Novel Bicyclic Lactams as XaaPro Type VI β Turn Mimics: Design, Synthesis, and Evaluation

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Received January 2, 1996[⊗]

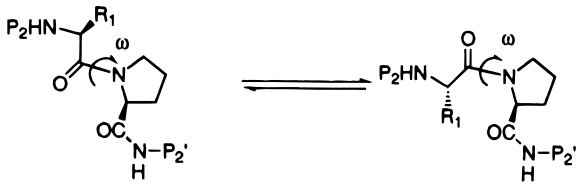
The design, enantioselective synthesis, and structural characterization of novel bicyclic lactams as peptide mimics of the type VI β turn is described. The mimics duplicate the conformation of the backbone and disposition of the side-chain atoms of the central two residues of the turn. The Gly L-Pro mimic, lactam **6**, was prepared in good overall yield starting from (*S*)-2-(2′-propenyl)proline. ^{1}H NMR spectroscopy defined the relative stereochemistry of the substituents and conformational characteristics of the six-membered ring of the lactam; X-ray crystallographic analysis confirmed the conformational and stereochemical assignment. Examination of the crystal structure of lactam **6** revealed that the central amide bond was twisted appreciably out of planarity. The twisting of the amide bond was attributed to angle strain resulting from the presence of the sp^2-hybridized nitrogen atom at the junction of the two rings. Alkylation of the enolate of the *N*,*N*-dimethylformamidine derivative of lactam **6** with benzyl bromide afforded stereoselectively the formamidine **11**, a mimic of an L-Phe L-Pro dipeptide in the type VI turn conformation. The efficient synthetic route to highly functionalized peptidomimetics such as **11** will prove highly useful in peptide structure−function studies.

Introduction

Of the 20 common amino acids, proline is unique by virtue of its secondary amino group, a feature that has a significant effect on its conformational properties (Scheme 1). For instance, the difference in free energy between the *trans* and *cis* isomers of amides involving proline is small ($\Delta G° = 0.5$ kcal/mol), in contrast to amides involving the primary amino acids, where the *trans* configurational isomer is substantially more stable than the *cis* isomer ($\Delta G° = 2.6$ kcal/mol).[1] Hence both *cis* and *trans* isomers of proline-containing peptides may be present in significant amounts under physiological conditions.[2]

Cis−*trans* isomerism of proline-containing peptides has been implicated in a number of biologically important processes. Due to the substantial barrier to interconversion of the isomers at room temperature ($\Delta G^‡ = 18$−21 kcal/mol),[3] the rate-determining step of folding of many proteins is the isomerization of specific prolyl peptide bonds from "non-native" to "native" states.[4] Isomerization of prolyl amide bonds has also been proposed to modulate the biological activity of certain peptide hormones,[5] to control the activities of membrane-spanning polypeptides,[6] and to influence peptide susceptibility to protease degradation.[7] It has recently become evident that all cells contain considerable amounts of enzymes termed peptidyl-prolyl isomerases (PPIases), which greatly accelerate the rate of interconversion of prolyl peptide bond isomers.[8] The PPIases have become the object of significant research focus due to their roles in modulating immunosuppression[9] and HIV infectivity.[10]

Scheme 1. Isomerism in Proline-Containing Peptides



trans-XaaPro ω = 180° *cis*-XaaPro ω = 0°

A common peptide conformational feature that incorporates a *cis* proline residue is the type VI β turn.[11] This conformation is characterized by a *cis* peptidyl linkage between the central two residues of the four amino acids that constitute the turn (Figure 1). The type VI turn is often found in peptides and proteins containing the sequence ArProAr, where Ar represents an amino acid with an aryl side chain; in these cases the prolyl pyrrolidine ring is sandwiched between the aryl rings of the neighboring amino acids.[12] The type VI turn has attracted a great deal of attention as a result of its unique structure and biological importance. For instance, the

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1996.

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S0022-3263(96)00012-6 CCC: $12.00

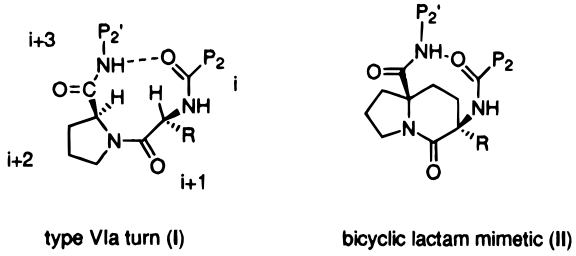


Figure 1. Conformation of the type VI β turn and general structure of the type VI β turn mimic.

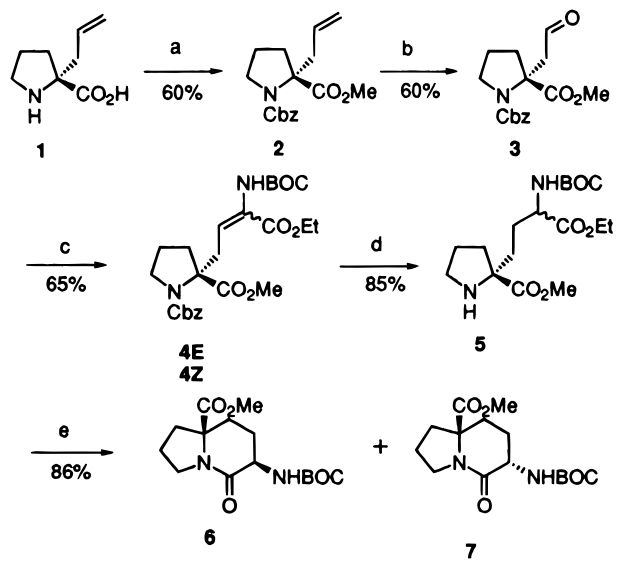
type VI turn conformation appears to be a basic recognition feature for peptide binding to PPIases[13] and is also found in the solution conformation of biologically active peptide hormones.[14]

