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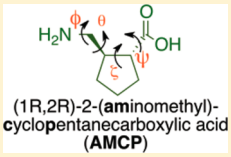
Evaluation of a Cyclopentane-Based γ-Amino Acid for the Ability to Promote α/γ-Peptide Secondary Structure

Michael W. Giuliano,[†] Stacy J. Maynard, Aaron M. Almeida, Andrew G. Reidenbach, Li Guo, Emily C. Ulrich, Ilia A. Guzei, and Samuel H. Gellman*

Department of Chemistry, University of Wisconsin-Madison, Madison, Wisconsin 53706, United States

Supporting Information

ABSTRACT: We report the asymmetric synthesis of the γ-amino acid (1*R*,2*R*)-2-aminomethyl-1-cyclopentane carboxylic acid (AMCP) and an evaluation of this residue's potential to promote secondary structure in α/γ-peptides. Simulated annealing calculations using NMR-derived distance restraints obtained for α/γ-peptides in chloroform reveal that AMCP-containing oligomers are conformationally flexible. However, additional evidence suggests that an internally hydrogen-bonded helical conformation is partially populated in solution. From these data, we propose characteristic NOE patterns for the formation of the α/γ-peptide 12/10-helix and discuss the apparent conformational frustration of AMCP-containing oligomers.



INTRODUCTION

γ-Amino acids are appealing as building blocks for peptidic foldamers because the conformational propensities of individual γ subunits can be modulated by varying substitution at the α, β, and/or γ carbons.[1,2] Pioneering work by Hanessian et al. showed that the folding behavior of γ-amino acid residues bearing one substituent at the α carbon and another at the γ carbon was critically dependent on the relative configurations at the two stereocenters, with one stereoisomeric form supporting helical secondary structure and the other stereoisomeric form favoring reverse-turn secondary structure.[1b,d] These trends were subsequently confirmed by Seebach et al., who also identified an α,β,γ-trisubstitution pattern that promotes a helical conformation (Figure 1a).[1c,f,h] Incorporation of cyclic constraints into the γ-amino acid backbone can promote sheet[1a,g,j,k] or helix secondary structure, depending on the ring size, the configurations of the stereogenic centers, and the location of the ring within the γ residue (i.e., incorporation of the Cα−Cβ bond, the Cβ−Cγ bond, or both the Cα−Cβ and Cβ−Cγ bonds into the ring).[1] Although initial studies focused on the folding of pure γ-peptide backbones, subsequent efforts have expanded to include heterogeneous backbones in which γ residues are combined with α and/or β residues to generate α/γ-, β/γ-, or α/β/γ-peptides.[3]

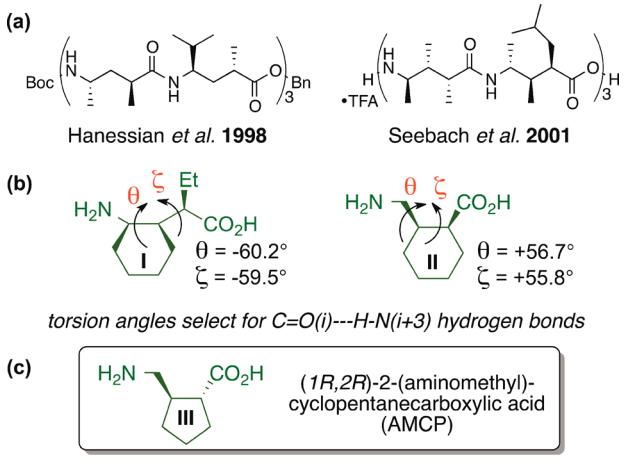


Figure 1. (a) Helix-forming oligomers of γ-residues studied by Hanessian[1b,d] and Seebach.[1c,f,h] (b) Constrained γ-amino acids that promote formation of helices that contain C=O(*i*)···H−N(*i* + 3) hydrogen bonds.[3] (c) γ-Amino acid AMCP.

