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Solution State Conformational Preferences of Dipeptides Derived from *N*-Aminoazetidinecarboxylic Acid: An Assessment of the Hydrazino Turn

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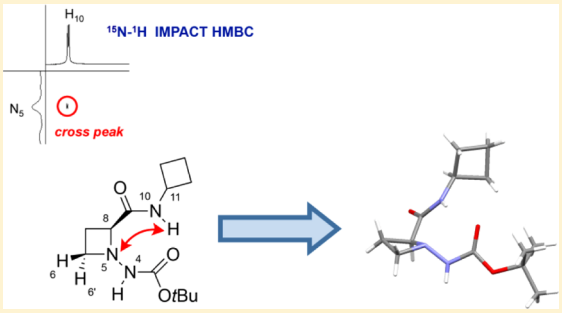
Supporting Information

ABSTRACT: Four model compounds and four dipeptides containing *N*-aminoazetidinecarboxylic acid (AAzC) and a particular stereoisomer of 2-aminocyclobutanecarboxylic acid (ACBC) were studied to establish their solution state conformational preferences, particularly regarding the ability of AAzC to induce a three-center hydrogen-bonded folding feature known as a "hydrazino turn". On the basis of IR and NMR experiments, supported by molecular modeling, the AAzC residue adopted a *trans* configuration amenable to the formation of a cyclic eight-membered hydrogen bond conformation in solution, in all cases studied. The implication of the heterocyclic nitrogen atom of AAzC in the *trans*-like structure was demonstrated via a refined $^{1}H-^{15}N$ HMBC experiment giving exploitable data at natural ^{15}N isotopic abundance, providing unprecedented evidence for the solution state hydrazino turn conformation. The predominance of this secondary structural feature depended on the configuration of the neighboring ACBC residue in the dipeptides: while the *trans*-ACBC derivatives prefer the hydrazino turn, the *cis*-ACBC derivatives may also populate low-energy 10-membered hydrogen-bonded ring structures. X-ray diffraction analysis of three compounds confirmed the presence of a solid state hydrazino turn in two cases, with geometries similar to those deduced from the solution state studies, but in the third compound, no intramolecular hydrogen-bonding feature was in evidence.



INTRODUCTION

The specific functions performed by natural peptides are the result of their well-defined architectures, which depend on locally ordered secondary structural features. Significant efforts have been made to understand and control the factors that determine the conformational preferences of peptides, and a key contemporary challenge at the interface of chemistry and biology is the rational design of specifically folded peptidomimetic materials. A fruitful approach has been to examine the behavior of short oligomer sequences assembled from monomer building blocks that are analogues of Nature's amino acids.[1−5] In this respect, peptides that contain β-amino acids are of considerable importance, in part, because they can behave as biologically active peptidomimetics[6−8] but also because they have emerged as self-structuring manifolds for the construction of foldamers.[9−13]

In the peptidomimetics area, hydrazino peptides have attracted particular attention. These compounds are obtained when one or more of the α-amino acids in a peptide sequence are replaced by an α-hydrazino acid. Conceptually, an α-hydrazino acid is an *aza*-analogue of a β-amino acid, whose β-carbon has been replaced by a nitrogen atom.[14] This strategy for the backbone modification of α-peptides has been known for some time,[15] and has provided peptidomimetic materials showing biological activity[16−18] or resistance to proteolysis.[19] One of the specific features of hydrazino peptides is their capacity to adopt an intramolecular eight-membered ring hydrogen bond, a conformational preference that is also known for oligomers of α-aminoxy acids.[20−23] On the basis of a number of X-ray crystal structures,[24−28] it was suggested that the additional backbone nitrogen in a hydrazino peptide might participate in a 3-center hydrogen bond, called a hydrazino turn, which stabilizes the eight-membered ring secondary structure (Figure 1). The significance of the hydrazino turn in solution has been more difficult to

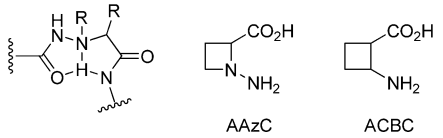


Figure 1. Hydrazino turn bonding pattern and the molecular structures of AAzC and ACBC.

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demonstrate, although some linear and cyclic *aza*-β^3-peptides do appear to have accessible eight-membered ring conformations.[19,29−36] Nonetheless, theoretical studies have not confirmed a decisive role for the 3-center hydrogen bond in determining the folding properties of hydrazino peptides.[37] Only one study of an alternating mixed peptide constructed from a cyclic β-amino acid (2-aminocyclopentanecarboxylic acid) and its *aza*-analogue has been carried out, revealing that the adoption of an 8-ring pseudocyclic network was configuration-dependent and did not appear to involve the 3-center hydrazino turn.[38]

Further examination of the conformational behavior of building blocks that combine a cyclic molecular structure with α-hydrazino acid is thus warranted, and these criteria are met by *N*-aminoazetidinecarboxylic acid (AAzC; Figure 1).[39,40] This compound is an *aza*-analogue of 2-aminocyclobutanecarboxylic acid (ACBC; Figure 1) whose *trans* configuration is reported to stabilize eight-membered hydrogen bond ring structures in short peptides,[41,42] whereas the *cis* configuration forms only intra-residue six-membered hydrogen bonds.[43] In this work, we report on the detailed structural analysis of dipeptide derivatives of AAzC, leading to direct solution state evidence for the bifurcated hydrogen bond of a hydrazino turn that stabilizes an eight-membered hydrogen bond ring.

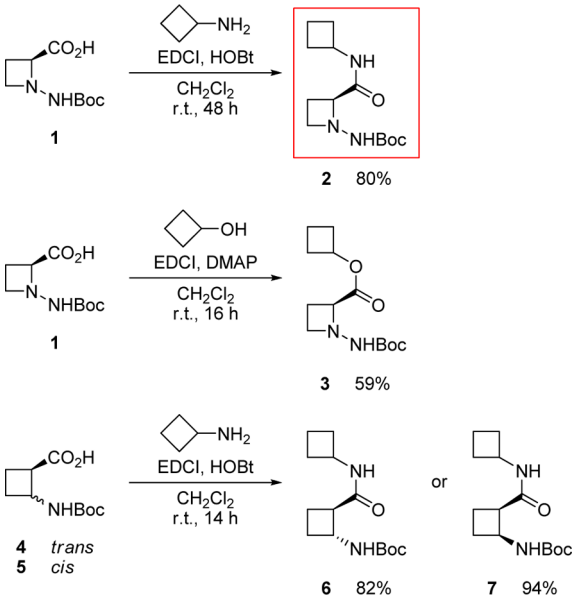
RESULTS AND DISCUSSION

To begin our studies, a model amide of (*S*)-AAzC was prepared. The Boc-protected hydrazino acid **1**, prepared from 6-azauracil according to the published procedure,[39] was condensed with cyclobutylamine to give amide **2**. For comparison purposes, the cyclobutyl ester **3** and the cyclobutylamides of *N*-Boc *trans*- and *cis*-ACBCs, **6** and **7**, respectively, were also prepared. The ACBC precursors **4** and **5** were readily available following the published protocols.[44] The syntheses of compounds **2**, **3**, **6**, and **7** are outlined in Scheme 1.