The correlation between a polypeptide's structure and its biological activity can often be clarified by assessing the biological properties of peptides constrained to specific conformations.[15] Such constrained molecules, sometimes termed peptidomimetics, are highly desirable as therapeutic agents, since they generally do not possess the pharmacological drawbacks of peptides, such as low oral availability and rapid proteolytic turnover.[16] Peptidomimetics of the type VI turn conformation would find considerable utility in probing the structure−function relationships of proline-containing peptides. Herein we report the design, stereo- and enantioselective synthesis, and structural evaluation of a series of substituted bicyclic lactams that represent the central two residues of an XaaPro dipeptide unit constrained to the type VI turn conformation (Figure 1).[17] A unique feature of the described synthetic method is the ease of construction of variants of the parent structure with functional groups that represent the side chain of the Xaa residue, a vital consideration for combinatorial chemical applications.

Results and Discussion

Synthesis and Structural Characterization of GlyPro Analogs 6 and 7. The bicyclic skeleton for the dipeptide mimic was suggested by a structural homology search algorithm, using the coordinates of the type VI turn found in residues 92 and 93 of the RNase A as the template (Figure 1).[18] Conceptually the five-membered ring of the bicycle **II** represents the pyrrolidine ring of the proline residue, the R group represents the side chain of the $i + 1$ amino acid residue, and the carboxyl and amino groups represent the carboxyl and amino groups of the $i + 2$ and $i + 1$ amino acid residues, respectively. According to molecular mechanics calculations, *cis*-bicycle **II** displayed a planar lactam amide bond and a pseudochair conformation for the six-membered ring with the amino group assuming a pseudoequatorial disposition.

Scheme 2



The starting material for the preparation of the mimic was (*R*)-2-(2-propenyl)proline (**1**), which was readily available as a single enantiomer from (*S*)-proline following the elegant protocol of Seebach.[19] Protection of the amino and carboxyl functionalities as (benzyloxy)carbamates and methyl esters, respectively, furnished the ester **2** (Scheme 2). Oxidative cleavage of the double bond with periodate and osmium tetroxide afforded the aldehyde **3** in good yield. Introduction of a glycyl anion equivalent was achieved by coupling aldehyde **3** with the anion of the phosphonate reagent *N*-(*tert*-butyloxycarbonyl)-α-phosphonoglycine dimethyl ethyl ester;[20] an equimolar mixture of alkenes **4E** and **4Z** was obtained after silica gel chromatography. Exposure of the isomeric mixture of alkenes to hydrogen in the presence of a palladium catalyst effected concomitant reduction of the double bond and hydrogenolysis of the benzyloxycarbonyl group to provide the amino ester **5** as a mixture of enantiomers at the chiral center of the pendant alkyl chain. Thermolysis of the amino ester **5** in refluxing toluene afforded two products, presumably the bicyclic lactams **6** and **7**. The lactams **6** and **7** could also be prepared in racemic form, starting from racemic ester **2**, obtained by allylation of the enolate of *N*-(benzyloxycarbonyl)proline methyl ester.

The thermolysis products were separated by silica gel chromatography and individually characterized. The similarities of their NMR spectral characteristics supported the hypothesis that these compounds were the isomeric lactams **6** and **7**. The relative stereochemistry of the substituents on the six-membered ring and the conformation of the bicyclic skeleton of each lactam isomer were investigated in detail, since these features would determine the structural similarity of the lactams to the native peptide conformation. The bicyclic lactams

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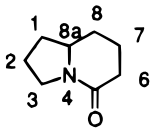
incorporated the 5(6*H*)-indolizidinone ring system, as in **III**, for which synthetic procedures had been described previously.[21] Since the precise conformational characteristics of this ring system had not been reported, however, detailed analysis of the conformational properties of lactams **6** and **7** was carried out by NMR spectroscopy as well as X-ray crystallography.



III

The relative stereochemistry of the substituents and solution phase conformation of the six-membered ring of each isomer were first elucidated by analysis of their NMR spectral characteristics. COSY was used to define the pyrrolidine and piperidinone ring spin systems of the ^{1}H spectrum of each lactam. Stereospecific assignments of the ^{1}H resonances were then carried out as far as possible by 1-D NOE difference spectroscopy and NOESY. The coupling constant values of each resolved signal were then obtained by inspection or by spectral simulation. For delineation of the splitting patterns of the C6 protons, spectra of samples that had been incubated in D_2O were utilized, since the absence of the carboxamide hydrogen in such samples greatly simplified spectral analysis.

The values of the coupling constants for the six-membered ring protons of the more polar isomer were consistent with hydrogens that occupied pseudoaxial or pseudoequatorial positions on a flattened chair.[22] For example the C6 proton displayed large (13.0 Hz) and medium (7.3 Hz) couplings to the two C7 protons, compatible with pseudoaxial−pseudoaxial and pseudoaxial−pseudoequatorial couplings, respectively.[22] The magnitudes of the C6−C7 ^{1}H−^{1}H coupling constants were indicative of a pseudoaxial C6 hydrogen. On the basis of the coupling constants, the more polar lactam was assigned the *cis* stereochemistry, as in **6**, with the angular carboxy group assuming a pseudoaxial disposition and the amido group a pseudoequatorial disposition on the six-membered ring.

The less polar isomer's six-membered ring ^{1}H splittings were significantly different from those of the more polar isomer. In particular no large pseudoaxial−pseudoaxial or small pseudoequatorial−pseudoequatorial coupling constants could be discerned. The spectral characteristics of this isomer suggested its six-membered ring adopted a twisted chair or boat conformation, a conformation seen in certain monocyclic piperidinones.[23] Hence the structure of the less polar isomer was assigned the *trans* stereochemistry.