We have explored two types of γ-residue in which a cyclohexyl ring provides a backbone constraint, **I** and **II** (Figure 1b). These residues differ in the position of the cyclohexyl ring along the backbone (involving the Cβ−Cγ vs Cα−Cβ bond) and whether or not the third backbone carbon bears a substituent. Trisubstituted residue **I** strongly promotes formation of helices that contain C=O(*i*)···H−N(*i* + 3) hydrogen bonds in both homogeneous and heterogeneous backbones.[3a−c] Disubstituted residue **II** has been examined only in α/γ backbones, where it can be accommodated into two different helices, one containing only C=O(*i*)···H−N(*i* + 3) H-bonds and the other featuring an alternation between C=O(*i*)···H−N(*i* + 3) H-bonds and C=O(*i*)···H−N(*i* − 1) H-bonds.[3d] The former helix appears to reflect the intrinsic preference of residue **II** on the basis of the similarity of its observed θ and ζ torsion angle values with those of residue **I**. Here, we describe the stereoselective synthesis of (1*R*,2*R*)-2-(aminomethyl)cyclopentanecarboxylic acid (**III**; AMCP, Figure 1c)[4] and the conformational behavior of α/γ-peptides containing AMCP residues.

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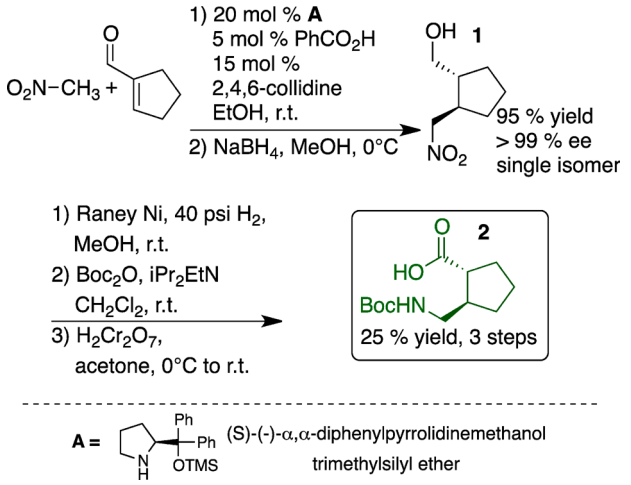
RESULTS AND DISCUSSION

Synthesis. Evaluation of the extent to which a chiral amino acid supports the adoption of discrete conformations when incorporated into peptidic oligomers requires access to a protected derivative of that amino acid in enantiopure form. We prepared the Boc-protected form of AMCP, as summarized in Scheme 1. This route follows the strategy previously employed

Scheme 1. Synthesis of *N*-Boc-(1*R*,2*R*)-2-aminomethyl-1-cyclopentanecarboxylic Acid 2 (AMCP)



to prepare protected derivatives of **II**; the key step is an asymmetric Michael addition of nitromethane to a cycloalkene-1-carboxaldehyde.[3d] Our approach to this reaction is based on precedents from Hayashi et al. and Wang et al., who reported highly enantioselective addition of nitromethane to β-substituted propenal derivatives catalyzed by pyrrolidine **A** and benzoic acid.[5] The analogous process with cyclohexene-1-carboxaldehyde gave rise to a ~4.5:1 trans/cis product mixture. In situ reduction provided the δ-nitro alcohols, each of which displayed >95% ee (reduction prevents epimerization during isolation).[3d] Adaptation of this method to the addition of nitromethane to cyclopentene-1-carboxaldehyde required us to replace benzoic acid as cocatalyst with a 3:1 2,4,6-collidine/benzoic acid mixture (see the Supporting Information). This reaction produced exclusively the trans δ-nitro alcohol (**1**) in 95% yield and >99% ee. A three-step procedure, involving nitro-group reduction, Boc-protection, and primary alcohol oxidation, converted δ-nitro alcohol **1** into protected γ-amino acid **2**. This AMCP building block can be readily prepared in multigram quantities.