Solution state FTIR absorption spectroscopic analysis of amide **2** was carried out in chloroform at a concentration of 10 mM (Figure 2). The NH stretching frequency domain generally shows a free amide absorption above 3400 cm^{-1}, whereas this band is shifted to lower frequencies (between 3350 and 3250 cm^{-1}) when the NH is involved in a hydrogen bond. The IR absorption spectrum of **2** revealed a stretching band at ca. 3310 cm^{-1}, attributed to the hydrogen-bonded amide $NH_{(10)}$ and a second band at ca. 3360 cm^{-1}, corresponding to the free carbazate $NH_{(4)}$ with a *Z* geometry.[31] Although the *Z* conformer is usually less favored, the formation of an intramolecular $C{=}O_{(3)}\cdots H_{(10)}N$ hydrogen bond stabilizes this conformer over the *E* conformer (Scheme 2). This behavior contrasts with that of the cyclobutyl ester **3**. The solution state IR absorption spectrum of **3** showed a strong absorption band at ca. 3440 cm^{-1} and a weak band at ca. 3360 cm^{-1}. In this case, no intramolecular hydrogen bond involving $C{=}O_{(3)}$ is possible, so ester **3** exists as a mixture of *E* and *Z* conformers in which the former predominates.

In comparison, the absorption spectrum of the reference *trans*-ACBC amide **6**, expected to adopt the eight-membered hydrogen bond ring, showed a band at ca. 3445 cm^{-1} corresponding to the carbamate NH and another band at ca. 3290 cm^{-1} assigned to the hydrogen-bonded amide NH. In contrast, *cis*-ACBC amide **7** showed a single absorption band at ca. 3435 cm^{-1} assigned to both the free amide NH and the hydrogen-bonded carbamate NH. The small red shift (10 cm^{-1}) observed for the carbamate NH suggests that the

Scheme 1. Preparation of Model Compound Amide 2 and Related Derivatives 3, 6, and 7



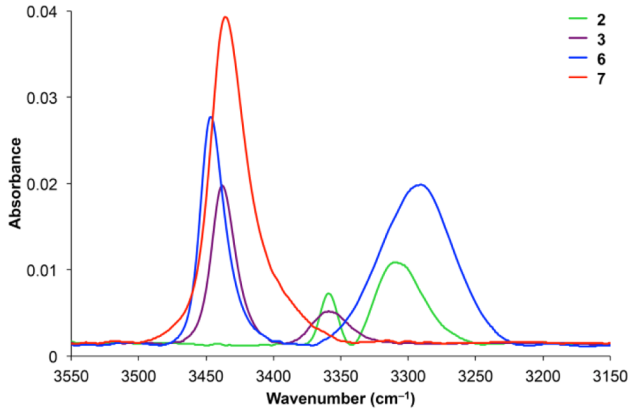
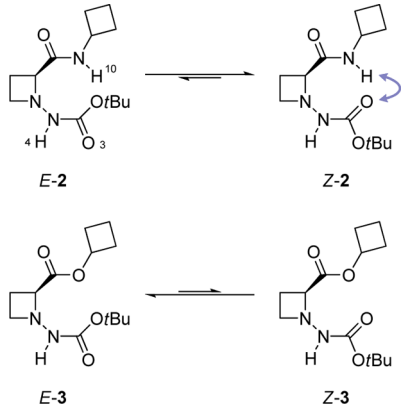


Figure 2. FTIR absorption spectra of compounds **2**, **3**, **6** ,and **7** (10 mM solution in $CHCl_3$).

Scheme 2. Equilibria for *E* and *Z* Conformers of Amide 2 and Ester 3



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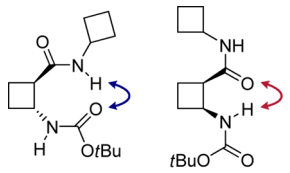
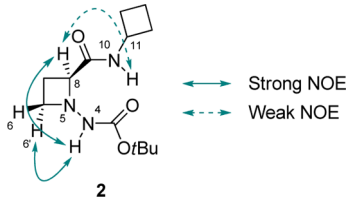
hydrogen bond interaction is of only moderate strength. These observations are in agreement with the formation of an eight-membered hydrogen bond ring for **6** and a six-membered hydrogen bond ring for **7** (Figure 3), which, in turn, supports the eight-membered hydrogen bond ring conformer proposed for AAzC amide **2** in the previous paragraph.



6 **7**

Figure 3. Structures of reference amides **6** and **7**.

NMR spectroscopic analysis of the AAzC amide **2** was carried out in $CDCl_3$ solution. Complete attribution of all ^1H and ^{13}C signals was achieved by means of 1D selective TOCSY and 2D HSQC experiments. The ^1H NMR spectrum showed a strongly deshielded signal for $NH_{(10)}$ (8.46 ppm), suggesting that this proton is implicated in a strong hydrogen bond. The intramolecular nature of this hydrogen bonding was confirmed by the absence of significant NH chemical shift variation with concentration in the range of 5−60 mM. In an isotopic exchange experiment (addition of methanol-d_4 to a 60 mM solution in $CDCl_3$), only the $NH_{(4)}$ signal moved to lower field and disappeared rapidly (see the Supporting Information). These results are in good agreement with an eight-membered hydrogen bond ring conformation. A series of NOESY experiments were performed on amide **2** in order to extract interatomic distances for application in molecular modeling studies. The main correlations are illustrated in Figure 4. A



2

Figure 4. NOE contacts observed for amide **2**.

hybrid Monte Carlo molecular mechanics (MCMM) conformational search was carried out on **2** in vacuum using SPARTAN'06 software[45] and the MMFF94 force field without restraints. Four low-energy conformer families emerged, and each was subjected to a DFT geometrical optimization using B3LYP 6-31G** basis sets. After refinement, the four conformer families were still accessible. Each family of conformers was assessed for its compatibility with the NOESY-derived interatomic distances using the DYNAMO molecular modeling facility in NMR PIPE.[46] The lowest energy family correlated perfectly with the NMR data and corresponded to an eight-membered hydrogen bond ring with the cyclobutyl group facing the *t*-butyl group. The minimum energy conformers are shown in Figure 5, and important structural parameters are presented in Table 1.