The structure of the more polar lactam **6** was unequivocally confirmed by X-ray crystallography (Figure 2).[24] In the crystalline state the six-membered ring of the bicycle indeed adopted a pseudochair conformation with the amido substituent oriented pseudoequatorially, as suggested by NMR spectroscopy. Furthermore the X-ray structure of lactam **6** revealed appreciable distortion of the lactam amide bond from a planar conformation.

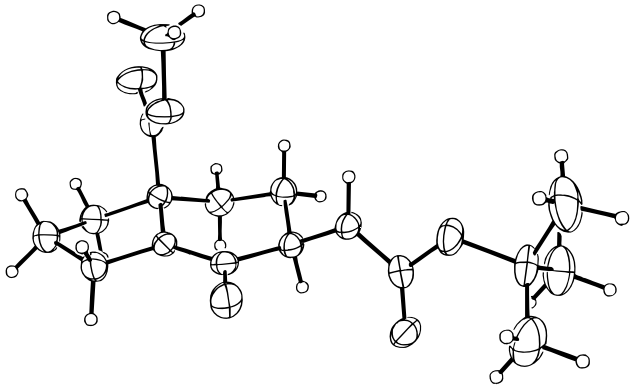


Figure 2. X-ray crystal structure of bicyclic lactam **6**.

Although amides generally adopt conformations in which the six atoms of the functional group are coplanar,[25] in unusual cases, such as in strained ring systems, amide bonds may adopt conformations where the amide bond is distorted from planarity.[26] In the case of the lactam **6**, the value of ω, or the dihedral angle incorporating the atoms C6−C5−N4−C8a, was found to be $-14.6 \pm 0.5°$. In contrast the value of ω for the crystallographically characterized, unstrained amide caprolactam, which also contains a *cis*-lactam bond, was $-4.2 + 0.4°$.[27] A more precise description of amide bond distortion is obtained from an analysis of atom positions by the method of Dunitz and Winkler.[28] The Dunitz parameters χN and τ' reflect the N-atom pyramidalization and rotation about the N−C(O) bond, respectively. Deviations of the values for these parameters from 0° signify distortion of a *cis* amide function. For the lactam bond of compound **6**, the values of χN and τ' are $6.8 \pm 0.5°$ and $-5.9 \pm 0.5°$, respectively. The values for χN and τ' for the *cis* amide bond of caprolactam are $-1.6°$ and $2.6°$, respectively. Thus the amide bond of lactam **6** displays a distorted conformation relative to analogous monocyclic lactam bonds; the degree of nonplanarity of the amide function of lactam **6** is similar in magnitude to that seen for the amide bond in *cis*-caprylolactam ($\chi N = -6.4°$ and $\tau' = 4.3°$),[28] one of the more strained monocyclic amides.

The origin of the angle strain of the indolizidinone ring system of lactam **6** was analyzed through comparison of the conformation of its six-membered ring with that of cyclohexene. In the absence of strain, the conformation of the six-membered ring of lactam **6** should resemble that of cyclohexene, with the CN bond corresponding to the double bond. Differences in conformation between these structures were noted, however, in the values for

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(24) The racemic derivative of the lower R_f lactam crystallized from ethyl acetate as flat plates as the monohydrate. The space group was determined to be *Pbca*. Crystallographic data, including the fractional atomic coordinates, together with distances and angles of covalent bonds involving non-hydrogen atoms have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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Table 1. X-ray Crystal Structure-Derived Torsion Angle Values for Bonds of Lactam 6 and Analogous Bonds of Cyclohexene

bond	lactam **6** torsion angle (deg)	bond	cyclohexene torsion angle (deg)
C5−C6	17.7	C1−C2	15.2
C6−C7	40.0	C2−C3	45.0
C7−C8	58.7	C3−C3′	60.0
C8−C8a	54.1	C2−C3	45.0
C8a−N4	33.4	C1−C2	15.2
N4−C5	14.6	C1−C1′	0.0

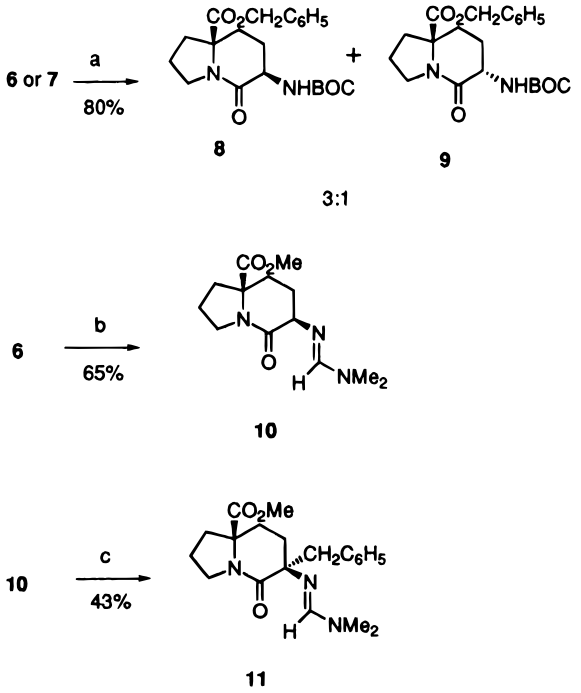
the intraring torsion angles. While the values for the torsions for the dihedral angles incorporating C5−C6, C6−C7, and C7−C8 of compound **6** were similar to those for the analogous bonds of cyclohexene,[29] the values for the remaining angles (C8−C8a, C8a−N4, and N4−C5) deviate significantly from those for cyclohexene (Table 1). These torsion angles all involve C8a and N4, the atoms common to both the six- and five-membered rings. Thus strain is introduced into the piperidinone ring of lactam **6** in order to accommodate fusion with the five-membered ring.

