# Incorporation of Ahc into Model Dipeptides as an Inducer of a β-Turn with a Distorted Amide Bond. Conformational Analysis

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The proline residue of dipeptides Ser-Pro and Pro-Ser has been replaced by 7-azabicyclo[2.2.1]-heptane-1-carboxylic acid (Ahc), a conformationally restricted analogue of proline that is capable of mimicking distorted amides. The conformational analysis of the new peptides in the solid state revealed that the Ahc-Ser sequence displays a type I β-turn, which includes a distorted amide bond. In contrast, the Ser-Ahc sequence exists in a nonfolded structure.

## Introduction

The design and synthesis of molecules to mimic biological events represents an area of increasing interest in the field of bioorganic chemistry and, in particular, the study of peptidomimetics is a topic that has received a great deal of attention.[1] The development of peptidomimetics has been increased by the appearance of new nonproteinogenic α-amino acids. These compounds confer attractive features on these new biomolecules and have helped to increase our knowledge of the conformational, topochemical, and electronic properties of these systems.[2] In general, α-amino acids have a high conformational flexibility, and there are several ways to stabilize certain structural conformations.[3] Among other possibilities, an excellent method involves the introduction of bridges between different parts of the α-amino acid. These new conformationally restricted amino acids, when incorportated into peptides, can stabilize β-turn conformations.[4]

On the other hand, it is well-known that the conversion between *cis* and *trans* amide conformations, among other processes, is necessary for protein folding. However, it is difficult to achieve such conversion since this process involves distortion of the planarity of the amide bond.[5] In this respect, Goodman and co-workers synthesized peptides that mimic the tilted or twisted amide structures—the transition state between *cis* and *trans* amide conformations—by incorporation of the aziridine residue in four dipeptides.[5a]

Among the proteinogenic amino acids, serine and proline are the most frequent residues included within turns in proteins and, indeed, the Pro-Ser or Ser-Pro sequences have been the subject of numerous studies.[6] In this context, the incorporation of conformationally restricted analogues of proline has often led to successful replacements.[7]

The Pro-Ser sequence has been widely studied in both the solid and solution state, with β-turns found for this structure.[8] Nevertheless, the only references regarding the dipeptide Ser-Pro concern its study in solution. The conformational heterogeneity of Xaa-Pro peptides leads to difficulties in the elucidation of this type of structure using NMR spectroscopy, a situation that is mainly due to the complexity caused by the *cis*−*trans* isomerization of the proline.[9]

The structural distortion of an amide plays an important role in chemical and biological processes,[10] and there are very few peptides that incorporate ground-state amides that are distorted out of plane.[5] With this situation in mind, the work described here involved an investigation into the replacement of Pro in the sequences

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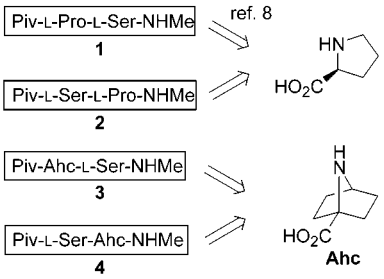
**Scheme 1. Retrosynthetic Analysis of Dipeptides**




Ser-Pro and Pro-Ser by the 7-azabicyclo[2.2.1]heptane carboxylic acid (Ahc), a conformationally restricted analogue of Pro[11,12] that is capable of mimicking distorted amides, in view of understanding the *cis*−*trans* isomerization of the amide bond. With this aim, and given the lack of information regarding the solid state of the Ser-Pro dipeptide, we first synthesized the Piv-L-Ser-L-Pro-NHMe (**2**) sequence. This novel system, along with the previously reported Piv-L-Pro-L-Ser-NHMe (**1**) sequence, were compared with the similar restricted systems Piv-L-Ser-Ahc-NHMe (**4**) and Piv-Ahc-L-Ser-NHMe (**3**), respectively, in order to establish the similarities and differences in the solid state (Scheme 1).

## Results and Discussion

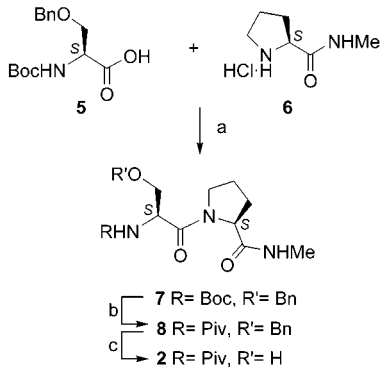
**Synthesis of Piv-L-Ser-L-Pro-NHMe (2).** This peptide was synthesized using the coupling reaction between Boc-L-Ser(OBn)-OH (**5**) and L-Pro-NHMe·HCl[13] (**6**). The coupling was carried out with *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU)[14] and diisopropylethylamine (DIEA) in acetonitrile, to give Boc-L-Ser(OBn)-L-Pro-NHMe (**7**) in an excellent yield. Removal of the Boc group and further acylation with pivaloyl chloride (PivCl) in the presence of DIEA gave the peptide **8**. The deprotection of the benzyl ether of **8** by standard hydrogenolysis gave the desired dipeptide Piv-L-Ser-L-Pro-NHMe (**2**) (Scheme 2).

**Synthesis of Piv-Ahc-L-Ser-NHMe (3) and Piv-L-Ser-Ahc-NHMe (4).** Ahc was synthesized using our previously published route from methyl 2-benzamidoacrylate.[11] The major difficulty in the synthesis of the restricted peptides concerns the significant steric interaction involving the quaternary amino acid, a situation that leads to low reactivity.[15] For the synthesis of Piv-Ahc-L-Ser-NHMe (**3**), Ahc was transformed into the corresponding protected amino acid Boc-Ahc-OBn (**9**) by following Rapoport's procedure.[16] This compound was converted into Piv-Ahc-OBn (**10**) by removal of the Boc group and subsequent acylation with PivCl. Hydrogenolysis of the resulting benzyl ester **10** gave Piv-Ahc-OH (**11**) (Scheme 3).

We also carried out a new synthesis of L-Ser(OBn)-NHMe·HCl (**13**) starting from the convenient protected serine **5**.[17] In this procedure, serine **5** was transformed into the corresponding amide **12**, using TBTU, and the Boc group was hydrolyzed to give **13** (Scheme 3).

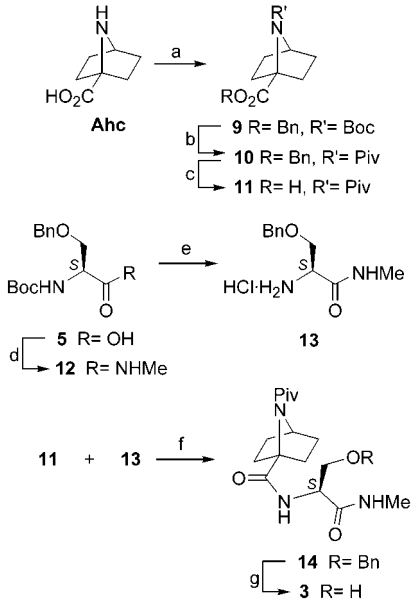
The coupling reaction between **11** and **13** was carried out with TBTU and DIEA to give Piv-Ahc-L-Ser(OBn)-

**Scheme 2. Synthesis of Piv-L-Ser-L-Pro-NHMe (2)[a]**




[a] (a) TBTU, DIEA, $CH_3CN$, rt, 86%. (b) (i) 1 N HCl, THF, rt. (ii) PivCl, DIEA, DMAP, $CH_2Cl_2$, rt, 85%. (c) $H_2$, Pd−C, MeOH, rt, 95%.

**Scheme 3. Synthesis of Piv-Ahc-L-Ser-NHMe (3)[a]**




[a] (a) Reference 16: (i) *p*-TsOH, BnOH, benzene. (ii) $(Boc)_2O$, DIEA, MeOH, 96%. (b) (i) 1 N HCl, THF, rt. (ii) PivCl, TEA, DMAP, $CH_2Cl_2$, rt, 85%. (c) $H_2$, Pd−C, MeOH, rt, 100%. (d) TBTU, DIEA, $CH_3CN$, $MeNH_2$·HCl, rt, 84%. (e) 1 N HCl, THF, rt, 100%. (f) TBTU, DIEA, $CH_3CN$, rt, 60%. (g) $H_2$, Pd−C, MeOH, rt, 99%.

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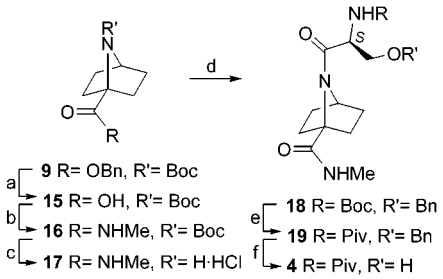
**Scheme 4. Synthesis of Piv-L-Ser-Ahc-NHMe (4)[a]**



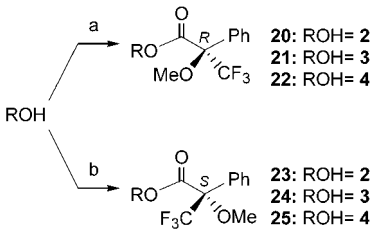

[a] (a) $H_2$, Pd−C, MeOH, rt, 100%. (b) TBTU, DIEA, $CH_3CN$, $MeNH_2$·HCl, rt, 88%. (c) 1N HCl, THF, rt, 100%. (d) Boc-L-Ser(OBn)-OH (**5**), TBTU, DIEA, $CH_3CN$, rt, 90%. (e) (i) 1 N HCl, THF, rt. (ii) PivCl, DIEA, DMAP, $CH_2Cl_2$, rt, 86%. (f) $H_2$, Pd−C, MeOH, rt, 87%.