The absolute configuration of AMCP prepared in this way was determined from the crystal structure of α/γ-dipeptide **3**, which was synthesized by coupling **2** to D-alanine benzyl ester (Figure 2). This analysis showed that use of **A** as the chiral

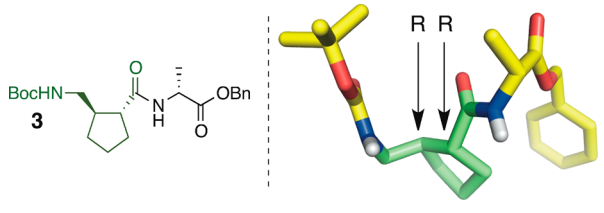


Figure 2. X-ray crystal structure of α/γ-dipeptide **3**.

catalyst (S configuration at the stereogenic center) provides the γ-amino aldehyde with R configuration at the two new stereogenic centers. The crystal structure of **3** showed θ and ζ torsion angles of 55° and −113°, respectively. This observation is intriguing because our previous crystallographic analysis of oligomers containing residues derived from γ-amino acids **I** or **II** show that both favor *gauche*$^+$,*gauche*$^+$ (g^+,g^+, or $g-,g-$, depending on absolute configuration) θ,ζ torsion angle sequences, which is consistent with the apparent preference of both residues for the formation of helices containing exclusively C=O(i)···H–N(i + 3) H-bonds.[3a−c] Hofmann et al. have used computational methods to explore the helical conformations available to γ-, α/γ-, and β/γ-peptide backbones (no side chains),[6] and their results suggest that the distinctive θ,ζ angles manifested by **3** in the solid state could lead to helical preferences for α/γ-peptides containing AMCP (**III**) that differ from those of analogous oligomers containing **I** or **II**.

We prepared a series of α/γ-peptides containing γ residue **III** and D-α-amino acid residues, with a 1:1 residue alternation, as summarized in Scheme 2. Tetramer **8**, hexamer **9**, and octamer **12** all contain D-alanine at the α positions, whereas decamer **15** contains both D-alanine and D-phenylalanine residues to promote dispersion of NMR resonances. These oligomers were prepared by condensation of α/γ dimers such as **6** and **7**, reactions in which the carboxyl group is provided by a γ-residue. This approach avoids epimerization, which can occur during peptide condensations in which the carboxyl group is provided by an α residue. Because the yields of fragment-coupling reactions declined with increasing length of the product oligomer among tetramer **8**, hexamer **9**, and octamer **10**, we replaced HOBt with Oxyma as the nucleophilic additive for the reaction to produce decamer **15**.[7] In addition, we switched from DMF to a 4:1 NMP/DMSO solvent mixture for this tetramer-plus-hexamer coupling reaction because the precursors were barely soluble in DMF.

Structural Characterization of α/γ-Peptides That Contain AMCP. α/γ-Peptides **8**, **9**, and **12** were analyzed by ^{1}H NMR in $CDCl_3$; 5% (v/v) CD_3OH in $CDCl_3$ was required to ensure complete dissolution of decamer **15**.[8] We observed invariant chemical shifts for the proton resonances of decamer **15** over a 50-fold range of concentrations (0.04−2 mM), which suggests that this α/γ-peptide does not self-associate under these conditions. Because **15** is the least soluble of the α/γ-peptides in this study, we suspect that smaller α/γ-peptides **8**, **9**, and **12** do not aggregate under the conditions used for NMR analysis (2−4 mM in chloroform; see the Supporting Information). Well-dispersed and amide proton resonances with chemical shifts >7.5 ppm were observed for 2−4 mM samples of hexamer **9**, octamer **12**, and decamer **15** (Figure 3a). Under conditions that do not support self-association, these downfield-shifted NH resonances suggest the formation of internally H-bonded conformations.[9] (Non-H-bonded amide NH resonances typically display chemical shifts <7.0 ppm.)

Overlap among the D-alanine HCα proton resonances between 4 and 5 ppm and among the γ-residue HCγ proton resonances between 3 and 4 ppm suggest the possibility of conformational averaging on the NMR time scale (Figure 3b). ^{1}H–^{1}H COSY, TOCSY, and ROESY data were obtained for α/γ-peptides **9**, **12**, and **15** (see the Supporting Information for resonance assignment). Several of the observed NOEs suggest at least partial population of folded conformations by these α/γ-peptides because the protons involved are separated by multiple covalent bonds (Figure 4).