To assess the conformational similarity between mimic **6** and a typical type VI turn, a superimposition of the main-chain and side-chain atoms of **6** with the corresponding atoms of the type VI turn from RNase (Tyr92-Pro93) was carried out using the molecular similarity algorithm of the QUANTA software package that minimizes the deviation between the positions of analogous atoms of the two structures. The two structures displayed exceptional similarity, with 0.15 Å rms overall deviation in backbone and five-membered ring atom positions.[17]

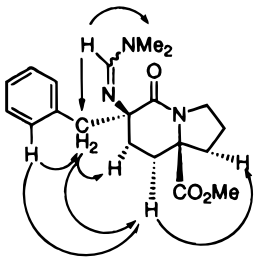
The difference in free energy between the isomeric lactams **6** and **7** was investigated by NMR spectroscopy. Incubation of either lactam in CD_3OD in the presence of CD_3ONa at room temperature in an NMR tube resulted in the appearance of the other stereoisomer, without appreciable decomposition. The reaction was judged to have reached equilibrium after a period of 7 days, when no further change in the ratio of isomers was noted. The ratio of the integral of the C-8α proton resonance of the *cis* isomer at 1.95 ppm, which was unobscured, to the integral of the multiplet at 2.3 ppm, which contained two non-exchangeable hydrogens of the *trans* isomer and one of the *cis* isomer, gave a thermodynamic equilibrium composition for **6** to **7** of 3:1. Incubation of the lactams in benzyl alcohol in the presence of sodium benzyloxide afforded a 4:1 *cis*:*trans* mixture of benzyl esters **8** and **9**. The benzyl esters will find particular utility in coupling reactions with amino acids due to the ease of unmasking the free carboxyl function (Scheme 3).

Stereoselective Route to XaaPro Analogs and Description of the Synthesis of PhePro Analog 11. The lactam **6** is a mimic for the dipeptide GlyPro constrained to the type VI turn conformation. Stereospecific replacement of the C-6 hydrogen atom of compound **6** with a functional group R would result in a new lactam whose structure mimics a constrained XaaPro dipeptide, where Xaa is the amino acid at the $i + 1$ position of the turn, as in **II** (Figure 1). The selection of the specific functional group R would be made to duplicate the side chain of the Xaa residue. In view of the importance of amino acid side-chain−receptor interactions in determining the selectivity and affinity of biologically active peptides, the development of an efficient synthetic route to such compounds became a prime objective.

Scheme 3



(a) $C_6H_5CH_2OH$, Na, RT, 24 h; (b) (i) CF_3CO_2H, RT (ii) $Me_2NCH(OMe)_2$, reflux, 6 h. (c) (i) $KN(TMS)_2$, -78 °C; (ii) $C_6H_5CH_2Br$



Graphical summary of prominent NOE's observed for compound **11**

Alkylation of the enolate of the lactam **6** was considered to be the most expedient route to XaaPro analogs. The alkylation reaction would be most straightforward if the acidic carboxamide hydrogen of compound **6** were masked during the deprotonation of the hydrogen of C-6. Vedejs and co-workers have shown that enolates of *N*,*N*-dimethylformamidino amino acid esters can be treated with various alkyl halides to generate α-substituted *N*,*N*-dimethylformamidino amino acid esters.[30] The formamidine functionality could be later removed under mild conditions to generate the free amino analog of the alkylated amino acid.[30] Inspired by these results, we endeavored to prepare the formamidine derivatives of lactams such as **6** and attempt their alkylation.

Removal of the carbamate function of lactam **6** was achieved with trifluoroacetic acid in CH_2Cl_2. The crude amine salt was then treated with an excess of *N*,*N*-dimethylformamide dimethyl acetal under reflux for 6 h

(29) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Sterochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; p 727.

(30) Vedejs, E.; Fields, S. C.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 11612−11613.

to afford a single formamidine product, according to the characteristics of the ^{1}H NMR spectrum. The spectrum of the product displayed a double doublet at δ 4.02 ppm (J = 11.4 and 6.9 Hz), a signal consistent with an axial C-6 hydrogen of the *cis* formamidine derivative **10** (Scheme 3). The absence of the isomeric *trans* formamidine in the reaction mixture signified that epimerization at C-6 did not take place during the sequence of transformations. The configuration of the amidine imine bond was not determined, but was assumed to be *trans*.

Treatment of the potassium enolate of amidine **10** in THF with benzyl bromide afforded a single product, according to the crude ^{1}H NMR spectrum. The ^{1}H NMR spectrum of the product isolated after chromatography lacked a signal for the C-6 proton; in addition, an unusually shielded signal, whose splitting pattern was consistent with a pseudoaxial hydrogen on the six-membered ring, was detected at 1.01 ppm. The ^{13}C NMR spectrum of the product displayed a total number of carbons equal to that expected for the alkylation product. The spectral characteristics of the alkylation product were in accord with an α-benzylindolizidinone, whose six-membered ring assumed a pseudochair conformation, as in *cis*-lactam **6**.

The stereochemical course of the benzylation was determined through analysis of the COSY and NOESY spectra of the alkylation product. First the ^{1}H resonances of the product were assigned to the five- or six-membered ring spin systems using through-bond connectivities revealed in the COSY spectrum. Through-space connectivities between the ^{1}H resonances were then extracted from the NOESY spectrum, and stereospecific assignments consistent with the distance restraints were made. For instance a strong NOE crosspeak was observed between the upfield signal at 1.01 ppm and the signal at 1.44 ppm, assigned to one of the C-1 protons of the five-membered ring. The upfield signal was thus assigned to the C-8β proton, because the C-8 hydrogens are the only six-membered ring hydrogens sufficiently close to C-1 to display NOEs, and due to its splitting pattern. According to the crystal structure of lactam **6**, the distance between the C-8β proton and the C-1β proton is 2.45 Å (Figure 2); hence the 1.47 ppm resonance was ascribed to the C-1β proton.