NHMe (**14**) in good yield. The required dipeptide Piv-Ahc-L-Ser-NHMe (**3**) was obtained by hydrogenolysis with Pd−C in MeOH (Scheme 3).

The synthesis of Piv-L-Ser-Ahc-NHMe (**4**) was achieved by following the same procedure as employed in the synthesis of the nonrestricted peptide Piv-L-Ser-Pro-NHMe (**2**). In this way, ester **9** was transformed into methylamide **16** by standard hydrogenolysis of the benzyl ester to give acid **15** and subsequent amide formation was performed with TBTU. The hydrolysis of the Boc group in amide **16** gave compound **17**, which was coupled with Boc-L-Ser(OBn)-OH (**5**) using TBTU to give Boc-L-Ser(OBn)-Ahc-NHMe (**18**) in good yield. Removal of the Boc group, followed by further acylation with PivCl and DIEA, gave the peptide **19**. Deprotection of the benzyl ether in peptide **19** led to the desired dipeptide Piv-L-Ser-Ahc-NHMe (**4**) (Scheme 4).

**Determination of Enantiomeric Purity**. To confirm the enantiomeric purity of these peptides, and to corroborate that enantiomerization had not taken place in any step, we synthesized the corresponding Mosher esters. It is worth noting that the dipeptide Piv-L-Ser-L-Pro-NHMe (**2**) exists as two conformers due to *cis*−*trans* isomerization of the amide bond in the proline residue—as reported for other Ser-Pro dipeptides (Ac-L-Ser-L-Pro-NHMe).[9b,f] Given this situation, the $^1$H NMR spectrum of dipeptide **2** at room temperature shows a ratio of 10:1 between the two isomers (coalescence temperature is 333 K). In accordance with the protocol described in the literature,[18] peptide **2** was coupled with (*R*)-(+)-methoxytrifluorophenylacetic acid [(*R*)-(+)-MTPA], in the presence of DCC and DMAP, to give the Mosher ester **20**. Analysis of the $^1$H NMR and $^{19}$F NMR spectra of ester **20** showed two signals corresponding to the *cis*−*trans* isomers of the proline amide in a 10:1 ratio. In any case, to confirm that compound **2** was essentially enantiomerically pure, we determined the cross-contamination by conversion of this compound into its Mosher ester derivative **23**. This was achieved by coupling **2**, under the same conditions, with (*S*)-(−)-methoxytrifluorophenylacetic acid [(*S*)-(−)-MTPA] and determining the purity, which was found to be identical to that described above. Thus, we can confirm that the enantiomeric purity of peptide **2** is >95%, since the signals for only one product were observed in the NMR spectra. The same synthetic protocol was carried out with the peptide Piv-Ahc-L-Ser-NHMe (**3**). Reaction of **3** with [(*R*)-(+)-MTPA] and [(*S*)-(−)-MTPA] gave the corresponding esters **21** and **24**, respectively. As in peptide **3**, analysis of the spectra of the Mosher esters **21** and **24** showed the absence of the *cis* conformer in the Ahc amide, a situation forced by the Piv group[19] as described for its nonrestricted analogue Piv-L-Pro-L-Ser-NHMe (**1**).[8] However, the amide isomerism appears to have a lower energy barrier in the peptide Piv-L-Ser-Ahc-NHMe (**4**), since at room temperature only one type of signal was observed, and this shows splitting at 253 K in a 4:1 ratio. The Mosher protocol was carried out on peptide **4**, to give compounds **22** and **25**, and these had the same *cis*−*trans* ratio at room temperature. Therefore, in both peptides **3** and **4** we can confirm that, once again, the enantiomeric purity of the compounds is >95% (Scheme 5).

**Scheme 5. Synthesis of Mosher Derivatives[a]**




[a] (a) (R)-(+)-MTPA, DCC, DMAP, $CH_2Cl_2$, rt. (b) (S)-(−)-MTPA, DCC, DMAP, $CH_2Cl_2$, rt.

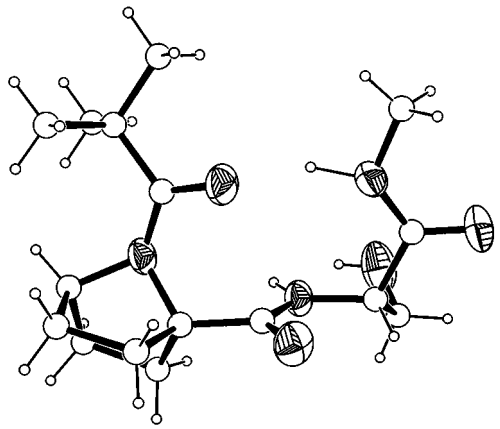


**Figure 1.** ORTEP diagram for Piv-Ahc-L-Ser-NHMe (**3**).

**Conformational Analysis in the Solid State by X-ray Diffraction.** Figure 1 shows the X-ray diffraction structure of peptide Piv-Ahc-L-Ser-NHMe (**3**).[20] The dimensions of the azabicycle skeleton in Ahc residue **A** are indicated in Figure 2. We can compare this structure, i.e. its bond distances and bond angles, with the pyrrolidine ring **B** from Piv-L-Pro-L-Ser-NHMe (**1**).[8a] The main difference is found in the bond angle $C^{\alpha}-N-C^{\delta}$, which

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(20) (a) Crystal data: $C_{16}H_{27}N_3O_4$, $M_w$ = 325.41, colourless prism of 0.55 × 0.42 × 0.4 mm, $T$ = 130 K, orthorhombic, space group $P2_1\,2_1\,2_1$, $Z$ = 4, $a$ = 10.6897(2) Å, $b$ = 11.3502(3) Å, $c$ = 14.3201(3) Å, $V$ = 1737.47(7) Å$^3$, $d_{calcd}$ = 1.244 g cm$^{-3}$, $F(000)$ = 704, $\lambda$ = 0.71073 Å (Mo, Kα), $\mu$ = 0.090 mm$^{-1}$, Nonius kappa CCD diffractometer, $\theta$ range 2.29−27.88°, 11123 collected reflections, 4058 unique, full-matrix least-squares (SHELXL97[20b]), $R_1$ = 0.0409, $wR_2$ = 0.0984, ($R_1$ = 0.0495, $wR_2$ = 0.1035 all data), goodness of fit = 1.034, residual electron density between 0.186 and −0.174 e Å$^{-3}$. Hydrogen atoms were located by mixed methods (electron-density maps and theoretical positions). (b) Sheldrick, G. M. SHELXL97. Program for the refinement of crystal structures. University of Göttingen, Germany, 1997.

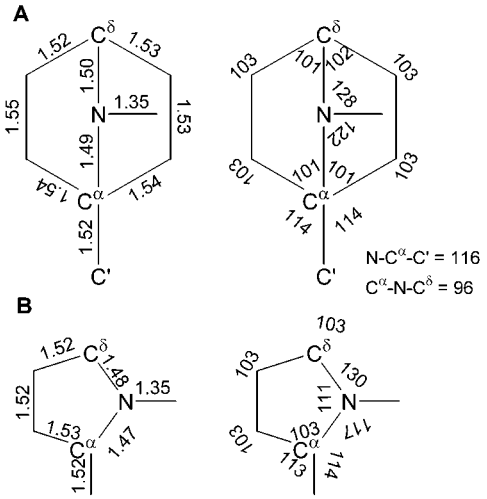


**Figure 2.** Bond distances (Å) and bond angles (deg) for the azabicycle system in the crystal molecular structure of Piv-Ahc-L-Ser-NHMe (**A**) and for the proline system in the crystal molecular structure of Piv-L-Pro-L-Ser-NHMe (**B**).

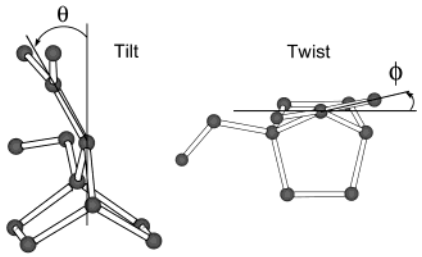


**Figure 3.** The tilt and twist angles of the amide bond in peptides containing Ahc.

has a value of 96° for the azabicycle and 111° for the proline residue. In fact, pyramidalization of the nitrogen atom is extremely strong and will undoubtedly influence the conformation of our dipeptide. The summation of the three valence angles around the nitrogen of the ideal trigonal planar nitrogen is 360°, whereas in the proline residue of the nonrestricted peptide it is 358° and in our bicycle this summation is 346°.[10h]

This characteristic of the amide is particularly interesting since the amide bond is a fundamental linkage in peptides. Few peptides are known to contain ground-state amides that are distorted out of plane by more than 4−6° about the bond torsion, for example the peptides containing the aziridine amides.[5] Other systems showing the lack of planarity of the amide groups, as the 7-azabicyclo-[2.2.1]heptane derivatives, have recently been studied.[10h] The distorted amides can be defined by the tilt and twist angles generated by the *N*-pyramidalization[21] (Figure 3). In the X-ray diffraction study of peptide **3** we found that the amide of the Ahc residue has a tilt angle of 29.2° and a twist angle of 10°.