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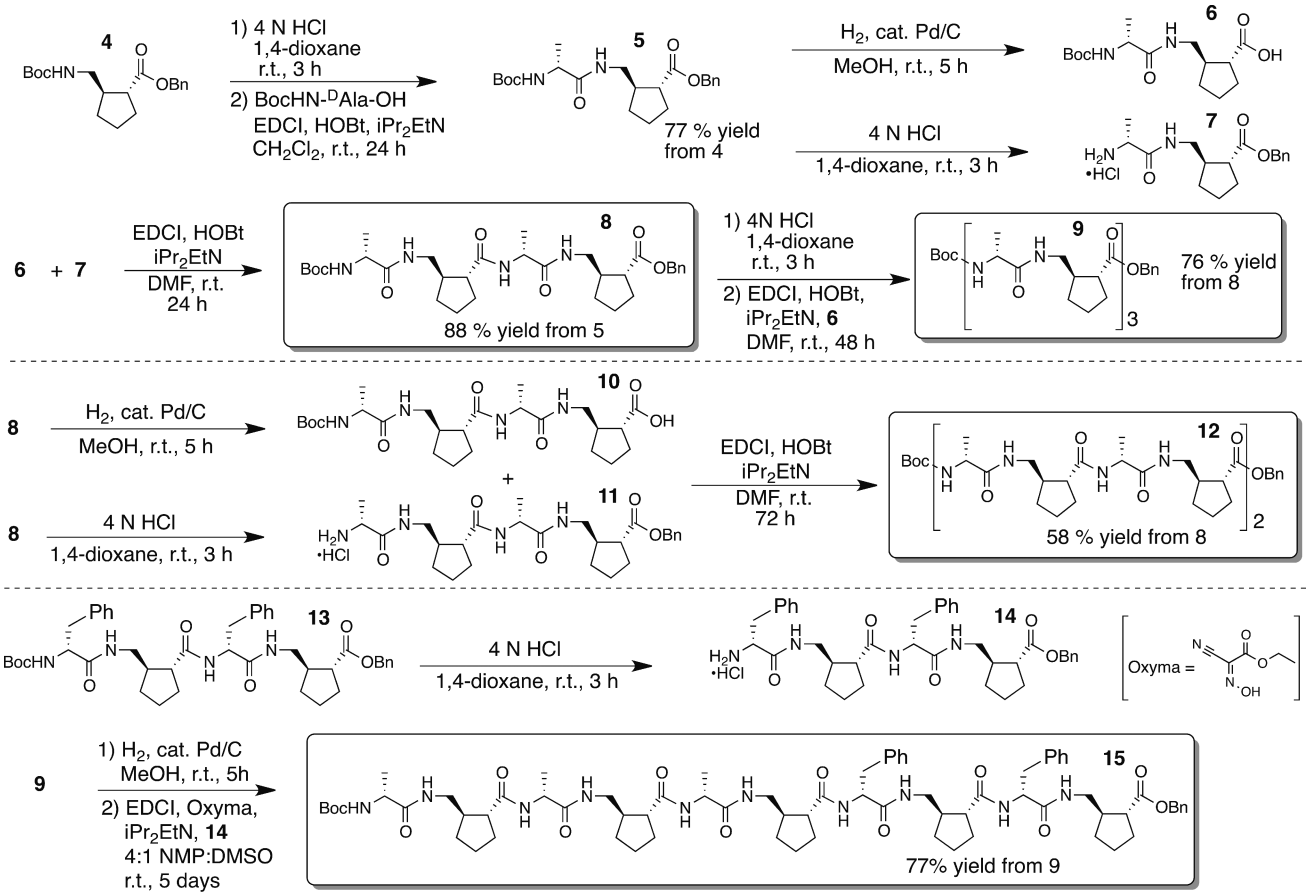
Scheme 2. Solution-Phase Synthesis of α/γ-Peptides That Contain AMCP