The potential implication of nitrogen $N_{(5)}$ in the stabilization of the eight-membered hydrogen bond ring in compound **2** was evaluated through a newly developed $^1H-^{15}N$ heteronuclear

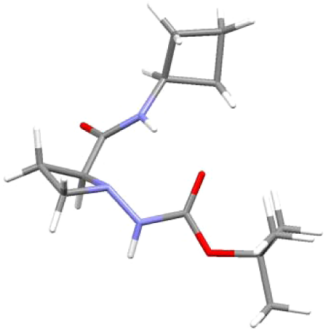


Figure 5. Lowest energy conformer of amide **2**.

NMR experiment. IMPACT HMBC (IMProved and Accelerated Constant-Time Heteronuclear Multiple-Bond Correlation) NMR spectroscopy is a variation of the 2D HMBC technique that provides a high-quality 2D spectrum with minimal artifacts and enhanced sensitivity, thus improving the detection of weak interactions, such as hydrogen bonds that involve nuclei (such as ^{15}N) that have low natural abundance.[47,48] First, unambiguous assignment of each of the three ^{15}N NMR signals of amide **2** was achieved via a $^1H-^{15}N$ HSQC experiment. The IMPACT HMBC experiment was then carried out and showed a correlation peak between $N_{(5)}$ and $H_{(10)}$, which was interpreted as the result of a hydrogen bond between these two atoms. These studies provide convincing evidence for the formation of a hydrazino turn in solution (Figure 6).

The ensemble of evidence presented above suggests that the AAzC residue presents its own preferred structural pattern based on a hydrazino turn stabilized eight-membered hydrogen bond. To establish the stability of this secondary structural feature, we decided to study dipeptides combining an AAzC unit and each of the stereoisomers of ACBC, which are also known to possess a pronounced local folding potential.

Four dipeptides combining (*S*)-AAzC with a designated stereoisomer of ACBC were prepared. Dipeptides **12**−**15** were synthesized in good yield by coupling the Boc-hydrazino acid **1** with the methyl ester of each stereoisomer of ACBC (obtained by deprotection of compounds **8**−**11**, which, in turn, were obtained by esterification of the appropriate ACBC stereoisomer), as shown in Scheme 3. The four dipeptides **12**−**15** were fully characterized using the same suite of structural analyses (IR, NMR, molecular modeling) as described above for the AAzC amide **2**.

FTIR analysis of the two dipeptides containing a *trans*-ACBC residue, **12** and **14**, gave results similar to those obtained for the model amide **2**, that is, a stretching band at ca. 3360 cm^{-1} assigned to the carbazate NH vibration and a strong band at ca. 3300 cm^{-1} from the hydrogen bonded amide NH (Figure 7). Thus, these two dipeptides appear to adopt the cyclic eight-membered hydrogen bond conformation. The case of the two *cis* derivatives **13** and **15** is less clear-cut, since three absorption bands are present: a small stretching band at ca. 3435 cm^{-1} associated with a free amide NH and/or to the carbazate NH vibration of the *E* conformer, a second absorption band at ca. 3360 cm^{-1} assigned to the carbazate NH vibration in the *Z* conformation, and a third band at ca. 3300 cm^{-1} corresponding to the hydrogen-bonded amide NH. Thus, dipeptides **13** and **15** exist as a mixture of conformers. Although these observations can be, in part, explained by the presence of a hydrazino turn conformer, they also indicate the presence of a

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Table 1. Significant Calculated Parameters for Compounds 2 and 12−15 in Solution State

	distances (Å)			H bond (Å)				torsion (deg)
				hydrazino turn		10-membered ring		
	$H_{(4)}$−$H_{(6')}$	$H_{(4)}$−$H_{(8')}$	$H_{(8)}$−$H_{(10)}$	C=$O_{(3)}$···$H_{(10)}$N	$N_{(5)}$···$H_{(10)}$N	C=$O_{(15)}$···$H_{(4)}$N	C=$O_{(15)}$···$H_{(10)}$N	$N_{(4)}$−$N_{(5)}$−$C_{(8)}$−$C_{(9)}$
2	2.58	2.69	3.36	2.18	2.29			−96.2
12	2.59	2.67	3.36	2.15	2.29			−96.7
13a	2.61	2.80	3.34	2.11	2.32			−96.3
13b	2.56	2.84	3.32	2.09	2.33			−96.7
13c	3.66	3.53	3.36			2.22	2.46	−91.9
13d	3.63	3.57	3.35			2.50	2.30	−92.3
14	2.60	2.66	3.36	2.14	2.26			−96.2
15a	2.62	2.71	3.37	2.21	2.26			−96.3
15b	2.59	2.65	3.39	2.27	2.31			−97.1

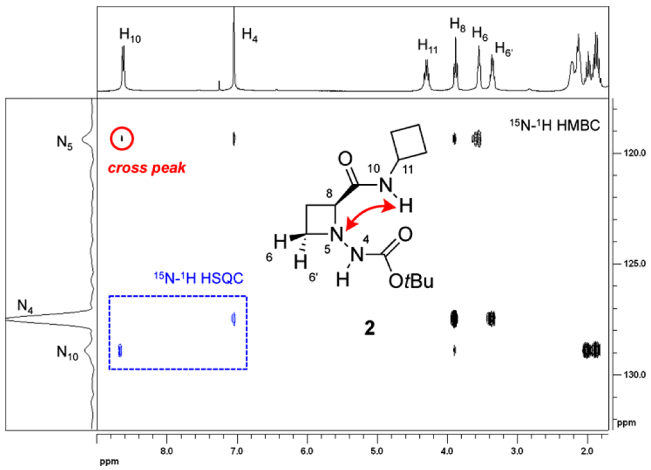
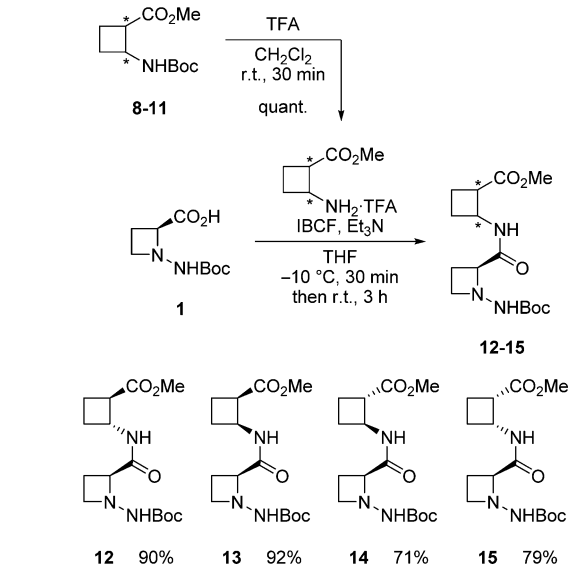


Figure 6. $^{1}H-^{15}N$ IMPACT HMBC NMR for compound **2** in $CDCl_3$ at 263 K with a superimposition of a part of the $^{1}H-^{15}N$ HSQC (in blue) allowing the attribution of the different nitrogen atoms.