The 1.01 ppm signal also displayed a NOESY crosspeak to a multiplet at 3.33 ppm, assigned to the benzyl hydrogens on the basis of strong NOEs to the phenyl hydrogens. In the structure of the (6*S*,8a*R*) stereoisomer of the alkylation product, the distance between the C-8β hydrogen and the benzyl methylene carbon is 2.58 Å; in the structure of the alternative (6*R*,8a*R*) stereoisomer, the analogous distance is 4.10 Å. The NOE between these sets of signals is more consistent with a compound with (6*S*,8a*R*) stereochemistry, as in compound **11** (Scheme 3), than with (6*R*,8a*R*) stereochemistry. The absence of NOE crosspeaks between the 1.01 ppm resonance and the formamidine resonances further confirmed the stereochemical assignment. The shielding properties of the aromatic ring would also explain the significant upfield shift of the C-8β proton of lactam **11** relative to the analogous hydrogen of lactam **10** ($\Delta\delta$ = 1.6 ppm).

Exclusive formation of the (6*S*,8a*R*) stereoisomer of lactam **11** resulted from stereoelectronically favored pseudoaxial attack of the electrophile onto the planar enolate of formamidine **10**. The stereochemistry of the alkylation product is analogous to that of a natural L-Phe L-Pro dipeptide. It is anticipated that other electrophiles would afford alkylated lactams with identical stereochemistry, yielding an unlimited series of constrained XaaPro dipeptide mimics. The formamidine functionality is easily removed under mildly acidic or basic conditions that are compatible with many common protecting groups.

In summary the outlined stereoselective synthetic scheme will afford access to a host of novel, highly functionalized dipeptide mimics for analysis of peptide conformation−activity relationships. The evaluation of the biological properties of several of these mimics is currently under investigation.

Experimental Section

General. Unless otherwise noted, all starting materials and solvents were obtained from commercial suppliers and used without further purification. Dimethylformamide (DMF) was distilled from CaH_2 under reduced pressure directly before use. Tetrahydrofuran (THF) and ether (Et_2O) were distilled just prior to use from sodium/benzophenone, and dichloromethane (CH_2Cl_2) was distilled from P_2O_5. Benzene was distilled from sodium, and methanol was distilled from magnesium. Reactions were carried out under a dry nitrogen atmosphere in glassware that had been flame- or oven-dried (T > 100 °C) overnight.

^{1}H and ^{13}C NMR spectra were recorded at 300 or 600 MHz, using $(CH_3)_4Si$ as an internal standard. COSY and NOESY spectra were recorded with 2048 by 512 data points and were zero filled to 2K × 2K sizes. A mixing time of 350 ms was used for the NOESY spectra.

Column chromatography was performed on silica gel (Merck reagents silica gel 60, 230−400 mesh ASTM). Thin layer chromatography (TLC) was carried out on Analtech Uniplate silica gel plates with a 0.25 mm coating containing fluorescent indicator. Spots were visualized using ninhydrin, phosphomolybdic acid, iodine, or UV light.

Molecular mechanics calculations and theoretical and structural analyses were performed with the Quanta package using the CHARMM force field.

(*R*)-(−)-*N*-(Benzyloxycarbonyl)-2-(2′-propenyl)proline. To an ice-cooled solution of amino acid hydrochloride **1**[19] (6.54 g, 34.2 mmol) and triethylamine (14.25 mL, 102.7 mmol) in 40 mL of CH_3CN/H_2O (1:1) was added dropwise a solution of triethylamine (4.75 mL) and benzyl chloroformate (9.8 mL, 68.5 mmol). The reaction mixture was then stirred at room temperature for 4 days. The acetonitrile was removed under reduced pressure, and the remaining aqueous solution was adjusted to pH 8−9 with saturated sodium bicarbonate, washed three times with ether, acidified to pH 1 with 6 N HCl, and then extracted with three portions of ether. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give 6.6 g (67%) of the acid as a dark orange oil: $[\alpha]^{25}_D = -18.0°$ (*c* 0.9, $CHCl_3$); IR (KBr) 3470, 3070, 2980, 2881, 2600, 1707, 1415, 1357, 1215, 1176, 1116, 920, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) *cis* + *trans* rotomers (1:1) δ 7.32 (m, 5H), 5.67 (m, 1H), 5.12 (m, 4H), 3.68, 3.78 (2 × m, 1H), 3.43 (m, 1H), 2.92, 3.02 (2 × m, 1H), 2.6, 2.72 (2 × m, 1H), 1.85, 2.05, 2.20, 2.35 (4 × m, 4H); ^{13}C NMR ($CDCl_3$) *cis* + *trans* rotomers (1:2) δ 176.4, 155.8, 136.21 (C Ar), 132.63, 132.1, 128.5, 128.4, 128.1, 127.9, 127.8, 127.6, 127.5, 126.9, 119.8, 119.4, 69.0, 67.5, 67.3, 49.2, 48.8, 39.0, 37.9, 35.0, 22.9, 22.5.

(*R*)-(−)-*N*-(Benzyloxycarbonyl)-2-(2′-propenyl)proline Methyl Ester (2). A fresh solution of diazomethane was made by adding 30 mL of a 50% KOH solution to a solution of nitrosomethylurea (10 g, 136.8 mmol) in 100 mL of ether. The reaction was stirred for 30 min. The ether layer was separated and added dropwise to an ice-cooled solution of crude acid from the previous procedure (6.6 g, 22.8 mmol) in 60 mL of ether until the color of the reaction mixture turned from orange to yellow. The solution was then stirred at room temperature for an additional 15 min, the reaction was quenched with acetic