We carried out NOE-restrained simulated-annealing calculations with the CNS program for **9**, **12**, and **15**.[10] In each case, the 10 structures with the lowest energy were selected for comparison with one another without any further minimization (see the Supporting Information). We did not observe any violation of our NOE-derived distance restraints in the lowest-energy structures. The resulting structural ensembles are diverse, lacking a contiguous network of H-bonds or consistent set of backbone torsion angles. As α/γ-peptide length increases from hexamer to octamer to decamer, the rmsd calculated for backbone atoms in the ensembles increases from 0.8 ± 0.1 to 2.0 ± 1.0 to 2.4 ± 0.4 Å (see the Supporting Information). The disordered ensembles suggest that AMCP-containing α/γ-peptides are dynamic in solution and do not adopt a single, highly populated secondary structure.

The lack of a significant conformational preference implied by analysis of the NOE restrained dynamics of α/γ- peptides **9**, **12**, and **15** seems somewhat inconsistent with the excellent dispersion of NH resonances observed for these oligomers and the regular pattern of *i*,*i* + 2 NOEs observed in all three cases (NOE type (*i*) in Figure 5). This type of *i*,*i* + 2 NOE has been attributed to 12/10-helix formation for α/γ-peptides of comparable lengths in comparable solvents;[11] in these previous α/γ-peptide studies, the γ-residues lacked a cyclic constraint. Our α/γ-peptides display a regular pattern of NOEs between the HN of a γ residue (*i*) and the HN of an adjacent α residue (*i* + 1) (NOE type (*ii*) in Figure 5). This type of NOE was not reported in the previous α/γ-peptide study.[11] On the basis of the examination of theoretical models from Hofmann et al.,[6] we conclude that this type of *i*,*i* + 1 NOE is consistent with 12/10-helix formation. Notably absent from our data are NOEs of type (*iii*) in Figure 5 between the HCγ of a γ-resiude (*i*) and the HN of an adjacent α residue (*i* + 1); this type of NOE is reported to be characteristic of 12/10-helix formation.[11] The lack of type (*iii*) NOEs in the NMR data for α/γ-peptides **9**, **12**, and **15** may partially explain why our simulated annealing calculations failed to produce well-defined conformational ensembles comparable to those previously reported.[11] Other possible explanations for this difference are mentioned below.

To test for the possibility of partial 12/10-helix formation in α/γ-peptides containing AMCP, we conducted a DMSO titration experiment with α/γ-peptide decamer **15** (Figure 6). Amide proton chemical shifts of **15** were monitored as small aliquots of DMSO were added to a solution of the α/γ-peptide in $CDCl_3$ containing 5% (v/v) CD_3OH. Because DMSO is a strong H-bond acceptor, added DMSO should form H-bonds with amide protons that are oriented toward the solvent, causing their NMR signals to move downfield. If an amide proton is engaged in intramolecular H-bonds, however, added DMSO should have little or no effect on chemical shift.

The data in Figure 6 suggest that decamer **15** experiences at least partial 12/10-helix formation in $CDCl_3$ containing 5% (v/v) CD_3OH. The NH resonances most strongly affected by DMSO addition are those at the N- and C-termini; the strong downfield shifting in these cases suggests that these NH groups do not form intramolecular H-bonds. In contrast, the resonances from the four internal NHs are only moderately influenced by DMSO addition, which suggests that these NH groups are, on average, at least partially engaged in intramolecular H-bonds. This pattern is consistent with partial