On the other hand, on comparing our peptide with Piv-L-Pro-L-Ser-NHMe (**1**), we observed that this pyramidalization markedly influences the peptide conformation (Figure 4). In the X-ray structure of peptide **3** we observed an intramolecular hydrogen bond between PivCO and NHMe (N → O distance = 2.84 Å and H → O distance = 1.88 Å), and the torsion angles are summarized in the Table 1. These data correspond to the

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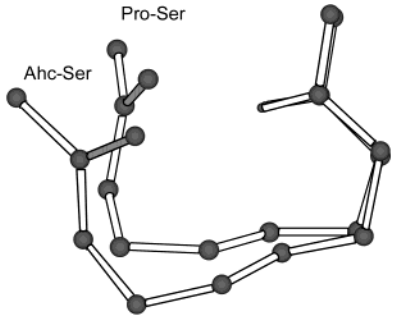


**Figure 4.** Superimposed $\beta$-turn backbones corresponding to Piv-L-Pro-L-Ser-NHMe (**1**) and Piv-Ahc-L-Ser-NHMe (**3**) in the solid state.

ideal type I $\beta$-turn,[22] and the significant differences in the angles corresponding to the $i + 1$ residue, in comparison with the nonrestricted peptide, are due to pyramidalization of the nitrogen (Figure 4). To the best of our knowledge, it is important to note that, although some peptides containing distorted amide bonds are described,[5] only one example of $\beta$-turns that include distorted amide bonds has been previously reported,[7e] therefore this report constitutes the second example on this aim. Unfortunately, we were unable to obtain monocrystalline structures from peptide **2**. Nevertheless, we could use the crystallographic data from some Ser-Pro sequences incorporated in peptidic chains. The main torsion angles for these sequences are given in Table 1. The X-ray diffraction patterns of the peptide Piv-L-Ser-Ahc-NHMe (**4**)[23] revealed two crystal structures, which have very similar conformations except for the $\psi$ angle of the $i + 2$ residue (Figure 5). Table 1 shows the torsion angles for both molecules, and these data indicate nonfolded structures. On comparing these data with the X-ray information from Ser-Pro sequences reported in the literature,[24,25] we can distinguish significant differences in the $\phi_{i+2}$ angle. Such differences can be attributed to the strain inherent in our proline analogue (Ahc), bearing in mind that the typical $\phi$ dihedral angles for nonrestricted proline are fixed at −75°.[6d]

To confirm the *N*-pyramidalization we measured the tilt and twist angles, identifying for molecule A a tilt angle of 33.6° and a twist angle of 5°, and for molecule B a tilt angle of 25° and a twist angle of 8.5°.

Moreover, both in peptide **3** and **4**, the X-ray structures confirm a *trans* disposition for the amide from proline analogue residue −Ahc−.

**Conformational Analysis in Solution.** All the dipeptides were characterized by means of $^1$H NMR, $^{13}$C NMR,

(22) (a) Venkatachalam, C. M. *Biopolymers* **1968**, *6*, 1425−1436. (b) Wilmot, C. M.; Thornton, J. M. *J. Mol. Biol.* **1988**, *203*, 221−232. (c) Ball, J. B.; Hughes, R. A.; Alewood, P. F.; Andrews, P. R. *Tetrahedron* **1993**, *49*, 3467−3478.

(23) (a) Crystal data: $C_{16}H_{27}N_3O_4$, $M_w = 325.41$, colorless prism of 0.33 × 0.2 × 0.1 mm, $T = 123$ K, monoclinic, space group $P2_1$, $Z = 4$, $a = 9.7429(5)$ Å, $b = 17.4021(9)$ Å, $c = 9.9842(6)$ Å, $\beta = 94.368(2)°$, $V = 1687.87(16)$ Å$^3$, $d_{calcd} = 1.281$ g cm$^{-3}$, $F(000) = 704$, $\lambda = 0.71073$ Å (Mo, Kα), $\mu = 0.092$ mm$^{-1}$, Nonius kappa CCD diffractometer, $\theta$ range 2.05−27.95°, 10516 collected reflections, 5600 unique, full-matrix least-squares (SHELXL97[20b]), $R_1 = 0.0804$, $wR_2 = 0.2183$, ($R_1 = 0.1188$, $wR_2 = 0.2507$ all data), goodness of fit = 1.031, residual electron density between 0.460 and −0.407 e Å$^{-3}$. Hydrogen atoms were located by mixed methods (electron-density maps and theoretical positions).

(24) Morita, H.; Gonda, A.; Takeya, K.; Itokawa, H.; Iitaka, Y. *Tetrahedron* **1997**, *53*, 1617−1626.

(25) Pettit, G. R.; Srirangam, J. K.; Herald, D. L.; Xu, J.-P.; Boyd, M. R.; Cichacz, Z.; Kamano, Y.; Schmidt, J. M.; Erickson, K. L. *J. Org. Chem.* **1995**, *60*, 8257−8261.

**Table 1. Main Torsion Angles for the Dipeptides**

| dipeptide | $\phi_{i+1}$ | $\psi_{i+1}$ | $\phi_{i+2}$ | $\psi_{i+2}$ | $\omega_1$ | $\omega_2$ | $\omega_3$ |
|---|---|---|---|---|---|---|---|
| Piv-L-Pro-L-Ser-NHMe | −59.8 | −27.9 | −75.0 | −11.0 | 179.4 | 176.4 | −178.6 |
| Piv-Ahc-L-Ser-NHMe | −35.9 | −61.5 | −88.4 | 0.2 | −168.1 | −174.3 | 179.3 |
| Piv-L-Ser-Ahc-NHMe A | −154.2 | 85.5 | 43.5 | 52.1 | −172.2 | 162.5 | 175.2 |
| Piv-L-Ser-Ahc-NHMe B | −157.5 | 125.0 | 39.8 | −139.5 | −174.1 | 167.9 | −174.7 |
| L-Ser-L-Pro[a] | −81 | 152 | −82 | 173 | −177 | 163 | −170 |
| L-Ser-L-Pro[b] | −48.5 | 133.6 | −88.1 | 8.2 | | | |
| ideal type I $\beta$-turn | −60 | −30 | −90 | 0 | | | |

[a] Dipeptide L-Ser-L-Pro extracted from Cycloleonuripeptide D shows a nonfolded structure, ref 24. [b] Dipeptide L-Ser-L-Pro extracted from Stylopeptide 1, shows a type VIa1 $\beta$-turn (cis conformation of the proline residue), ref 25.

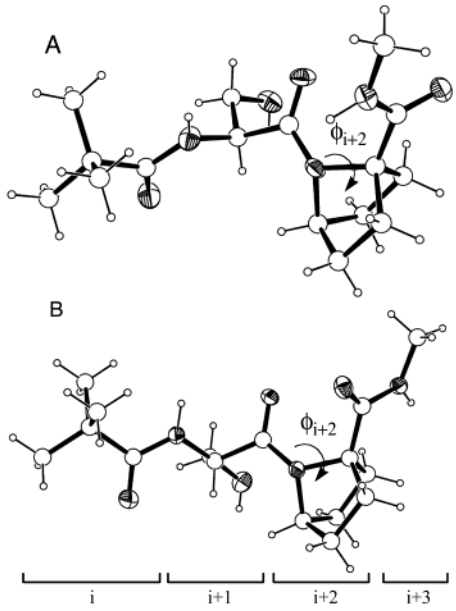


**Figure 5.** ORTEP diagram for Piv-L-Ser-Ahc-NHMe (**4**).

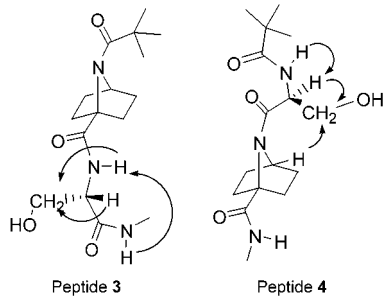


**Figure 6.** Significant NOE enhancements for peptides **3** and **4**.

and $^1H-^1H$ and $^1H-^{13}C$ correlation NMR experiments. The signal assignments were consistent with the expected products. In addition, peptides **3** and **4** were studied in greater depth by NOE studies.[26] The most relevant NOE enhancement observed in peptide **3** was the corresponding to the NHSer when the proton NHMe was irradiated. This observed NOE enhancement suggests certain folding of the peptide **3** due to the close presence of the amide protons. However, the peptide **4** seems to show an extended backbone, taking into account the NOE enhancements observed. These NOE enhancements are represented in Figure 6.