acid to destroy excess diazomethane, and the solution was washed three times with water and evaporated under reduced pressure to give a brown oil. Chromatography of the oil on silica gel eluting with hexane/ethyl acetate (3:1) gave 6.0 g (87%) of ester **2** as a yellow oil: $[\alpha]^{25}_D = -19.2°$ (*c* 0.7, $CHCl_3$); IR (KBr) 3059, 2955, 2883, 1737, 1701, 1410, 1356 cm^{-1}; ^1H NMR ($CDCl_3$) *cis* + *trans* rotomers (1:2) δ 7.34 (m, 5H), 5.71 (m, 1H), 5.13 (m, 4H), 3.70, 3.47 (2 × s, 3H), 3.70, 3.47 (2 × m, 2H) 2.90, 3.11 (2 × m, 1H), 2.64 (m, 1H), 1.85, 2.09 (2 × m, 4H); ^{13}C NMR ($CDCl_3$) *cis* + *trans* rotomers (1:2) δ 174.5, 154.2, 136.9, 136.3, 133.2, 132.9, 128.4, 128.3, 128.1, 128.0, 127.7, 127.5, 119.1, 119.0, 68.0, 67.0, 66.5, 52.3, 52.1, 49.1, 48.2, 39.3, 38.0, 37.0, 35.5, 23.0, 22.5. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 64.59; H, 7.00; N, 4.12. Found: C, 64.19; H, 6.70; N, 3.74.

(*R*,*S*)-*N*-(Benzyloxycarbonyl)-2-(2′-propenyl)proline Methyl Ester (2). To a solution of *N*-(benzyloxycarbonyl)-proline methyl ester (21.1 g, 80.0 mmol) and allyl iodide (30.0 g, 178.0 mmol) in THF (500 mL) was added dropwise with stirring a solution of potassium hexamethyldisalizide (25.0 g, 125 mmol) in toluene (250 mL) at −78 °C. A cloudy yellow solution formed immediately. After the mixture was stirred at this temperature for 1 h, the reaction was quenched with water (300 mL) the solution was and allowed to warm to room temperature. The crude reaction mixture was extracted with three portions of ether (150 mL), and the organic extracts were combined and washed with saturated brine and dried over $MgSO_4$. After filtration and removal of solvent, the crude product was distilled in a Kugelrohr apparatus to afford the racemic ester **2** as an oil (20.4 g, 84%).

(R)-(−)-*N*-(Benzyloxycarbonyl)-2-(2′-oxoethyl)proline Methyl Ester (3). To a solution of methyl ester **2** (1.0 g, 3.3 mmol) in 60 mL of methanol/water (2:1) was added 0.25 mL of a solution of OsO_4 in *tert*-butyl alcohol (2.5% w/w). The mixture was stirred for 30 min until a dark brown color developed and then was treated with sodium periodate (2.06 g, 9.9 mmol) in small portions over a period of 30 min under vigorous stirring, resulting in a white precipitate. After an additional stirring period of 2 h, the solution was poured onto 150 mL of water and extracted five times with ethyl acetate. The organic extracts were dried over anhydrous $MgSO_4$, filtered through a layer of anhydrous $MgSO_4$, and then evaporated under reduced pressure to give 0.8 g (80%) of aldehyde **3** as a brown oil: $[\alpha]^{25}_D = -20.6°$ (*c* 1.0, $CHCl_3$); IR (KBr) 2955, 2883, 1739, 1705, 1410, 1356, 1216, 1170, 1053 cm^{-1}; ^1H NMR ($CDCl_3$) *cis* + *trans* rotomers (1:2) δ 9.80, 9.71 (s, 1H), 7.26 (m, 5H), 5.12 (m, 2H), 3.71, 3.56, 3.47 (3 × m, 5H), 3.30-2.97 (m, 2H), 2.29, 1.96 (2 × m, 4H); ^{13}C NMR ($CDCl_3$) δ 199.5, 199.3, 173.5, 173.3, 154.5, 153.7, 136.4, 135.8, 128.7, 128.5, 128.4, 128.3, 127.9, 127.8, 127.6, 67.4, 67.0, 66.5, 65.7, 52.7, 52.5, 48.9, 48.5, 48.2, 47.7, 38.2, 37.0, 23.1, 22.6.

(*R*)-(−)-(*E* and *Z*)-*N*-(Benzyloxycarbonyl)-2-(3′-(*N*-(*tert*-butoxycarbonyl)amino-3′-carboethoxy-2′-propenyl)proline Methyl Ester (4E, 4Z). To a solution of LDA (1.51 mmol) in 4.0 mL of THF/hexane (1:3) was added dropwise a solution of *N*-(*tert*-butoxycarbonyl)-1-amino-1-(carboxymethyl)phosphonic acid dimethyl ethyl ester (0.537 g, 1.47 mmol) in 3.0 mL of THF. The temperature was allowed to warm to −10 °C to dissolve the precipitate. The resulting orange solution was again cooled to −78 °C and then treated with a solution of aldehyde **3** (0.440 g, 1.44 mmol) in 3.0 mL of THF. The mixture was warmed to room temperature and stirred for an extra 2 h. The solvent was evaporated under reduced pressure and the residue dissolved in ethyl acetate. The organic layer was then washed with water, dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give a crude brown oil. Chromatography column on silica eluting with hexane/ethyl acetate (3:1) afforded the alkene as *Z*/*E* isomers (2:1) in 60% yield. **4Z**: 0.16 g (40%); R_f 0.13; $[\alpha]^{25}_D = -18.8°$ (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 3670,3545, 3423, 3040, 2984, 2955, 2885, 1726, 1709, 1691,1483, 1454,1437, 1354, 1259, 1163, 910 cm^{-1}; ^1H NMR ($CDCl_3$) *cis* + *trans* rotomers (1:1) δ 7.35 (m, 5H), 6.49, 6.36 (2 × t, J = 10 Hz, 1H), 5.23−4.88 (m, 2H), 3.76, 3.72, 3.42 (3 × s, 6H), 3.54 (m, 2H), 3.17 (dd, J = 14 Hz, J = 8 Hz, 1H), 2.92 (dd, J = 14 Hz, J = 8 Hz, 1H), 2.12−2.09 (m, 2H), 1.92−1.85 (m, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) *cis* + *trans* rotomers (1:1) δ 174.0, 173.8, 165.2, 165.0, 154.8, 154.1, 153.4, 153.2, 136.6, 136.0, 130.3, 129.5,128.6, 128.4, 128.2, 127.8, 127.6, 80.7, 80.5, 67.9, 67.2, 66.9, 52.5, 52.3, 52.2, 49.0, 48.2, 37.7, 36.3, 34.2, 32.8, 28.1, 22.9, 22.6. **4E**: 0.08 g (20%); R_f 0.21; $[\alpha]^{25}_D = -18.2°$ (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3667, 3541, 3423, 3040, 2984, 2955, 1726, 1707, 1693, 1512, 1437, 1356, 1249, 1163, 908 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (m, 5H), 6.54 (m, 1H), 5.23−4.89 (m, 2H), 3.81, 3.76, 3.71, 3.45 (4 × s, 6H), 3.57 (m, 2H), 3.40 (m, 1H), 3.25 (dd, J = 15 Hz, J = 8 Hz, 1H), 2.16 (m, 2H), 1.92 (m, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) *cis* + *trans* rotomers (1:1) δ 174.3, 174.2, 164.6, 164.4, 154.2, 152.9, 137,5, 136.9, 128.8, 127.7, 127.6, 127.4, 127.1, 123.9, 123.8, 80.6, 80.5, 68.4, 67.7, 66.6, 52.2, 52.1, 49.1, 48.3, 37.4, 36.3, 33.6, 32.5, 28.1, 23.0, 22.5. Anal. Calcd for $C_{25}H_{34}N_2O_8$: C, 58.99; H, 7.00; N, 5.71. Found: C, 58.79; H, 6.65; N, 6.21.