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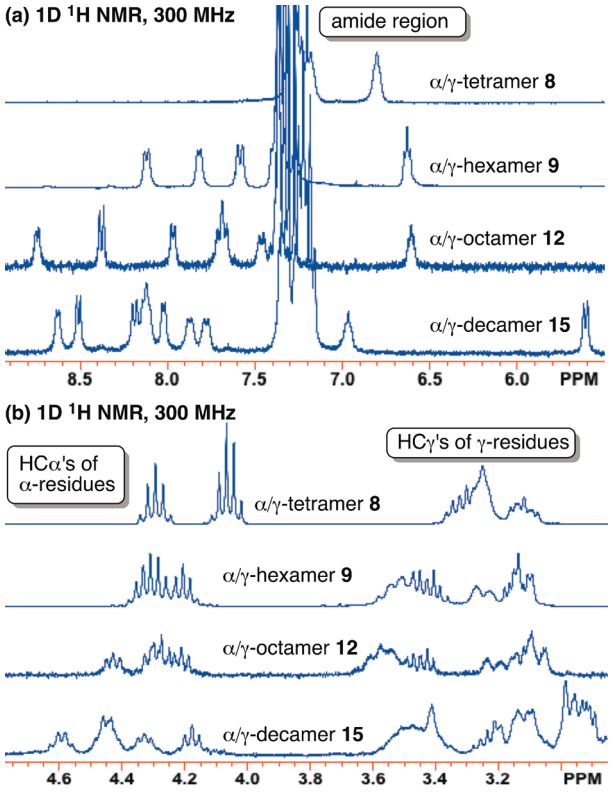

Figure 3. (a) Amide proton region of the ^{1}H NMR spectra ($CDCl_3$) of α/γ-peptides **8**, **9**, **12**, and **15**. (b) HCα and HCγ proton region of the ^{1}H NMR spectra ($CDCl_3$) of α/γ-peptides **8**, **9**, **12**, and **15**. Samples were collected at peptide concentrations of 4, 2, 2, and 2 mM, respectively. α/γ-Decamer **15** was dissolved in 5% (v/v) CD_3OH.[8]

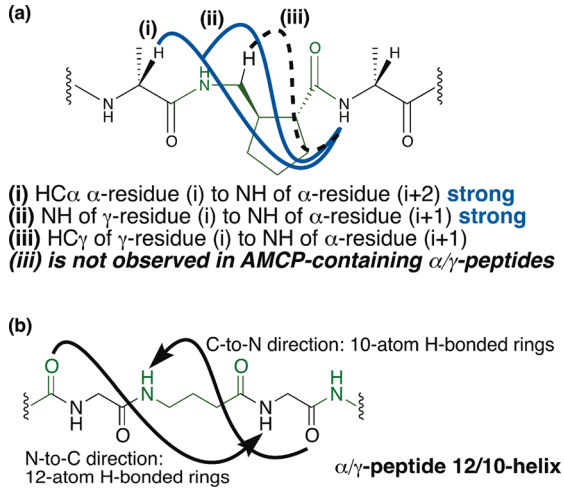

Figure 5. (a) NOEs characteristic of 12/10-helix formation. (*i*) NOEs observed in α/γ-peptides **9**, **12**, and **15** consistent with those reported for the α/γ-peptide 12/10-helix by Sharma and Kunwar.[11] (*ii*) NOE observed in our study of α/γ-peptides **9**, **12**, and **15**. (*iii*) NOE observed in 12/10-helical peptides of Sharma and Kunwar (not observed in NMR study of **9**, **12**, and **15**). (b) Diagram of hydrogen bonding in the α/γ-peptide 12/10-helix. γ-Residues shown in green.

population of the 12/10-helical conformation, which features both C═O(*i*)···H–N(*i* + 3) H-bonds and C═O(*i*)···H–N(*i* − 1) H-bonds.[6d,11] Because the H-bonds run in both directions relative to the helix axis, non-H-bonded NH groups are found at both termini (Figures 5b and 6b). In contrast, for a helix in which all H-bonds are oriented in the same direction (e.g., an α-helix), non-H-bonded NH groups would be found at only one terminus. The conclusion we draw from the DMSO titration experiment, that the terminal NH groups of **15** do not form intramolecular H-bonds in $CDCl_3$ containing 5% (v/v) CD_3OH while the internal NH groups are at least partially intramolecularly H-bonded, is consistent with the pattern in chemical shifts observed in the absence of DMSO: the terminal NH resonances are 2 to 3 ppm upfield relative to the internal NH resonances.

