, 27.7, 29.6, 33.3, 45.7, 54.4, 63.1, 83.9, 123.8, 127.0, 131.3, 132.1, 139.3, 147.7, 169.5, 170.8, 175.3; IR 1651, 1539, 1261, 1154, 1050 cm^{-1}; HRMS calcd for $[M + 1]^+$ $C_{20}H_{26}N_4O_7Cl$ 469.1490, found 469.1490.

Ac-D-Ala-(cyclo-Cl,NO$_2$-C$_6$H$_3$CH)-Asn-NHMe (5). Compound **4** (0.375 g, 0.80 mmol) was dissolved in trifluoroacetic acid (TFA, 8 mL). The resultant solution was stirred at room temperature for 1 h. TFA was removed in vacuo. Methanol (3 × 3 mL) was added to the residue and evaporated in vacuo prior to drying.

The above product (0.336 g) was dissolved in THF (8 mL) at 0 °C, followed by addition of *N*-methylmorpholine (0.10 mL, 0.910 mmol) and ethyl chloroformate (0.09 mL, 0.94 mmol). After the mixture stirred at 0 °C for 10 min, $MeNH_2$ (0.50 mL, 2 M solution in THF) was added. The resulting solution was stirred at room temperature for 20 h, and THF was removed in vacuo. The residue was purified by column chromatography on silica gel using methylene chloride/methanol as eluent to afford 0.255 g (74%) of desired material: mp 130−133 °C; $[\alpha]^{25}_D = -14.2$ [c = 0.59, MeOH]; ^{1}H NMR (DMSO-d_6) δ 1.18 and 1.21 (d, J = 6.5 Hz, 3 H), 1.45 and 1.83 (s, 3 H), 2.10−2.28 (m, 2 H), 2.51 and 2.56 (d, J = 4.0 Hz, 3 H), 4.31 and 4.88 (m, 1 H), 4.66 and 5.07 (m, 1 H), 6.26 and 6.70 (d, J = 6.0 Hz, 1 H), 7.77−7.81 (m, 1 H), 7.88 and 8.24 (d, J = 4.5 Hz, 1 H), 8.00 (d, J = 4.0 Hz, 1 H), 8.12 and 8.55 (s, 1 H), 8.45∼8.47 (m, 1 H), 8.97 and 9.29 (d, J = 5.0 Hz, 1 H); ^{13}C NMR (MeOH-d_4) δ 17.2, 21.8, 26.4, 34.0, 35.1, 55.5, 56.0, 64.0, 65.9, 67.1, 125.1, 127.1, 132.7, 141.3, 141.7, 149.3, 171.9, 172.2, 172.5, 172.9, 174.6, 175.9; IR 3325, 3075, 2950, 1688, 1650, 1538, 1425, 1062 cm^{-1}; HRMS calcd for $[M + 1]^+$ $C_{17}H_{21}N_5O_6Cl$ 426.1180, found 426.1178.

Acknowledgment. Partial support of this work by the American Cancer Society (DHP-79) is gratefully acknowledged. Grants for the purchase of NMR equipment from NSF (BIR-94-19409) and the Elsa U. Pardee Foundation are gratefully acknowledged. We wish to express our sincere thanks to the China Scholarship Council for support for Y.W. In addition, we thank our collaborators in the group of Professor G. Cardillo (Bologna) for many stimulating discussions and NATO (Collaborative Research Grant CRG 950049) for funding of that collaboration.

Supporting Information Available: Experimental procedures for the synthesis of **1** and other compounds not specifically numbered in the text, as well as ^{1}H NMR spectra for key compounds, and X-ray data for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9901790