Scheme 3. Preparation of Dipeptides 12−15



conformation in which the amide $NH_{(10)}$ is non-hydrogen-bonded or in which $NH_{(4)}$ and C=$O_{(3)}$ are not involved in a hydrogen bond, leaving the carbazate function to adopt its preferred *E* geometry. Although this additional conformer is of interest, it was not possible at this stage to identify it unambiguously. If a longer-distance intramolecular noncovalent interaction were implicated, such as a 10-membered ring, the carbazate moiety could be in either an *E* or a *Z* geometry, but $NH_{(4)}$ would be hydrogen-bonded, giving an absorption at ca. 3300 cm^{-1}, whereas the nonbonded $NH_{(10)}$ would appear at ca. 3440 cm^{-1}. On the other hand, an extended conformation would imply a free $NH_{(4)}$ and an "unrestrained" carbazate geometry (i.e., $E > Z$), as long as a nonbonded $NH_{(10)}$ giving rise to an intense absorption signal at 3440 cm^{-1} and a low absorption at 3360 cm^{-1}.

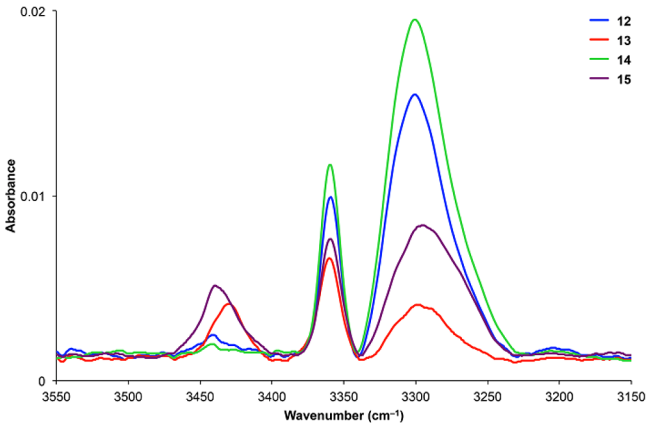


Figure 7. FTIR absorption spectra of dipeptides **12−15** (10 mM solution in $CHCl_3$).

After complete attribution of all ^{1}H and ^{13}C signals, 1D NMR experiments (concentration dependence, isotopic exchange) showed that dipeptides **12−15** behaved in a similar fashion to the model amide **2**: a low-field, non concentration-dependent chemical shift for $NH_{(10)}$ and an isotopic exchange sensitive $NH_{(4)}$ signal again indicated a cyclic eight-membered hydrogen bond conformer in all four cases.

NOESY experiments on dipeptides **12−15** provided correlation patterns similar to that observed for the model amide **2** and were used to extract interatomic distances (see the Supporting Information). A MCMM conformational search, followed by DFT geometry optimization, was carried out as described above for amide **2** (data are collected in Table 1). For the two dipeptides containing a *trans*-ACBC residue, **12** and **14**, the conformational search gave, respectively, two and three low-energy conformer families that remained after DFT geometry optimization. In both cases, the lowest potential energy corresponded to the hydrazino turn conformation and fitted perfectly with the NOESY NMR data (Figure 8). The situation was more complex for the two *cis*-ACBC peptides **13**

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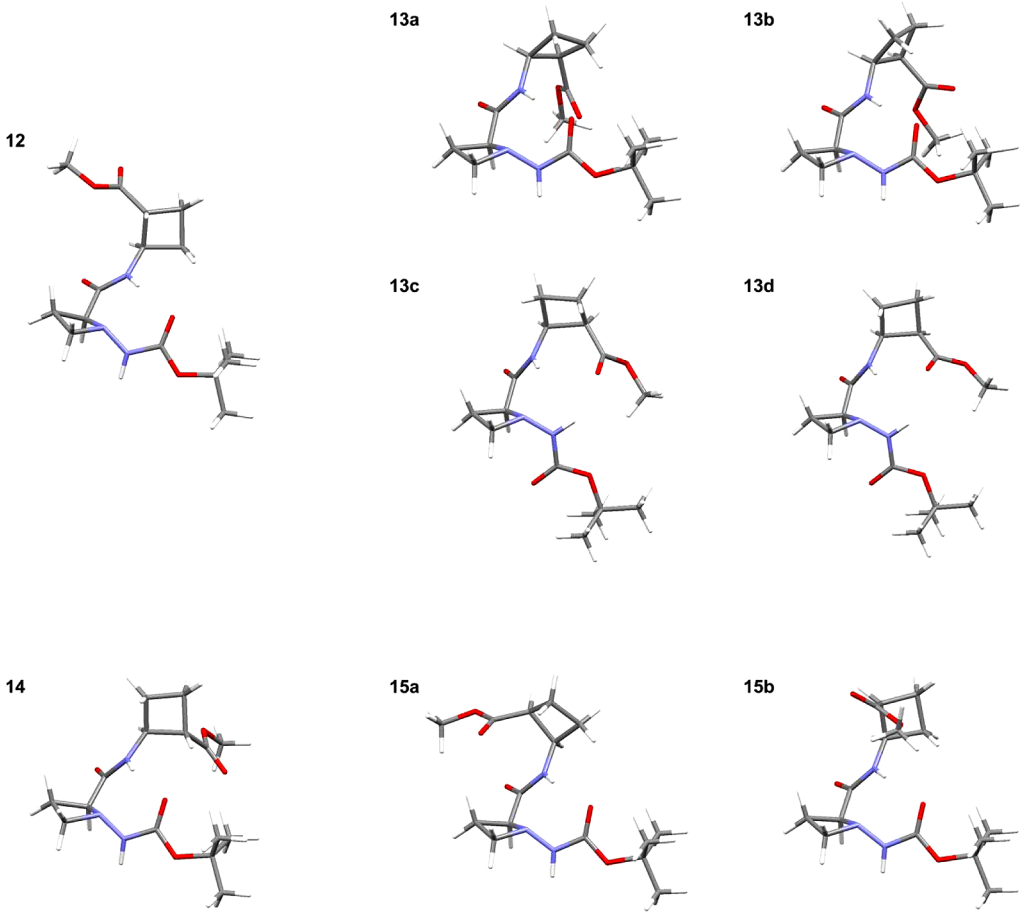

Figure 8. Lowest-energy conformers of compounds **12**–**15**.

and **15**. The conformational search gave nine and eight families of conformers, respectively. Conformational refinement reduced the number of accessible families of conformers to six and five, respectively. The large number of conformer families is partly due to "family twins" arising from the two conformations that a *cis*-ACBC unit can adopt, each with one substituent pseudoaxial and the other pseudoequatorial. For dipeptide **15**, the two hydrazino turn conformations **15a** and **15b** emerged as the lowest energy families, and appear to be populated equally. In the case of dipeptide **13**, the hydrazino turn was relinquished in favor of a 10-membered hydrogen bond ring in the two lowest energy conformers, **13c** and **13d**, although this observation alone does not explain the FTIR and 1D NMR isotopic exchange data described above. The four low-energy conformer families were, therefore, subjected to an ab initio geometrical optimization at the B3LYP 6-31G** level of theory in chloroform (implicit method) using Gaussian 09 software.[49] The four low-energy conformer families—two hydrazino turn families **13a** and **13b** and two 10-membered hydrogen bond ring families **13c** and **13d**—emerged with very similar energies, suggesting roughly equal populations. This situation best explains the FTIR results and is consistent with the NOESY NMR data.