Additional NMR experiments of chemical shift and addition of a competitive solvent were performed to study the conformational analysis. Thus, it is well-known that in $CDCl_3$, NH amide protons involved in hydrogen bonding resonate around 7−8 ppm. In the $^1H$ NMR spectrum of peptide **3** the NHMe proton resonates at 7.72 ppm and the NHSer proton at 6.28 ppm. This suggests that in $CDCl_3$ the NHSer is free, while the NHMe proton is involved in an hydrogen bond. In peptide **4**, the shifts of the amide protons are 6.28 ppm for the NHMe proton and 6.90 ppm for the NHPiv proton showing that both protons are non-hydrogen-bonded. The addition of a competitive solvent[27] as DMSO-$d_6$ allows to evaluate the strength of the hydrogen bond. Thus, in DMSO-$d_6$, protons that are non-hydrogen-bonded or intermolecularly hydrogen-bonded are consequently shift downfield, while intramolecularly hydrogen-bonded protons are less accessible to DMSO. In our case, the NHSer proton of peptide **3** shows $\Delta\delta = 1.09$ ppm and NHMe and NHPiv protons of peptide **4** have $\Delta\delta = 1.17$ ppm and $\Delta\delta = 0.47$ ppm, respectively. This shift is slight in the case of the NHMe of peptide **3** ($\Delta\delta = 0.17$ ppm), proving that this proton would be establish an intramolecular hydrogen bond (Table 2). Figure 7 shows the $^1H$ NMR chemical shift of the NH protons of peptides **3** and **4**, running the $^1H$ NMR spectrum in a gradient of DMSO-$d_6$ in $CDCl_3$. We can observe two features; the NHMe proton of peptide **3** is not accessible to solvent in any concentration, corroborating the intramolecular hydrogen bond, and the NHPiv proton of peptide **4** is slightly accessible in low concentrations of DMSO and accessible in high concentrations. Possibly, it is involved in a weak hydrogen bond.

The temperature dependence is another essential aspect to examine the hydrogen bonds. The most significant results are frequently obtained in DMSO-$d_6$.[28] Coefficients lower than −3.0 ppb/K indicate shielding from the solvent. This is the case of the NHMe proton of the peptide **3** with a $\Delta\delta/\Delta T = -2.6$ ppb/K showing the possible existence of an hydrogen bond. The other amide protons from peptides **3** and **4** exhibit high $\Delta\delta/\Delta T$ (Table 2).

Recently, the hydrogen-bonding state of amide protons in $CDCl_3$ has been overviewed by Scolastico and coworkers,[29] establishing a classification taking into account all its $^1H$ NMR parameters (chemical shift, temperature coefficient, proton−deuterium exchange rates and $\Delta\delta$(NH) upon addition of a competitive solvent). In our case, the temperature coefficients in $CDCl_3$ for the NHSer proton of the peptide **3** and for NHMe and NHPiv

(26) Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989.

(27) (a) Pitner, T. P.; Urry, D. W. *J. Am. Chem. Soc.* **1972**, *94*, 1399. (b) Hruby, V. J. in *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, Weinstein, B. Ed.; Dekker: New York, 1974; vol. 3, pp 1−188.

(28) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 512−523.

(29) Belvisi, L.; Gennari, C.; Mielgo, A.; Potenza, D.; Scolastico, C. *Eur. J. Org. Chem.* **1999**, 389−400.

**Table 2. Chemical Shift, Solvent Sensitivity (ppm), and Temperature Sensitivity (ppb/K)**

| | Piv-Ahc-L-Ser-NHMe (**3**) | | Piv-L-Ser-Ahc-NHMe (**4**) | |
|---|---|---|---|---|
| | NHSer | NHMe | NHMe | NHPiv |
| $CDCl_3$ 100%, 290 K, (ppm) | 6.28 | 7.72 | 6.28 | 6.90 |
| DMSO 100%, 290 K, (ppm) | 7.37 | 7.89 | 7.45 | 7.37 |
| $\Delta\delta$ (ppm) | 1.09 | 0.17 | 1.17 | 0.47 |
| DMSO, 353 K, (ppm) | 7.11 | 7.76 | 7.21 | 7.09 |
| DMSO, 293 K, (ppm) | 7.41 | 7.92 | 7.45 | 7.37 |
| DMSO $\delta/\Delta T$, (ppb/K) | −5.0 | −2.6 | −4.0 | −4.6 |
| $CDCl_3$, 323 K, (ppm) | 6.27 | 7.56 | 6.26 | 6.80 |
| $CDCl_3$ 253 K, (ppm) | 6.47 | 8.13 | 6.30 | 6.94 |
| $CDCl_3$ $\Delta\delta/\Delta T$, (ppb/K) | −2.8 | −8.1 | −0.5 | −2.0 |

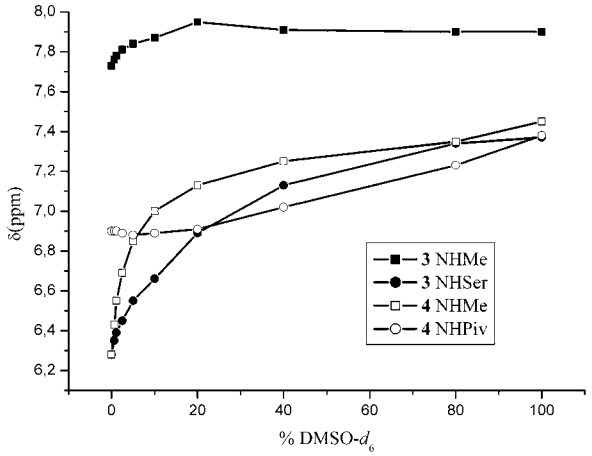


**Figure 7.** Experiments corresponding to the additon of a competitive solvent: $\delta$ ($^1$H NMR) of the NH protons of peptides **3** and **4** at different proportions of DMSO-$d_6$ in $CDCl_3$ (25 °C).

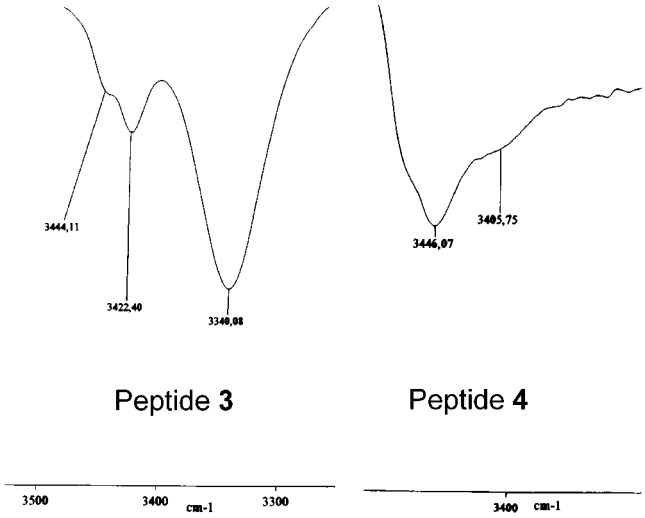


**Figure 8.** NH region of the infrared spectra of peptides **3** and **4**.

protons of the peptide **4** were lower than −3.0 ppb/K, while the temperature coefficient for NHMe proton of the peptide **3** was larger than −3.0 ppb/K (Table 2). According to these data and to the classification described by Scolastico, our results indicate that the NHMe proton of peptide **3** is in equilibrium between hydrogen-bonded and non-hydrogen bonded states. All the other amide protons have values corresponding to non-hydrogen-bonded state (low-temperature coefficient, low chemical shift, and high $\Delta\delta$(NH) upon addition of a competitive solvent).

This information indicates that in solution ($CDCl_3$) the hydrogen bonding between the NHMe proton and $^t$BuCO or AhcCO corresponding to the peptide Piv-Ahc-L-Ser-NHMe (**3**) is maintained in equilibrium with a non-hydrogen bonded state.

FT-IR spectra data of **3** and **4** in the $CH_2Cl_2$ solution (0.003 M) provided some evidence that the conformational differences observed in the solid state are reflected in solution. The spectrum of compound **3** shows a strong peak at 3340 $cm^{-1}$, assigned as the stretching band of the hydrogen-bonded NHMe amide.[30] This signal is not present in the spectrum of compound **4** (Figure 8).

All these facts, NOE experiments, chemical shifts, addition of a competitive solvent, temperature coefficients in $CDCl_3$ and DMSO-$d_6$, and FT-IR studies, are consistent with the conformation of both peptides in solid state, a turn conformation for peptide **3** and an extended conformation for peptide **4**.

## Conclusion

The incorporation of distorted amides into peptides has been reported on very few occasions. In this publication we describe the way in which a distorted amide, generated by incorporating a conformationally constrained amino acid, influences the conformation of the peptide backbone. The inclusion of such a unit alters the secondary structure $\beta$-turn in the solid state. Conformational analysis of these peptides in solution is agree with the conformations observed in solid state. The study of the reactivity of Ahc with other amino acids is under way in order to explore the importance of this structure in peptide chemistry and biology.

## Experimental Section

**General Procedures**. Melting points are uncorrected. All manipulations with air-sensitive reagents were carried out under a dry argon atmosphere using standard Schlenk techniques.[31] Solvents were purified according to standard procedures. The chemical reagents were purchased from Aldrich Chemical Co. Analytical TLC was performed using Polychrom SI $F_{254}$ plates. Column chromatography was performed using Kieselgel 60 (230−400 mesh). Organic solutions were dried over anhydrous $Na_2SO_4$ and, when necessary, concentrated under reduced pressure using a rotary evaporator. $\upsilon_{max}$ ($cm^{-1}$) values in IR spectra are given for the main absorption bands. NMR spectra were recorded at 300 MHz ($^1$H) and at 75 MHz ($^{13}$C) and signals are reported in ppm downfield from TMS. Mass spectra were obtained by electrospray ionization (ESI).

**Boc-L-Ser(OBn)-L-Pro-NHMe (7)**. A solution of Boc-L-Ser-(OBn)-OH (**5**) (354 mg, 1.2 mmol) in $CH_3CN$ (10 mL) was treated with DIEA (0.67 mL, 3.8 mmol), L-Pro-NHMe·HCl (**6**) (164 mg, 1.0 mmol), and TBTU (397 mg, 1.2 mmol) under an inert atmosphere. The reaction mixture was stirred at room

(30) Gardner, R. R.; Liang, G.-B.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 3280−3281.