(2*R*,3′*R*,*S*)-2-(3′-(*N*-(*tert*-Butoxycarbonyl)amino)-3′-carboethoxypropyl)proline Methyl Ester (5). The *E*/*Z* mixture of alkenes **4E** and **4Z** (0.0525 g, 0.11 mmol) was dissolved in 2.0 mL of methanol and nitrogen was bubbled through. To this was added Pd/C (10%, 0.008 g), and the mixture was flushed again with nitrogen. The solution was stirred for 45 min under a hydrogen atmosphere before being filtered through Celite to remove the catalyst. The solvent was then removed under reduced pressure to give 0.0355 g (93%) of amine **5** as a clear oil: $[\alpha]^{25}_D = -17.2°$ (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.85, 5.57 (2 × d, J =12 Hz, 1H), 4.15 (m, 1H), 3.69 (s, 6H), 2.92 (m, 2H), 2.48 (m, 1H), 2.09 (m, 1H), 1.81−1.51 (m, 6H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 177.1, 172.6, 155.5, 105.3, 68.8, 68.7, 61.2, 53.3, 52.4, 46.6, 46.5, 36.2, 34.9, 28.3, 25.2, 14.1.

(6*R*,8a*R*)- and (6*S*,8a*R*)-*N*-(*tert*-Butoxycarbonyl)-6-amino-8a-carboxyindolizidin-5-one Methyl Ester (6 and 7). A solution of amine **5** (0.550 g, 1.54 mmol) in 20 mL of toluene and 0.8 mL of triethylamine was refluxed for 48 h under a nitrogen atmosphere. The solvent was removed under reduced pressure to give 0.5 g of a yellow oil. Chromatography on silica gel eluting with hexane/ethyl acetate (1:2) provided the bicyclic lactams **6** and **7** as crystalline solids. **6:** 0.07 g (50%); R_f 0.31; mp 89−92 °C; $[\alpha]^{25}_D = -20.0°$ (*c* 0.6, $CHCl_3$); IR ($CHCl_3$), 3672, 3428, 2979, 2897, 1735, 1698, 1651, 1494, 1440, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.22 (br s, 1H), 4.06 (ddd, J =13.0, 6.7, 7.3 Hz, 1H), 3.75 (s, 3H), 3.63 (m, 1H), 3.54 (dt, J = 11.0 Hz and J = 3 Hz, 1H), 2.58 (ddd, J = 13.8, 3.3, 3.3 Hz, 1H), 2.50 (m, 1 H), 2.40 (dd, J = 14.0, 5.3 Hz, 1H), 1.92 (dddd, J = 11.3, 7.3, 3.3, 3.3 Hz, 1H), 1.80−1.65 (m, 3H), 1.49, (m, 1H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.7, 167.7, 156.1, 79.5, 70.1, 52.9, 51.8, 45.0, 37.6, 30.7, 28.2, 26.8, 20.6. Anal. Calcd for $C_{15}H_{24}N_2O_5 \cdot H_2O$: C, 54.52; H, 7.95; N, 8.48. Found: C, 54.78; H, 7.80; N, 8.38.

7: 0.140 g (20%); R_f 0.47; $[\alpha]^{25}_D = -18.2°$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3695, 3433, 2984, 2957, 1736, 1709, 1649, 1495, 1442, 1167 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.63 (br s, 1H), 3.95 (ddd, J = 7.6, 7.6, 5.6 Hz, 1H), 3.75 (s, 3H), 3.71 (dt, J = 11.0, 3.0 Hz, 1H), 3.50 (m, 1H), 2.53 (ddd, J = 14.0, 7.3, 7.3 Hz, 1H), 2.48 (m, 1H), 2.36 (dddd, J = 14.0, 7.6, 7.6, 7.6 Hz, 1H), 1.95−1.76 (m, 4H), 1.60 (dddd, J = 14.0, 7.6, 7.6, 7.6 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.8, 168.7, 155.6, 79.5, 67.9, 53.0, 49.3, 45.7, 39.3, 29.8, 28.3, 26.4, 21.6.