The four dipeptides **12**–**15** were analyzed by the $^{1}H-^{15}N$ IMPACT HMBC NMR experiment in $CDCl_3$ to search for an interaction between $NH_{(10)}$ and $N_{(5)}$. The sensitivity of all $^{1}H-^{15}N$ correlations was enhanced by a factor in the range of 2–8 compared to the standard $^{1}H-^{15}N$ HMBC experiment, and a specific correlation between $NH_{(10)}$ and $N_{(5)}$ was observed in all four cases. These observations provide convincing evidence for the presence of the bifurcated hydrogen-bonding system of a hydrazino turn in solution.

We were able to deduce the coupling constants ($^{h1}J_{NH}$) through the hydrogen bond between $NH_{(10)}$ and $N_{(5)}$ and then use the values to evaluate the distance between the two atoms. For each peptide **12**–**15**, a deconvolution procedure allowed the comparison of a reconstructed ^{1}H spectrum with the extracted rows from the $^{1}H-^{15}N$ IMPACT HMBC spectra.[50] The reconstructed spectra that showed the best fit with the extracted spectra provided the value of the $^{h1}J_{NH}$ coupling constant. These coupling constants were then applied in an empirical equation that had previously been developed to assess the distance between an amide NH and an imidazole N in proteins.[51] In the event, the $^{h1}J_{NH}$ coupling constants for dipeptides **12**–**15** were in the range of 2.8–3.4 Hz, which corresponds to a $N_{(5)}\cdots H_{(10)}$ distance of 2.8–2.9 Å. The same analysis conducted on the model amide **2** provided a $^{h1}J_{NH}$ value of 3.2 Hz, which corresponds to a $N_{(5)}\cdots H_{(10)}$ distance of 2.9 Å. The interatomic distances deduced by this method are slightly higher than those obtained from the molecular modeling studies (Table 1), but still constitute a reasonable approximation considering that the equation used is purely empirical.

While the principle objective of this work was to study AAzC derivatives in the solution state, it was instructive to examine and compare the results with solid state data when available. Single crystals of model AAzC amide **2** and dipeptide **14** were amenable to X-ray diffraction analysis, and the crystal structure

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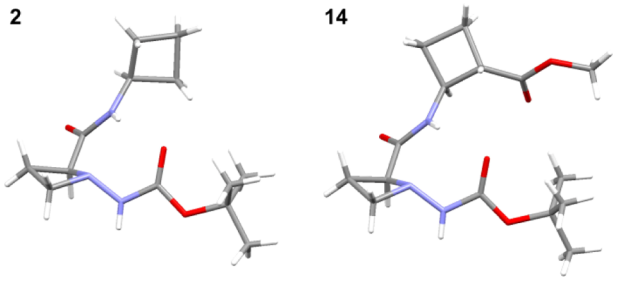

Figure 9. X-ray structures of amide **2** and dipeptide **14**.

conformations of these compounds are shown in Figure 9. Each compound adopts a conformation very similar to its lowest-energy solution state structure with a hydrazino turn evidently contributing to the eight-membered hydrogen bond ring. In both cases, the AAzC unit adopts a *trans*-like configuration, with a backbone torsion angle of −97.3° for **2** and −93.9° for **14**. This latter value is slightly lower than those calculated from solution state studies (Table 1), which might be the result of packing effects in the solid state. In each case, $H_{(10)}$ participates in a three-center hydrogen bond with $C{=}O_{(3)}$ and $N_{(5)}$ for which distances are in the range of 2.2−2.3 Å (Table 2).

Intriguingly, single-crystal analysis of dipeptide **15** showed an extended molecular structure in which no intramolecular interactions were present (Figure 10). The offset head-to-head alignment of the molecules in the crystal facilitates the formation of a network of intermolecular $C{=}O_{(9)}\cdots H_{(4')}N$ hydrogen bonds. $N_{(5)}$ is not involved in any noncovalent interaction.

CONCLUSION

This first detailed structural study of AAzC derivatives in solution indicates that the title compound conveniently combines the rigidity of a cyclic molecular skeleton with a hydrazino acid function in order to facilitate the formation of a hydrazino turn conformer in small peptides. NMR data, in particular, provided strong evidence for a noncovalent interaction between the AAzC ring nitrogen and the amide NH of the adjacent residue, consistent with the tenet that a bifurcated hydrogen bond is a central feature of the cyclic eight-membered hydrazino turn feature. Nonetheless, low-energy conformations structured around a cyclic 10-membered ring hydrogen bond also appears accessible, which suggests that AAzC might be able to adapt its local structure to accommodate the demands of neighboring residues. AAzC thus emerges as a potentially useful building block for inclusion in peptides with predictable, yet malleable, conformational behavior.

EXPERIMENTAL SECTION

All reagents and solvents were of commercial grade and were used without further purification. Dichloromethane was dried over activated alumina, and THF was distilled from sodium/benzophenone. Flash chromatography was performed with SDS silica gel (35−70 μm).

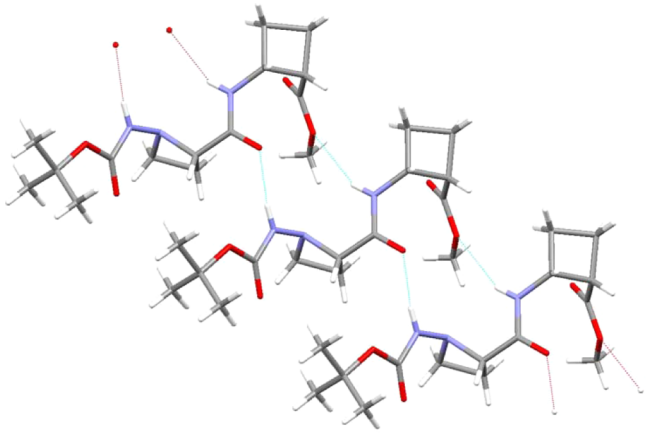

Figure 10. X-ray structure of dipeptide **15**.