(31) Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry*, 2nd ed.; Blackie Academic & Professional: London, 1995; pp 36−53.

temperature for 18 h and partitioned between brine (4 mL) and EtOAc (10 mL). The organic layer was washed with 0.1 N HCl (2 × 5 mL) and 5% $NaHCO_3$ (2 × 5 mL), dried over anhydrous $Na_2SO_4$, filtered, and evaporated to give a residue that was purified by silica gel column chromatography, eluting with MeOH/EtOAc (5:95) to yield 350 mg (86%) of **7** as a white solid (mp = 39−41 °C). $R_f$ = 0.48 (MeOH/EtOAc, 5:95). $[\alpha]^{22}_D$ (*c* 1.02, $CHCl_3$) = −35.3. ESI + (*m*/*z*) = 406.3. IR ($CH_2Cl_2$, $cm^{-1}$): 3420, 3398, 1710, 1668, 1655. NMR data for the major conformer: $^1$H NMR ($CDCl_3$): $\delta$ 1.43 (s, 9H), 1.79−2.05 (m, 3H), 2.21−2.29 (m, 1H), 2.36 (d, 3H, *J* = 4.8 Hz), 3.62−3.87 (m, 4H), 4.52−4.59 (m, 2H), 4.60−4.67 (m, 1H), 4.74−4.85 (m, 1H), 5.68 (d, 1H, *J* = 8.1 Hz), 6.61−6.73 (m, 1H), 7.22−7.40 (m, 5H). $^{13}$C NMR ($CDCl_3$): $\delta$ 24.0, 25.4, 28.0, 28.2, 47.1, 50.8, 59.9, 70.9, 73.4, 79.6, 127.0, 127.8, 128.3, 136.7, 154.8, 170.1, 171.0. Anal. Calcd for $C_{21}H_{31}N_3O_5$: C, 62.20; H, 7.71; N, 10.36. Found: C, 62.12; H, 7.65; N, 10.25.

**Piv-L-Ser(OBn)-L-Pro-NHMe (8)**. Boc-L-Ser(OBn)-L-Pro-NHMe (**7**) (200 mg, 0.49 mmol) was dissolved in 10 mL of 1 N HCl/THF (3:7), and the solution was stirred at room temperature for 15 min. The solvent was evaporated in vacuo to give quantitatively the corresponding hydrochloride derivative. This compound was suspended in $CH_2Cl_2$ (15 mL), and DIEA (0.17 mL, 0.96 mmol), PivCl (0.07 mL, 0.58 mmol), and DMAP (1 mg) were added at 0 °C, under an inert atmosphere. The mixture was allowed to warm to rt and, after stirring for 3 h at this temperature, the reaction mixture was washed with water (2 × 10 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered, and evaporated to give a residue that was purified by silica gel column chromatography, eluting with MeOH/EtOAc (5:95) to yield 160 mg (85%) of **8** as a colorless oil. $R_f$ = 0.46 (MeOH/EtOAc, 5:95). $[\alpha]^{23}_D$ (*c* 0.83, $CHCl_3$) = −36.5. ESI + (*m*/*z*) = 390.5. IR ($CH_2Cl_2$, $cm^{-1}$): 3434, 3393, 1.666, 1647. NMR data for the major conformer:$^1$H NMR ($CDCl_3$): $\delta$ 1.20 (s, 9H), 1.82−2.09 (m, 3H), 2.21−2.32 (m, 1H), 2.42 (d, 3H, *J* = 4.5 Hz), 3.59−3.72 (m, 2H), 3.74−3.83 (m, 1H), 3.90 (dd, 1H, *J* = 9.0 Hz, *J* = 5.4 Hz), 4.48−4.66 (m, 3H), 4.97−5.06 (m, 1H), 6.60−6.71 (m, 2H), 7.24−7.41 (m, 5H). $^{13}$C NMR ($CDCl_3$): $\delta$ 24.3, 25.7, 27.2, 28.3, 38.5, 47.4, 50.1, 60.2, 70.6, 73.7, 127.3, 128.1, 128.5, 136.8, 169.8, 171.0, 178.1. Anal. Calcd for $C_{21}H_{31}N_3O_4$: C, 64.76; H, 8.02; N, 10.79. Found: C, 64.86; H, 7.94; N, 10.71.

**Piv-L-Ser-L-Pro-NHMe (2)**. A solution of Piv-L-Ser(OBn)-L-Pro-NHMe (**8**) (120 mg, 0.30 mmol) in MeOH (20 mL) was hydrogenated, using 50 mg of 10% Pd−C as a catalyst, at room temperature for 2 h. The catalyst and solvent were removed, and the residue was purified by silica gel column chromatography, eluting with MeOH/EtOAc (15:85) to give 87 mg (94%) of **2** as a white solid (mp = 45−47 °C). $R_f$ = 0.32 (MeOH/EtOAc, 15:85). $[\alpha]^{25}_D$ (*c* 0.76, $CHCl_3$) = −53.1. ESI + (*m*/*z*) = 300.3 IR ($CH_2Cl_2$, $cm^{-1}$): 3668, 3609, 3442, 3361, 1671, 1641. NMR data for the major conformer: $^1$H NMR ($CDCl_3$): $\delta$ 1.20 (s, 9H), 1.87−2.20 (m, 4H), 2.76 (d, 3H, *J* = 4.8 Hz), 3.53−3.74 (m, 2H), 3.84−4.02 (m, 2H), 4.59 (dd, 1H, *J* = 7.5 Hz, *J* = 4.5 Hz), 4.77−4.96 (m, 2H), 6.77 (d, 1H, *J* = 7.5 Hz), 7.14−7.24 (m, 1H).$^{13}$C NMR ($CDCl_3$): $\delta$ 24.6, 26.2, 27.2, 29.1, 38.6, 47.6, 52.3, 60.4, 63.5, 169.8, 172.3, 178.7. Anal. Calcd for $C_{14}H_{25}N_3O_4$: C, 56.17; H, 8.42; N,14.04. Found: C, 56.07; H, 8.50; N, 14.10.

**Piv-Ahc-OBn (10)**. Boc-Ahc-OBn (**9**) (253 mg, 0.76 mmol) was dissolved in 10 mL of 4 N HCl/THF (3:7), and the solution was stirred at room temperature for 16 h. The solvent was evaporated in vacuo to give quantitatively the corresponding hydrochloride derivative. This compound was suspended in $CH_2Cl_2$ (15 mL), and TEA (0.25 mL, 1.76 mmol) and PivCl (0.12 mL, 0.92 mmol) were added, at 0 °C, under an inert atmosphere. The mixture was allowed to warm to rt, and, after stirring for 24 h at this temperature, the reaction was washed with water (2 × 10 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered, and evaporated to give a residue that was purified by silica gel column chromatography, eluting with hexane/EtOAc (8:2) to yield 204 mg (85%) of **10** as a white solid (mp = 44−46 °C). $R_f$ = 0.36 (hexane/EtOAc, 8:2). ESI + (*m*/*z*) = 316.2. IR ($CH_2Cl_2$, $cm^{-1}$): 1734, 1639. $^1$H NMR ($CDCl_3$): $\delta$ 1.16 (s, 9H), 1.46−1.57 (m, 2H), 1.58−1.69 (m, 2H), 1.77−1.92 (m, 2H), 2.07−2.20 (m, 2H), 4.43−4.52 (m, 1H), 5.14 (s, 2H), 7.17−7.32 (m, 5H).$^{13}$C NMR ($CDCl_3$): $\delta$ 28.0, 30.6, 31.5, 39.6, 59.3, 66.5, 68.2, 127.7, 127.9, 128.2, 136.1, 170.8, 179.2. Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.25; H, 7.87; N, 4.53.

**Piv-Ahc-OH (11)**. A solution of Piv-Ahc-OBn (**10**) (130 mg, 0.41 mmol) in MeOH (20 mL) was hydrogenated, using 50 mg of 10% Pd−C as a catalyst, at room temperature for 2 h. The catalyst and the solvent were removed to give **11** quantitatively as a white solid (mp = 136−138 °C). ESI − (*m*/*z*) = 224.3. IR-($CH_2Cl_2$, $cm^{-1}$): 3680, 1709.$^1$H NMR ($CD_3OD$): $\delta$ 1.25 (s, 9H), 1.55−1.74 (m, 4H), 1.80−1.95 (m, 2H), 2.03−2.19 (m, 2H), 4.59−4.67 (m, 1H).$^{13}$C NMR ($CD_3OD$): $\delta$ 28.4, 31.6, 33.2, 40.9, 61.0, 71.5, 178.8, 181.2. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.91; H, 8.53; N, 6.15.