(6*R*,8a*R*)- and (6*S*,8a*R*)-*N*-(*tert*-Butoxycarbonyl)-6-amino-8a-carboxyindolizidin-5-one Benzyl Ester (8 and 9). To a solution of ester **7** (1.00 g, 3.4 mmol) in benzyl alcohol (50 mL) was added a piece of sodium metal (0.01 g, 0.5 mmol). The mixture was stirred for 24 h at rt, then poured into 10% aqueous NH_4Cl, and then extracted with $CHCl_3$. The organic layer was washed with water and saturated NaCl and dried with $MgSO_4$. Excess benzyl alcohol and other volatile liquids were removed under reduced pressure to afford a yellow oil of a mixture of benzyl esters **8** and **9**. Chromatography on silica gel eluting with hexanes:ethyl acetate (3:1) afforded esters **8** and **9** as oils. **8:** 0.79 g (60%); $[\alpha]^{25}_D = -18.0°$ (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3650, 2980, 1738, 1700, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.21−7.23 (m, 5H), 5.10 (s, 2H), 5.03 (br s, 1H), 3.96 (ddd, J = 11.4, 5.7, 5.7 Hz, 1H), 3.40−3.55 (m, 2H), 2.52 (ddd, J = 13.0, 3.3, 3.3 Hz, 1H), 2.43 (dd, J = 12.0, 6.9 Hz, 1H), 1.90 (m, 1H), 1.65−1.72 (m, 4H), 1.43 (s, 9H), 0.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.5, 168.2, 156.5, 135.6, 129.1, 129.0, 128.6, 80.1, 70.5, 68.0, 52.2, 45.5, 38.1, 31.2, 28.7, 27.2, 21.1.

9: 0.077 g (20%); $[\alpha]^{25}_D = -20.0°$ (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3700, 3430, 2982, 1732, 1710, 1659 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23−7.33 (m, 5H), 5.59 (br s, 1H), 5.18 (d, J = 12.3 Hz, 1H), 5.12 (d, J = 12.3 Hz, 1H), 3.94 (m, 1H), 3.70 (m, 1H), 3.52 (m, 2H), 2.30−2.52 (m, 3H), 1.53−1.87 (m, 4H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.0, 168.7, 155.6, 135.1, 128.5, 128.6, 128.2, 79.5, 68.0, 67.6, 49.4, 45.7, 39.2, 29.7, 28.3, 26.4, 21.5.

(6*R*,8a*R*)-6-(((*N*,*N*-Dimethylamino)methylene)amino)-8a-carboxyindolizidin-5-one Methyl Ester (10). To a solution of ester **6** (0.090 g, 0.31 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (0.18 mL, 2.44 mmol), and the solution was stirred at rt. After 2 h, CH_2Cl_2 and trifluoroacetic acid were removed under reduced pressure to give a yellowish oil. The crude amine salt was suspended in dimethylformamide dimethyl acetal (0.5 mL, 3.76 mmol) and the solution refluxed under N_2 for 6 h. Columm chromatography on silica eluting with a solution of CH_2Cl_2 and MeOH (9:1) afforded 0.074 g of a colorless oil of **10** (65%): IR ($CHCl_3$) 2980, 1730, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47 (s, 1H), 3.75 (s, 3H), 3.66−3.39 (m, 3H), 2.90 (s, 6H), 2.63 (ddd, J = 13.8, 3.3, 3.3 Hz, 1H), 2.40 (dd, J = 10.8, 5.8 Hz, 1H), 2.09 (m, 1H), 1.95 (m, 1H), 1.82−1.72 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 173.2, 166.3, 156.6, 70.1, 56.8, 53.3, 45.5, 37.6, 30.9, 25.6, 20.7.

(6*S*,8a*R*)-6-Benzyl-6-(((*N*,*N*-dimethylamino)methylene-)amino)-8a-carboxyindolizidin-5-one Methyl Ester (11). Formamidine **10** (0.20 g, 0.78 mmol) and benzyl bromide (0.46 mL, 3.92 mmol) were dissolved in dry THF (15 mL) and cooled to −78 °C under N_2. A solution of potassium hexamethyldisilazide (0.18 g in 1 mL of THF) was then added dropwise to the solution. After 1 h, the reaction was quenched with 0.2 mL of an aqueous 10% NH_4Cl solution. Volatile material was removed under reduced pressure to give an oil that was subjected to flash colum chromatography, eluting with CH_2Cl_2 to afford 0.11 g (43%) of formamidine **11** as a white foam: IR ($CHCl_3$) 2985, 1734, 1647, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (s, 1H), 7.26−7.21 (m, 5H), 3.74 (m, 1H), 3.65 (s, 3H), 3.58 (m, 1H), 3.33 (d, J = 12.9 Hz, 2H), 2.84 (s, 6H), 2.25 (dd, J = 12.1, 6.7 Hz, 1H), 2.17 (ddd, J = 14.4, 4.7, 4.7 Hz, 1H), 1.97 (ddd, J = 14.4, 4.3, 4.3 Hz, 1H), 1.83 (m, 1H), 1.66−1.62 (m, 2H), 1.47 (ddd, J = 12.6, 12.6, 7.8 Hz, 1H), 1.01 (ddd, J = 13.3, 12.7, 3.6, 1H); ^{13}C NMR ($CDCl_3$) δ174.5, 172.5, 154.32, 138.2, 130.5, 127.8, 126.2, 69.0, 63.5, 52.4, 47.3, 45.4, 38.6, 34.1, 29.5, 20.8.

Acknowledgment. We are grateful to the R. A. Welch Foundation, the American Heart Association—Texas Affiliate (Grant 95G-448), American Cyanamid, and the University of Houston for financial support.

Supporting Information Available: ^1H NMR spectra of **3**, **5**, **7**, **8**, and **9**, ^{13}C spectra of **10** and **11**, and COSY and NOESY spectra of the benzyl derivative of **11** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960012W