Analytical thin-layer chromatography was performed with 0.25 mm commercial silica gel plates (EMD, Silica Gel $60F_{254}$). TLC plates were visualized by UV fluorescence at 254 nm, then revealed using a phosphomolybdic acid solution (10% in EtOH) or a ninhydrin solution (0.3% in *n*-BuOH). Retention factors (R_f) are given for such analyses. Routine nuclear magnetic resonance (NMR) data were acquired on a spectrometer operating at 360 MHz for ^{1}H and at 90 MHz for ^{13}C. Chemical shifts (δ) are reported in parts per million from tetramethylsilane. Splitting patterns for ^{1}H NMR signals are designated as: s (singlet), d (doublet), t (triplet), q (quadruplet), quint (quintuplet), bs (broad singlet), or m (multiplet). Coupling constants (^nJ) are reported in hertz. High-resolution mass spectrometry (HRMS) data were recorded using the electrospray ionization technique in positive mode (ESI+) with a tandem Q-TOF analyzer. Samples for Fourier-transform infrared spectroscopy (IR) were prepared as solution in $CHCl_3$ (10 mM) in a NaCl solution cell. Maximum absorbances (ν) are given for significant bands in cm^{-1}. Melting points were obtained in open capillary tubes and are uncorrected. Optical rotations were measured using a 10 cm quartz cell. Values for $[\alpha]_D^T$ were obtained with the D-line of sodium at the indicated temperature T, using solutions of concentration (c) in units of g·100 mL^{-1}.

General Procedure for the Preparation of Cyclobutylamide Derivatives. To an ice cold solution of Boc-hydrazino acid **1** or Boc-amino acid **4** or **5** (1.0 mmol, 1 equiv) in dry CH_2Cl_2 (20 mL) were added 1-hydroxybenzotriazole monohydrate (189.2 mg, 1.4 mmol, 1.4 equiv) and cyclobutylamine (94 μL, 1.1 mmol, 1.1 equiv). The mixture was stirred for 10 min at 0 °C; then 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (287.6 mg, 1.5 mmol, 1.5 equiv) was added. The resulting mixture was then stirred for 14−48 h at room temperature and then washed successively with 1 M aqueous $KHSO_4$ (10 mL) and saturated $NaHCO_3$ (10 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography (CH_2Cl_2/EtOAc) gave the cyclobutylamide derivative **2**, **6**, or **7**.

*N-Cyclobutyl-(S)-1-(t-butyloxycarbonylamino)azetidine-2-carboxamide (**2**).* Coupling of Boc-(*S*)-AAzC **1** with cyclobutylamine according to the general procedure, followed by flash chromatography (CH_2Cl_2/EtOAc = 50/50), gave the cyclobutylamide (−)-**2** (216.2 mg, 80%) as a white solid. mp 190.5−191.1 °C (dec.); R_f 0.22 (CH_2Cl_2/EtOAc = 50/50); $[\alpha]_D^{24}$ −53 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) ν 3359, 3310, 3020, 3006, 2980, 2940, 2896, 2873, 1714, 1652, 1544,

Table 2. Significant Parameters for Crystal Structure of Compounds 2 and 14

	distances (Å)			H bond (Å)		torsion (deg)
	$H_{(4)}{-}H_{(6')}$	$H_{(4)}{-}H_{(8)}$	$H_{(8)}{-}H_{(10)}$	$C{=}O_{(3)}\cdots H_{(10)}N$	$N_{(5)}\cdots H_{(10)}N$	$N_{(4)}{-}N_{(5)}{-}C_{(8)}{-}C_{(9)}$
2	2.51	2.66	3.20	2.22	2.25	−97.3
14	2.48	2.62	3.22	2.29	2.29	−93.9

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1497; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.58−1.78 (m, 2H), 1.86−2.10 (m, 3H), 2.13−2.38 (m, 3H), 3.32 (pseudo dd, 1H, ^2J = 15.7 Hz, ^3J = 8.8 Hz), 3.61−3.68 (m, 1H), 3.88 (pseudo t, 1H, ^3J = 8.8 Hz), 4.30−4.43 (m, 1H), 6.15 (bs, 1H), 8.46 (bs, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 15.3, 19.8, 28.3, 30.7, 31.0, 44.2, 54.7, 72.2, 81.1, 155.6, 170.4; HRMS (ESI+) Calcd for $C_{13}H_{23}N_3NaO_3$ $[M + Na]^+$: 292.1632, found 292.1622.

*N-Cyclobutyl-(1R,2R)-2-(t-butyloxycarbonylamino)cyclobutanecarboxamide (**6**).* Coupling of Boc-(1*R*,2*R*)-ACBC **4** with cyclobutylamine according to the general procedure, followed by flash chromatography (CH_2Cl_2/EtOAc = 70/30), gave the cyclobutylamide (−)−**6** (219.9 mg, 82%) as a white solid. mp 225−226 °C (dec.); R_f 0.26 (CH_2Cl_2/EtOAc = 70/30); $[\alpha]_D^{23}$ −9 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) ν 3446, 3290, 3019, 2981, 2938, 2897, 2874, 1694, 1644, 1554, 1501; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.60−1.79 (m, 3H), 1.80−2.03 (m, 3H), 2.03−2.22 (m, 2H), 2.22−2.39 (m, 2H), 2.85 (pseudo dd, 1H, ^2J = 18.2 Hz, ^3J = 9.2 Hz), 4.05−4.17 (m, 1H), 4.28−4.44 (m, 1H), 4.93 (bs, 1H), 8.17 (bs, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 15.4, 18.7, 24.9, 28.5, 30.9, 31.2, 44.7, 48.8, 50.4, 80.6, 156.4, 172.0; HRMS (ESI+) Calcd for $C_{14}H_{24}N_2NaO_3$ $[M + Na]^+$: 291.1679, found 291.1667.

*N-Cyclobutyl-(1R,2S)-2-(t-butyloxycarbonylamino)cyclobutanecarboxamide (**7**).* Coupling of (1*R*,2*S*)-ACBC **5** with cyclobutylamine according to the general procedure, followed by flash chromatography (CH_2Cl_2/EtOAc = 80/20), gave the cyclobutylamide (−)−**7** (253.5 mg, 94%) as a white solid. mp 174−175 °C (dec.); R_f 0.50 (CH_2Cl_2/EtOAc = 70/30); $[\alpha]_D^{24}$ −108 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) ν 3436, 3021, 2980, 2951, 2897, 1699, 1657, 1502; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.63−1.74 (m, 2H), 1.75−1.91 (m, 3H), 2.01−2.11 (m, 1H), 2.13−2.37 (m, 4H), 3.11 (pseudo dt, 1H, ^3J = 8.2 Hz, ^3J = 2.6 Hz), 3.29−3.42 (m, 2H), 5.29 (bs, 1H), 5.73 (bs, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 15.3, 18.3, 25.5, 29.2, 31.2, 31.4, 44.9, 46.5, 79.4, 155.4, 171.9; HRMS (ESI+) Calcd for $C_{14}H_{24}N_2NaO_3$ $[M + Na]^+$: 291.1679, found 291.1674.