**Boc-L-Ser(OBn)-NHMe (12)**. A solution of Boc-L-Ser(OBn)-OH (**5**) (591 mg, 2 mmol) in $CH_3CN$ (20 mL) was treated with DIEA (1.76 mL, 10 mmol), methylamine hydrochloride (275 mg, 4 mmol) and TBTU (794 mg, 2.4 mmol) under an inert atmosphere. The reaction mixture was stirred at room temperature for 16 h and then partitioned between brine (16 mL) and EtOAc (40 mL). The organic layer was washed with 0.1 N HCl (2 × 25 mL) and 5% $NaHCO_3$ (2 × 25 mL), dried over anhydrous $Na_2SO_4$, filtered, and evaporated to give a residue that was purified by silica gel column chromatography, eluting with hexane/EtOAc (3:7) to yield 524 mg (84%) of **12** as a white solid (mp = 91−93 °C). $R_f$ = 0.35 (hexane/EtOAc, 3:7). $[\alpha]^{22}_D$ (*c* 1.19, $CH_3OH$) = +45.1. ESI + (*m*/*z*) = 309.2. IR ($CH_2Cl_2$, $cm^{-1}$): 3440, 3420, 1714, 1678.$^1$H NMR ($CDCl_3$): $\delta$ 1.37 (s, 9H), 2.75 (d, 3H, *J* = 4.8 Hz), 3.50 (dd, 1H, *J* = 9.3 Hz, *J* = 6.3 Hz), 3.85 (dd, 1H, *J* = 9.3 Hz, *J* = 3.6 Hz), 4.13−4.25 (m, 1H), 4.51 (d, 1H, *J* = 11.7 Hz), 5.33 (d, 1H, *J* = 11.7 Hz), 5.33 (br s, 1H), 6.31−6.42 (m, 1H), 7.16−7.32 (m, 5H). $^{13}$C NMR ($CDCl_3$): $\delta$ 26.3, 28.2, 53.8, 69.8, 73.4, 80.2, 127.7, 127.9, 128.5, 137.4, 155.5, 170.8. Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.84; N, 9.08 Found: C, 62.45; H, 7.78; N, 9.16.

**L-Ser(OBn)-NHMe·HCl (13)**. Boc-L-Ser(OBn)-NHMe (**12**) (108 mg, 0.35 mmol) was dissolved in 10 mL of 1 N HCl/THF (3:7), and the solution was stirred at room temperature for 1 h. The solvent was evaporated in vacuo to give quantitatively **13** as a white solid (mp = 45−47 °C). ESI + (*m*/*z*) = 316.2. $^1$H NMR ($CD_3OD$): $\delta$ 2.77 (s, 3H), 3.73−3.92 (m, 2H), 4.08−4.20 (m, 1H), 4.57 (d, 1H, *J* = 12.3 Hz), 4.63 (d, 1H, *J* = 12.3 Hz), 7.20−7.41 (m, 5H).$^{13}$C NMR ($CD_3OD$): $\delta$ 26.5, 54.5, 69.0, 74.3, 128.9, 129.0, 129.4, 138.5, 168.2. Anal. Calcd for $C_{11}H_{17}N_2O_2$-Cl: C, 53.99; H, 7.00; N, 11.45. Found: C, 54.07; H, 6.98; N, 11.53.

**Piv-Ahc-L-Ser(OBn)-NHMe (14)**. A solution of L-Ser(OBn)-NHMe·HCl (**13**) (54 mg, 0.22 mmol), Piv-Ahc-OH **11** (50 mg, 0.22 mmol), and DIEA (0.15 mL, 0.84 mmol) in $CH_3CN$ (3 mL) was treated with TBTU (73 mg, 0.22 mmol) at 0 °C, under an inert atmosphere, and the reaction mixure was stirred for 16 h at room temperature. Brine (5 mL) was added to the reaction solution, which was extracted with $CH_2Cl_2$ (2 × 5 mL). The combined organic layers were washed with 0.1 N HCl (2 × 5 mL), 5% $NaHCO_3$ (2 × 5 mL), and brine (5 mL), dried over anhydrous $Na_2SO_4$, filtered, and evaporated to give a residue that was purified by silica gel column chromatography, eluting with EtOAc to yield 58 mg (63%) of **14** as a white solid (mp = 126−128 °C). $R_f$ = 0.22 (EtOAc). $[\alpha]^{20}_D$ (*c* = 0.97, $CHCl_3$) = +25.8. ESI + (*m*/*z*) = 416.2. IR ($CH_2Cl_2$, $cm^{-1}$): 3426, 3351, 1673, 1634.$^1$H NMR ($CDCl_3$): $\delta$ 1.17 (s, 9H), 1.51−1.95 (m, 7H), 2.13−2.27 (m, 1H), 2.75 (d, 3H, *J* = 4.8 Hz), 3.52 (dd, 1H, *J* = 9.3 Hz, *J* = 3.9 Hz), 4.19 (dd, 1H, *J* = 9.3 Hz, *J* = 2.7 Hz), 4.36 (d, 1H, *J* = 12.0 Hz), 4.42−4.61 (m, 3H), 6.23 (d, 1H, *J* = 8.1 Hz), 7.13−7.31 (m, 5H), 7.80−7.90 (m, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 26.2, 27.8, 30.1, 30.2, 30.9, 33.4, 40.2, 52.8, 60.2, 68.9, 69.8, 72.9, 127.5, 127.6, 128.3, 137.7, 170.2, 170.3, 182.0. Anal. Calcd for $C_{23}H_{33}N_3O_4$: C, 66.48; H, 8.00; N, 10.11. Found: C, 66.42; H, 8.02; N, 10.07.

**Piv-Ahc-L-Ser-NHMe (3)**. A solution of Piv-Ahc-L-Ser-(OBn)-NHMe (**14**) (90 mg, 0.22 mmol) in MeOH (20 mL) was hydrogenated, using 45 mg of 10% Pd−C as a catalyst, at room temperature for 2 h. The catalyst and the solvent were removed, and the residue was purified by silica gel column chromatography, eluting with MeOH/EtOAc (1:4) to give 70

mg (99%) of **3** as a white solid (mp = 36−38 °C). $R_f$ = 0.52 (MeOH/EtOAc, 1:4). $[\alpha]^{25}_D$ (*c* 0.91, $CHCl_3$) = −2.5. ESI + (*m*/*z*) = 326.2. IR ($CH_2Cl_2$, $cm^{-1}$): 3444, 3422, 3340, 1667, 1633.$^1$H NMR ($CDCl_3$): δ 1.18 (s, 9H), 1.53−2.02 (m, 7H), 2.13−2.26 (m, 1H), 2.69 (d, 3H, *J* = 4.8 Hz), 3.61 (dd, 1H, *J* = 11.4 Hz, *J* = 3.6 Hz), 4.11 ('t', 1H, *J* = 6.0 Hz), 4.23 (dd, 1H, *J* = 11.4 Hz, *J* = 2.7 Hz), 4.39−4.49 (m, 1H), 4.52−4.62 (m, 1H), 6.51 (d, 1H, *J* = 8.4 Hz), 7.84−8.01 (m, 1H). $^{13}$C NMR ($CDCl_3$): δ 26.2, 28.0, 30.3, 30.8, 30.9, 33.1, 40.2, 54.6, 60.2, 62.2, 69.9, 170.7, 171.4, 181.7. Anal. Calcd for $C_{16}H_{27}N_3O_4$: C, 59.06; H, 8.36; N, 12.91. Found: C, 58.98; H, 8.31; N, 12.99.

**Boc-Ahc-OH (15)**. Boc-Ahc-OBn (**9**) (570 mg, 1.72 mmol) in MeOH (25 mL) was hydrogenated, using 70 mg of 10% Pd−C as a catalyst, at room temperature for 3 h. The catalyst and the solvent were removed to give quantitatively **15** as a white solid (mp = 54−56 °C). ESI − (*m*/*z*) = 240.1. IR ($CH_2Cl_2$, $cm^{-1}$): 1692, 1599. $^1$H NMR ($CDCl_3$): δ 1.19−1.38 (m, 11H), 1.51−1.77 (m, 4H), 1.99−2.18 (m, 2H), 4.09−4.18 (m, 1H). $^{13}$C NMR ($CDCl_3$): δ 28.3, 29.2, 34.0, 59.7, 70.7, 80.7, 156.9, 178.4. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.80; H, 7.92; N, 5.89.

**Boc-Ahc-NHMe (16)**. A solution of Boc-Ahc-OH (**15**) (246 mg, 1.02 mmol) in $CH_3CN$ (10 mL) was treated with DIEA (0.9 mL, 5.10 mmol), methylamine hydrochloride (138 mg, 2.04 mmol), and TBTU (393 mg, 1.22 mmol) under an inert atmosphere. The reaction mixture was stirred at room temperature for 16 h and partitioned between brine (8 mL) and EtOAc (20 mL). The organic layer was washed with 0.1 N HCl (2 × 10 mL) and 5% $NaHCO_3$ (2 × 10 mL), dried over anhydrous $Na_2SO_4$, filtered, and evaporated to give a residue that was purified by silica gel column chromatography, eluting with EtOAc, to yield 230 mg (88%) of **16** as a white solid (mp = 89−91 °C). $R_f$ = 0.40 (EtOAc). ESI + (*m*/*z*) = 255.4. IR ($CH_2Cl_2$, $cm^{-1}$): 3444, 1702, 1681. $^1$H NMR ($CDCl_3$): δ 1.35 (s, 9H), 1.38−1.49 (m, 2H), 1.72−1.91 (m, 4H), 1.92−2.07 (m, 2H), 2.80 (d, 3H, *J* = 4.8 Hz), 4.21−4.30 (m, 1H), 5.99−6.11 (m, 1H).$^{13}$C NMR ($CDCl_3$): δ 26.1, 27.9, 28.9, 34.0, 60.3, 70.4, 80.5, 157.0, 172.2. Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.41; H, 8.62; N, 11.13.