*Cyclobutyl (S)-1-(t-Butyloxycarbonylamino)azetidine-2-carboxylate (**3**).* To a solution of Boc-(*S*)-AAzC **1** (46.5 mg, 0.22 mmol, 1 equiv) in CH_2Cl_2 (2.5 mL) were added successively DMAP (39.4 mg, 0.32 mmol, 1.5 equiv) and cyclobutanol (19 μL, 0.24 mmol, 1.1 equiv). The mixture was then cooled to 0 °C, and EDCI·HCl (61.8 mg, 0.32 mmol, 1.1 equiv) was added. The solution was stirred for 5 min at 0 °C and then 16 h at room temperature, at which point the solvent was evaporated under reduced pressure. Flash chromatography (petroleum ether/EtOAc = 90/10) gave the methyl ester (−)−**3** (34.3 mg, 59%) as a colorless oil. R_f 0.25 (petroleum ether/EtOAc = 80/20); $[\alpha]_D^{20}$ −110 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) ν 3438, 3359, 3019, 2984, 2891, 1728, 1717, 1477, 1467; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.51−1.66 (m, 1H), 1.70−1.83 (m, 1H), 1.92−2.15 (m, 3H), 2.16−2.38 (m, 3H), 3.54 (ddd, 1H, ^2J = 14.1 Hz, ^3J = 5.9 Hz, ^3J = 4.5 Hz), 3.99 (pseudo dd, 1H, ^2J = 14.1 Hz, ^3J = 7.7 Hz), 4.72 (pseudo t, 1H, ^3J = 7.5 Hz), 5.01 (pseudo quint., 1H, ^3J = 7.6 Hz), 6.36 (bs, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.5, 18.6, 28.4, 30.3, 53.8, 66.4, 69.2, 80.4, 154.8, 171.8; HRMS (ESI+) Calcd for $C_{13}H_{22}N_2NaO_4$ $[M + Na]^+$: 293.1472, found 293.1457.

General Procedure for the Preparation of Methyl Esters. To a solution of Boc-amino acid **4** or **5** (215.3 mg, 1.0 mmol, 1 equiv) in CH_2Cl_2 (11 mL) were added successively DMAP (12.2 mg, 0.1 mmol, 0.1 equiv) and MeOH (0.13 mL, 13 mmol, 13 equiv). The mixture was then cooled to 0 °C, and EDCI·HCl (210.9 mg, 1.1 mmol, 1.1 equiv) was added. The solution was stirred for 5 min at 0 °C and then 15 h at room temperature, at which point the solvent was evaporated under reduced pressure. Flash chromatography (petroleum ether/EtOAc = 90/10) gave the methyl ester **8**−**11**.

*Methyl (1R,2R)-2-(t-Butyloxycarbonylamino)cyclobutanecarboxylate (**8**).* Coupling of Boc-(1*R*,2*R*)-ACBC **4** with methanol according to the general procedure, followed by flash chromatography (petroleum ether/EtOAc = 90/10), gave the methyl ester (−)−**8** (192.6 mg, 84%) as a white solid. R_f 0.32 (petroleum ether/EtOAc = 80/20); $[\alpha]_D^{19}$ −53 (*c* 1.08, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.78−1.96 (m, 3H), 2.11−2.25 (m, 1H), 2.87−3.06 (m, 1H), 3.63 (s, 3H), 4.08−4.24 (m, 1H), 5.02 (bs, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 18.2, 27.3, 28.4, 46.8, 48.9, 51.7, 79.5, 154.7, 173.5.

*Methyl (1R,2S)-2-(t-Butyloxycarbonylamino)cyclobutanecarboxylate (**9**).* Coupling of Boc-(1*R*,2*S*)-ACBC **5** with methanol according to the general procedure, followed by flash chromatography (petroleum ether/EtOAc = 90/10), gave the methyl ester (−)−**9** (174.4 mg, 79%) as a white solid. R_f 0.44 (petroleum ether/EtOAc = 80/20); $[\alpha]_D^{20}$ −130 (*c* 1.09, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.84−2.03 (m, 2H), 2.11−2.37 (m, 2H), 3.29−3.40 (m, 1H), 3.66 (s, 3H), 4.43−4.49 (m, 1H), 5.33 (bs, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 18.5, 28.4, 29.5, 45.3, 45.9, 51.7, 79.4, 154.8, 174.7.

*Methyl (1S,2S)-2-(t-Butyloxycarbonylamino)cyclobutanecarboxylate (**10**).* Coupling of Boc-(1*S*,2*S*)-ACBC *ent*-**4** with methanol according to the general procedure, followed by flash chromatography (petroleum ether/EtOAc = 90/10), gave the methyl ester (+)−**10** (190.3 mg, 83%) as a white solid. R_f 0.32 (petroleum ether/EtOAc = 80/20); $[\alpha]_D^{18}$ +58 (*c* 1.08, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.41 (s, 9H), 1.81−2.00 (m, 3H), 2.17−2.28 (m, 1H), 2.89−3.05 (m, 1H), 3.67 (s, 3H), 4.13−4.26 (m, 1H), 4.84 (bs, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 18.3, 27.4, 28.4, 47.0, 49.0, 51.8, 79.7, 154.8, 173.5.

*Methyl (1S,2R)-2-(t-Butyloxycarbonylamino)cyclobutanecarboxylate (**11**).* Coupling of Boc-(1*S*,2*R*)-ACBC *ent*-**5** with methanol according to the general procedure, followed by flash chromatography (petroleum ether/EtOAc = 90/10), gave the methyl ester (+)−**11** (167.4 mg, 73%) as a white solid. R_f 0.44 (petroleum ether/EtOAc = 80/20); $[\alpha]_D^{20}$ +124 (*c* 1.09, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.83−2.02 (m, 2H), 2.10−2.38 (m, 2H), 3.28−3.40 (m, 1H), 3.65 (s, 3H), 4.32−4.49 (m, 1H), 5.34 (bs, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 18.5, 28.4, 29.5, 45.3, 45.9, 51.7, 79.4, 154.8, 174.7.

General Procedure for the Preparation of Dipeptides. TFA (0.69 mL, 9 mmol, 30 equiv) was added dropwise to a solution of Boc-amino ester **8**−**11** (68.8 mg, 0.3 mmol, 1 equiv) in CH_2Cl_2 (2.1 mL). The mixture was stirred for 30 min at room temperature; then the solvent and the excess TFA were evaporated under reduced pressure to give an oil (*c.* 110 mg). The resulting TFA salt **TFA·H$_2$N-ACBC-OMe** was used directly in the next reaction.

To a cold (−10 °C) solution of Boc-(*S*)-AAzC **1** (64.9 mg, 0.3 mmol, 1 equiv) in dry THF (0.3 mL) were added successively Et_3N (132 μL, 0.95 mmol, 3.2 equiv) and IBCF (39 μL, 0.3 mmol, 1 equiv). The solution was stirred for 5 min at −10 °C; then a solution of **TFA·H$_2$N-ACBC-OMe** in dry THF (0.3 mL) was added. Residual salts were taken up by rinsing with dry THF (0.3 mL) and added to the cold reaction mixture. The resulting mixture was stirred for 30 min at −10 °C and then for 3 h at room temperature, at which point the solution was filtered and evaporated under reduced pressure. Flash chromatography (CH_2Cl_2/EtOAc = 50/50) of the residue gave the dipeptide **12**−**15**.