**Ahc-NHMe·HCl (17).** Boc-Ahc-NHMe (**16**) (230 mg, 0.90 mmol) was dissolved in 10 mL of 1 N HCl-THF (3:7) and the mixture was stirred at room temperature for 1.5 h. The solvent was evaporated in vacuo to give quantitatively **17** as a white solid (mp > 200 °C).$^1$H NMR ($CD_3OD$): δ 1.82−2.26 (m, 8H), 2.80 (s, 3H), 4.13−4.22 (m, 1H).$^{13}$C NMR ($CD_3OD$): δ 26.5, 29.2, 31.7, 59.1, 74.7, 170.1. Anal. Calcd for $C_8H_{15}N_2OCl$: C, 50.39; H, 7.93; N, 14.69. Found: C, 50.47; H, 7.82; N, 14.81.

**Boc-L-Ser(OBn)-Ahc-NHMe (18)**. A solution of Boc-L-Ser-(OBn)-OH (**5**) (94 mg, 0.32 mmol) in $CH_3CN$ (4 mL) was treated with DIEA (0.23 mL, 1.31 mmol), Ahc-NHMe·HCl **17** (50 mg, 0.26 mmol) and TBTU (104 mg, 0.32 mmol) under an inert atmosphere. The reaction mixture was stirred at room temperature for 16 h and partitioned between brine (4 mL) and EtOAc (10 mL). The organic layer was washed with 0.1 N HCl (2 × 5 mL) and 5% $NaHCO_3$ (2 × 5 mL), dried over anhydrous $Na_2SO_4$, filtered and evaporated to give a residue that was purified by silica gel column chromatography, eluting with EtOAc, to yield 98 mg (87%) of **18** as a white solid (mp = 38−40 °C). $R_f$ = 0.24 (EtOAc). $[\alpha]^{22}_D$ (*c* 0.98, $CHCl_3$) = +1.9. ESI + (*m*/*z*) = 432.5. IR ($CH_2Cl_2$, $cm^{-1}$): 3470, 3429, 1710, 1681, 1671.$^1$H NMR ($CDCl_3$): δ 1.35 (s, 9H), 1.43−2.05 (m, 8H), 2.69 (d, 3H, *J* = 4.8 Hz), 3.52−3.64 (m, 2H), 4.25−4.35 (m, 1H), 4.39 (d, 1H, *J* = 12.0 Hz), 4.42−4.58 (m, 2H), 5.40 (d, 1H, *J* = 8.1 Hz), 6.27−6.36 (m, 1H), 7.14−7.29 (m, 5H). $^{13}$C NMR ($CDCl_3$): δ 26.3, 28.2, 29.3, 30.6, 31.3, 35.0, 52.7, 60.0, 69.7, 70.9, 73.3, 79.8, 127.6, 127.7, 128.2, 137.4, 155.2, 171.1, 171.2. Anal. Calcd for $C_{23}H_{33}N_3O_5$: C, 64.02; H, 7.71; N, 9.74. Found: C, 64.08; H, 7.63; N, 9.68.

**Piv-L-Ser(OBn)-Ahc-NHMe (19)**. Boc-L-Ser(OBn)-Ahc-NHMe (**18**) (175 mg, 0.41 mmol) was dissolved in 10 mL of 1 N HCl/THF (3:7), and the solution was stirred at room temperature for 15 min. The solvent was evaporated in vacuo to give quantitatively the corresponding hydrochloride derivative. This compound was suspended in $CH_2Cl_2$ (15 mL), and DIEA (0.13 mL, 0.90 mmol), PivCl (0.06 mL, 0.49 mmol), and DMAP (1 mg) were added, at 0 °C, under an inert atmosphere. The mixture was allowed to warm at room temperature, and, after stirring for 3 h, the reaction was washed with water (2 × 10 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered, and evaporated to give a residue that was purified by silica gel column chromatography, eluting with MeOH/EtOAc (5:95) to yield 145 mg (86%) of **19** as a white solid (mp = 28−30 °C). $R_f$ = 0.2 (MeOH/EtOAc, 5:95) $[\alpha]^{23}_D$ (*c* 0.95, $CHCl_3$) = +7.4. ESI + (*m*/*z*) = 416.6. IR ($CH_2Cl_2$, $cm^{-1}$): 3469, 3436, 1681, 1658.$^1$H NMR ($CDCl_3$): δ 1.12 (s, 9H), 1.31−1.57 (m, 2H), 1.58−1.82 (m, 4H), 1.83−2.11 (m, 2H), 2.70 (d, 3H, *J* = 4.8 Hz), 3.52−3.65 (m, 2H), 4.26−4.34 (m, 1H), 4.40 (d, 1H, *J* = 12.0 Hz), 4.50 (d, 1H, *J* = 12.0 Hz), 4.74−4.83 (m, 1H), 6.26−6.35 (m, 1H), 6.61 (d, 1H, *J* = 7.2 Hz), 7.14−7.32 (m, 5H).$^{13}$C NMR ($CDCl_3$): δ 26.2, 27.2, 29.1, 30.6, 30.8, 35.2, 38.5, 51.4, 60.0, 69.5, 70.4, 73.2, 127.7, 127.8, 128.3, 137.3, 170.8, 170.9, 178.1. Anal. Calcd for $C_{23}H_{33}N_3O_4$: C, 66.48; H, 8.00; N, 10.11. Found: C, 66.56; H, 7.91; N, 10.06.

**Piv-L-Ser-Ahc-NHMe (4)**. A solution of Piv-L-Ser(OBn)-Ahc-NHMe (**19**) (90 mg, 0.22 mmol) in MeOH (20 mL) was hydrogenated, using 50 mg of 10% Pd−C as a catalyst, at room temperature for 2 h. The catalyst and the solvent were removed, and the residue was purified by silica gel column chromatography, eluting with MeOH/EtOAc (1:9) to give 65 mg (99%) of **4** as a white solid (mp = 53−55 °C). $R_f$ = 0.15 (MeOH/EtOAc, 1:9). $[\alpha]^{25}_D$ (*c* 0.94, $CHCl_3$) = −0.3. ESI + (*m*/*z*) = 326.4. IR ($CH_2Cl_2$, $cm^{-1}$): 3685, 3602, 3446, 3406, 1681, 1658.$^1$H NMR ($CDCl_3$): δ 1.14 (s, 9H), 1.49−1.64 (m, 2H), 1.67−1.90 (m, 3H), 1.91−2.16 (m, 3H), 2.82 (d, 3H, *J* = 4.8 Hz), 3.71 (dd, 1H, *J* = 11.4 Hz, *J* = 4.5 Hz); 3.80 (dd, 1H, *J* = 11.4, *J* = 4.2 Hz), 4.38−4.47 (m, 1H), 4.61−4.69 (m, 1H), 6.21−6.34 (m, 1H), 6.82 (d, 1H, *J* = 6.9 Hz).$^{13}$C NMR ($CDCl_3$): δ 26.7, 27.4, 29.6, 30.8, 35.2, 35.3, 38.7, 53.6, 59.8, 64.8, 69.4, 171.0, 171.0, 179.0. Anal. Calcd for $C_{16}H_{27}N_3O_4$: C, 59.06; H, 8.36; N, 12.91. Found: C, 59.17; H, 8.52; N, 12.83.

**Preparation of MTPA Esters**. A solution of MTPA (0.071 mmol) in $CH_2Cl_2$ (1 mL) was added to a solution of the peptide (0.062 mmol), DCC (0.068 mmol), and DMAP (0.062 mmol) in $CH_2Cl_2$ (1.0 mL). The mixture was stirred at room temperature for 4.5 h. The resulting white suspension was filtered to remove the *N*,*N*′-dicyclohexylurea. The filtrate was concentrated to give a white slurry, to which $Et_2O$ was added. The resulting suspension was filtered to remove the *N*-acyl-*N*′-cyclohexylurea and then concentrated to give the crude product, which was purified by column chromatography on silica gel, eluting with MeOH/EtOAc (5:95).

**Piv-L-Ser(*O*-(+)-MTPA)-L-Pro-NHMe (20)**. 82% yield as a white solid (mp = 42−44 °C). $R_f$ = 0.38 (MeOH/EtOAc, 5:95). $[\alpha]^{27}_D$ (*c* 0.79, $CHCl_3$) = −21.0. ESI + (*m*/*z*) = 516.6. IR ($CH_2Cl_2$, $cm^{-1}$): 3434, 3357, 1753, 1671, 1654. NMR data for the major conformer: $^1$H NMR ($CDCl_3$): δ 1.16 (s, 9H), 1.85−2.14 (m, 3H), 2.32−2.43 (m, 1H), 2.66 (d, 3H, *J* = 4.8 Hz), 3.54 (s, 3H), 3.61−3.70 (m, 2H), 4.44−4.57 (m, 2H), 4.69 (dd, 1H, *J* = 11.4 Hz, *J* = 4.2 Hz), 4.98−5.06 (m, 1H), 6.46−6.54 (m, 1H), 6.62 (d, 1H, *J* = 7.2 Hz), 7.38−7.51 (m, 5H). $^{19}$F NMR ($CDCl_3$): δ −78.81. $^{13}$C NMR ($CDCl_3$): δ 25.6, 26.1, 27.2, 27.8, 38.7, 47.6, 50.0, 55.5, 60.8, 64.5, 121.2, 125.0, 127.3, 128.6, 129.8, 131.6, 167.0, 168.9, 170.9, 178.3. Anal. Calcd for $C_{24}H_{32}F_3N_3O_6$: C, 55.92; H, 6.21; N, 8.16. Found: C, 55.83; H, 6.18; N, 8.12.