*(1R,2R)-Methyl 2-((S)-1-(t-Butyloxycarbonylamino)azetidine-2-carboxamido)cyclobutane carboxylate (**12**).* Coupling of Boc-(*S*)-AAzC **1** with **TFA·H$_2$N-(1*R*,2*R*)-*t*-ACBC-OMe** according to the general procedure, followed by flash chromatography (CH_2Cl_2/EtOAc = 50/50), gave the dipeptide (−)−**12** (87.9 mg, 90%) as a white solid. mp 110 °C; R_f 0.16 (CH_2Cl_2/EtOAc = 50/50); $[\alpha]_D^{26}$ −82 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) ν 3359, 3301, 3019, 2982, 2870, 1724, 1661, 1544, 1498; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.82−2.06 (m, 4H), 2.11−2.28 (m, 2H), 3.09−3.20 (m, 1H), 3.34 (pseudo dd, 1H, ^2J = 15.9 Hz, ^3J = 8.5 Hz), 3.56−3.72 (m, 1H), 3.64 (s, 3H), 3.86 (pseudo t, 1H, ^3J = 8.8 Hz), 4.51 (pseudo quint, 1H, ^3J = 8.3 Hz), 6.32 (bs, 1H), 8.67 (bs, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 18.7, 19.8, 26.8, 28.3, 46.4, 46.7, 51.8, 54.5, 72.0, 81.0, 155.7, 170.7, 173.5; HRMS (ESI+) Calcd for $C_{15}H_{25}N_3NaO_5$ $[M + Na]^+$: 350.1686, found 350.1685.

*(1R,2S)-Methyl 2-((S)-1-(t-Butyloxycarbonylamino)azetidine-2-carboxamido)cyclobutane carboxylate (**13**).* Coupling of Boc-(*S*)-AAzC **1** with **TFA·H$_2$N-(1*R*,2*S*)-*c*-ACBC-OMe** according to the general procedure, followed by flash chromatography (CH_2Cl_2/EtOAc = 50/50), gave the dipeptide (−)−**13** (90.4 mg, 92%) as a white solid. mp 153 °C; R_f 0.15 (CH_2Cl_2/EtOAc = 50/50); $[\alpha]_D^{25}$ −166 (*c* 0.50,

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$CHCl_3$); IR ($CHCl_3$) ν 3430, 3360, 3299, 3012, 2979, 2894, 1723, 1661, 1527, 1501; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.82−2.01 (m, 2H), 2.11−2.40 (m, 4H), 3.37 (pseudo dd, 1H, ^3J = 11.7 Hz, ^3J = 8.2 Hz), 3.51 (pseudo dd, 1H, ^2J = 15.6 Hz, ^3J = 8.6 Hz), 3.56−3.64 (m, 1H), 3.58 (s, 3H), 4.07 (pseudo t, 1H, ^3J = 8.8 Hz), 4.62 (pseudo quint, 1H, ^3J = 8.2 Hz), 6.22 (bs, 1H), 8.30 (bs, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 19.2, 19.7, 27.7, 28.4, 44.6, 45.3, 51.5, 54.3, 70.4, 81.0, 155.3, 171.5, 173.4; HRMS (ESI+) Calcd for $C_{15}H_{25}N_3NaO_5$ $[M + Na]^+$: 350.1686, found 350.1679.

*(1S,2S)-Methyl 2-((S)-1-(t-Butyloxycarbonylamino)azetidine-2-carboxamido)cyclobutane carboxylate (**14**).* Coupling of Boc-(*S*)-AAzC **1** with **TFA·H$_2$N-(1*S*,2*S*)-*t*-ACBC-OMe** according to the general procedure, followed by flash chromatography (CH_2Cl_2/EtOAc = 50/50), gave the dipeptide (+)−**14** (69.7 mg, 71%) as a white solid. mp 120 °C; R_f 0.17 (CH_2Cl_2/EtOAc = 50/50); $[\alpha]_D^{24}$ +4 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) ν 3360, 3301, 3020, 2981, 2955, 2934, 2871, 1725, 1661, 1542, 1497; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.81−2.02 (m, 4H), 2.11−2.27 (m, 2H), 2.98−3.08 (m, 1H), 3.35 (pseudo dd, 1H, ^2J = 15.7 Hz, ^3J = 8.8 Hz), 3.55 (s, 3H), 3.53−3.62 (m, 1H), 3.88 (pseudo t, 1H, ^3J = 8.8 Hz), 4.47 (pseudo quint, 1H, ^3J = 8.1 Hz), 6.68 (bs, 1H), 8.71 (bs, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 18.8, 19.6, 27.1, 28.2, 46.0, 46.6, 51.6, 54.3, 71.7, 80.8, 155.8, 170.9, 173.5; HRMS (ESI+) Calcd for $C_{15}H_{25}N_3NaO_5$ $[M + Na]^+$: 350.1686, found 350.1694.

*(1S,2R)-Methyl 2-((S)-1-(t-Butyloxycarbonylamino)azetidine-2-carboxamido)cyclobutane carboxylate (**15**).* Coupling of Boc-(*S*)-AAzC **1** with **TFA·H$_2$N-(1*S*,2*R*)-*c*-ACBC-OMe** according to the general procedure, followed by flash chromatography (CH_2Cl_2/EtOAc = 50/50), gave the dipeptide (+)−**15** (77.7 mg, 79%) as a white solid. mp 109 °C; R_f 0.19 (CH_2Cl_2/EtOAc = 50/50); $[\alpha]_D^{26}$ +40 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) ν 3439, 3359, 3295, 3019, 2979, 2955, 2895, 2871, 1726, 1660, 1531, 1496; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.76−2.00 (m, 2H), 2.13−2.41 (m, 4H), 3.34−3.45 (m, 2H), 3.55−3.64 (m, 1H), 3.72 (s, 3H), 3.94 (pseudo t, 1H, ^3J = 8.7 Hz), 4.68 (pseudo quint, 1H, ^3J = 8.3 Hz), 6.15 (bs, 1H), 8.59 (bs, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 18.7, 19.9, 27.7, 28.3, 44.6, 45.3, 51.7, 54.5, 71.5, 80.7, 155.1, 171.1, 173.3; HRMS (ESI+) Calcd for $C_{15}H_{25}N_3NaO_5$ $[M + Na]^+$: 350.1686, found 350.1690.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General information, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, ^{1}H−^{15}N IMPACT HMBC NMR spectra, and X-ray diffraction data for compounds **2**, **14**, and **15** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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