**Piv-L-Ser(*O*-(−)-MTPA)-L-Pro-NHMe (23)**. 87% yield as a white solid (mp = 47−49 °C). $R_f$ = 0.46 (MeOH/EtOAc, 5:95). $[\alpha]^{21}_D$ (*c* 0.81, $CHCl_3$) = −71.9. ESI + (*m*/*z*) = 516.6. IR ($CH_2Cl_2$, $cm^{-1}$): 3434, 3357, 1754, 1672, 1650. NMR data for the major conformer: $^1$H NMR ($CDCl_3$): δ 1.14 (s, 9H), 1.83−2.11 (m, 3H), 2.34−2.45 (m, 1H), 2.73 (d, 3H, *J* = 4.8 Hz), 3.52 (s, 3H), 3.55−3.76 (m, 2H), 4.53−4.61 (m, 2H), 4.69 (dd, 1H, *J* = 11.4 Hz, *J* = 4.2 Hz), 4.94−5.05 (m, 1H), 6.51−6.64 (m, 2H), 7.39−7.53 (m, 5H). $^{19}$F NMR ($CDCl_3$): δ −71.77. $^{13}$C NMR ($CDCl_3$): δ 24.9, 26.1, 27.2, 27.8, 38.7, 47.5, 49.9, 55.3, 60.9, 64.3, 121.2, 125.0, 127.2, 128.6, 129.8, 131.8, 166.8, 168.9, 170.9, 178.3. Anal. Calcd for $C_{24}H_{32}F_3N_3O_6$: C, 55.92; H, 6.21; N, 8.16. Found: C, 55.81; H, 6.15; N, 8.10.

**Piv-Ahc-L-Ser(*O*-(+)-MTPA)-NHMe (21)**. 78% yield as a white solid (mp = 158−160 °C). $R_f$ = 0.70 (MeOH/EtOAc, 5:95). $[\alpha]^{25}_D$ (*c* 0.81, $CHCl_3$) = +52.0. ESI + (*m*/*z*) = 542.3. IR ($CH_2Cl_2$, $cm^{-1}$): 3434, 3341, 1760, 1688, 1678, 1630. $^1H$ NMR ($CDCl_3$): $\delta$ 1.21 (s, 9H), 1.54−2.03 (m, 7H), 2.18−2.32 (m, 1H), 2.77 (d, 3H, *J* = 4.8 Hz), 3.49 (s, 3H), 4.37 (dd, 1H, *J* = 11.1 Hz, *J* = 3.3 Hz), 4.57−4.66 (m, 1H), 4.92 ('dt', 1H, *J* = 9.3 Hz, *J* = 3.3 Hz), 5.20 (dd, 1H, *J* = 11.1 Hz, *J* = 3.3 Hz), 5.99 (d, 1H, *J* = 9.3 Hz), 7.35−7.52 (m, 5H), 7.89−8.02 (m, 1H). $^{19}F$ NMR ($CDCl_3$): $\delta$ −71.94. $^{13}C$ NMR ($CDCl_3$): $\delta$ 26.4, 27.8, 30.2, 30.3, 31.0, 33.6, 40.2, 51.7, 55.2, 60.3, 66.3, 69.9, 121.4, 125.2, 127.5, 128.6, 129.8, 131.3, 166.0, 168.8, 170.4, 182.0. Anal. Calcd for $C_{26}H_{34}F_3N_3O_6$: C, 57.67; H, 6.28; N, 7.76. Found: C, 57.54; H, 6.19; N, 7.82.

**Piv-Ahc-L-Ser(*O*-(−)-MTPA)-NHMe (24).** 72% yield as a white solid (mp = 130−132 °C). $R_f$ = 0.70 (MeOH/EtOAc, 5:95). $[\alpha]^{27}_D$ (*c* 0.72, $CHCl_3$) = −1.4. ESI + (*m*/*z*) = 542.3. IR ($CH_2Cl_2$, $cm^{-1}$): 3434, 3342, 1755, 1688, 1678, 1630. $^1H$ NMR ($CDCl_3$): $\delta$ 1.24 (s, 9H), 1.56−2.06 (m, 7H), 2.19−2.33 (m, 1H), 2.77 (d, 3H, *J* = 4.8 Hz), 3.44 (s, 3H), 4.49 (dd, 1H, *J* = 11.1 Hz, *J* = 3.3 Hz), 4.58−4.65 (m, 1H), 4.86−4.93 (m, 1H), 5.10 (dd, 1H, *J* = 11.1 Hz, *J* = 4.2 Hz), 6.11 (d, 1H, *J* = 9.0 Hz), 7.33−7.52 (m, 5H), 7.88−8.03 (m, 1H). $^{19}F$ NMR ($CDCl_3$): $\delta$ −72.50. $^{13}C$ NMR ($CDCl_3$): $\delta$ 26.3, 27.8, 30.1, 30.2, 31.0, 33.7, 40.3, 52.1, 55.2, 60.4, 66.2, 69.9, 121.2, 125.0, 127.6, 128.5, 129.8, 131.3, 166.3, 168.6, 170.5, 182.1. Anal. Calcd for $C_{26}H_{34}F_3N_3O_6$: C, 57.67; H, 6.28; N, 7.76. Found: C, 57.56; H, 6.18; N, 7.77.

**Piv-L-Ser(*O*-(+)-MTPA)-Ahc-NHMe (22)**. 69% yield as a white solid (mp = 119−121 °C). $R_f$ = 0.46 (MeOH/EtOAc, 5:95). $[\alpha]^{25}_D$ (*c* 0.79, $CHCl_3$) = +25.0. ESI + (*m*/*z*) = 542.3. IR ($CH_2Cl_2$, $cm^{-1}$): 3470, 3429, 1753, 1681, 1666, 1649. NMR data for the major conformer: $^1H$ NMR ($CDCl_3$): $\delta$ 1.12 (s, 9H), 1.57−2.04 (m, 7H), 2.08−2.22 (m, 1H), 2.77 (d, 3H, *J* = 4.8 Hz), 3.51 (s, 3H), 4.39−4.47 (m, 1H), 4.54 (dd, 1H, *J* = 11.1 Hz, *J* = 3.3 Hz), 4.67 (dd, 1H, *J* = 11.1 Hz, *J* = 3.9 Hz), 4.91−5.00 (m, 1H), 5.94−6.19 (m, 1H), 6.68 (d, 1H, *J* = 6.6 Hz), 7.37−7.53 (m, 5H). $^{19}F$ NMR ($CDCl_3$): $\delta$ −72.00. $^{13}C$ NMR ($CDCl_3$): $\delta$ 26.4, 27.2, 29.4, 30.7, 30.8, 35.4, 38.7, 50.5, 55.5, 60.4, 66.0, 69.8, 121.2, 125.0, 127.4, 128.6, 129.9, 131.5, 166.7, 169.5, 170.7, 178.4. Anal. Calcd for $C_{26}H_{34}F_3N_3O_6$: C, 57.67; H, 6.28; N, 7.76. Found: C, 57.58; H, 6.22; N, 7.76.

**Piv-L-Ser(*O*-(−)-MTPA)-Ahc-NHMe (25)**. 66% yield as a white solid (mp = 152−154 °C). $R_f$ = 0.38 (MeOH/EtOAc, 5:95). $[\alpha]^{27}_D$ (*c* 0.83, $CHCl_3$) = −7.7. ESI + (*m*/*z*) = 542.3. IR ($CH_2Cl_2$, $cm^{-1}$): 3470, 3429, 1753, 1682, 1666, 1649. NMR data for the major conformer: $^1H$ NMR ($CDCl_3$): $\delta$ 1.09 (s, 9H), 1.54−2.06 (m, 7H), 2.09−2.23 (m, 1H), 2.79 (d, 3H, *J* = 4.8 Hz), 3.53 (s, 3H), 4.37−4.44 (m, 1H), 4.61 (dd, 1H, *J* = 11.1 Hz, *J* = 3.3 Hz), 4.67 (dd, 1H, *J* = 11.1 Hz, *J* = 3.3 Hz), 4.87−4.95 (m, 1H), 5.94−6.10 (m, 1H), 6.60 (d, 1H, *J* = 6.9 Hz), 7.37−7.53 (m, 5H). $^{19}F$ NMR ($CDCl_3$): $\delta$ −72.05. $^{13}C$ NMR ($CDCl_3$): $\delta$ 26.4, 27.2, 29.3, 30.3, 30.9, 35.8, 38.6, 50.6, 55.5, 60.4, 65.8, 69.8, 121.2, 125.0, 127.3, 128.6, 129.9, 131.8, 166.7, 169.5, 170.8, 178.4. Anal. Calcd for $C_{26}H_{34}F_3N_3O_6$: C, 57.67; H, 6.28; N, 7.76. Found: C, 57.52; H, 6.21; N, 7.74.

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**Supporting Information Available:** A full listing of $^1H$ and $^{13}C$ NMR data of all the new compounds with peak assignments, copies of $^1H$ and $^{13}C$ NMR spectra, $^1H-^1H$ and $^1H-^{13}C$ correlations and NOE experiments as well as the crystal structure data for **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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