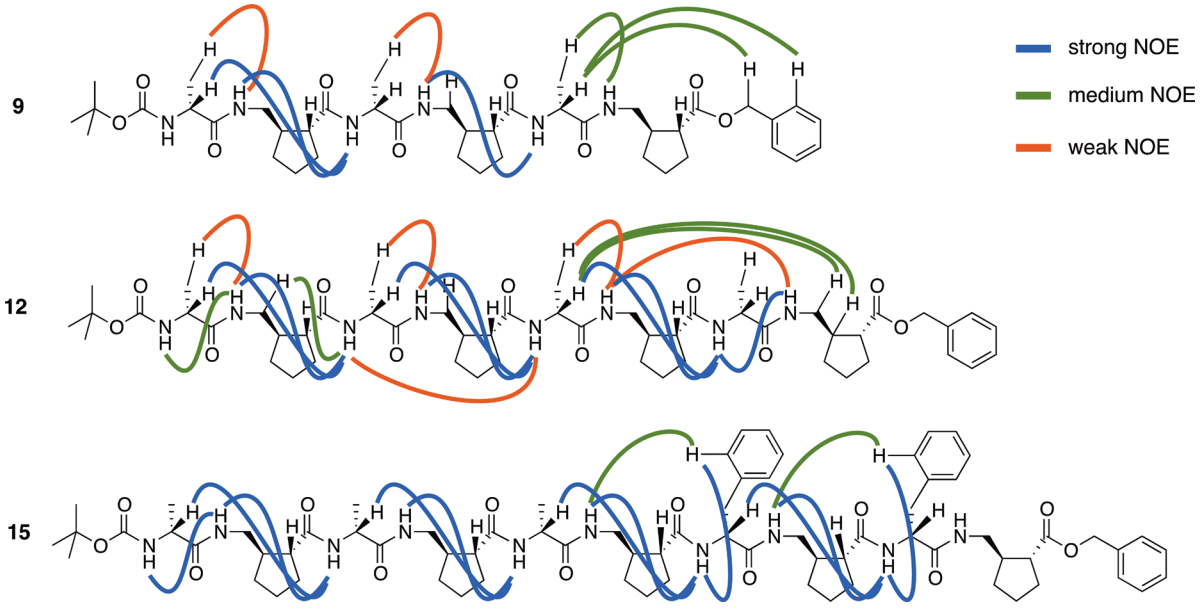

Figure 4. Selected NOEs observed in ROESY experiments for α/γ-peptides **9**, **12**, and **15.** Data were collected at peptide concentrations 2 mM in $CDCl_3$ solution. α/γ-Decamer **15** was dissolved with the addition of 5% (v/v) CD_3OH. See the Supporting Information for tabulated sequence assignments and NOEs for each α/γ-peptide.

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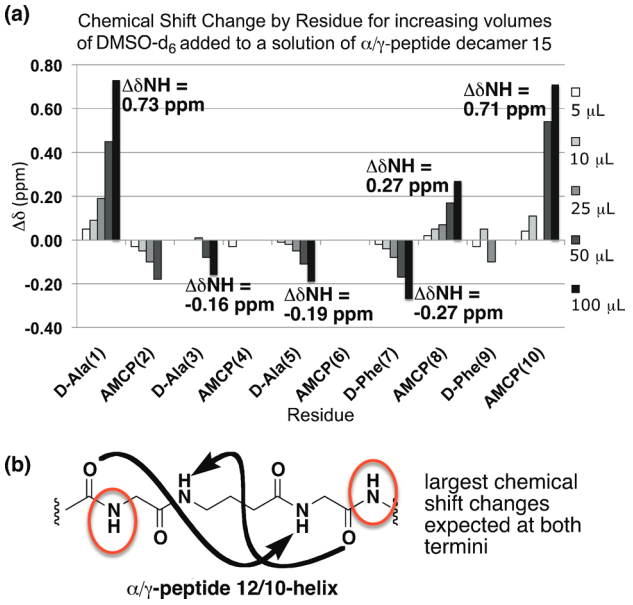

Figure 6. (a) DMSO titration of 2 mM α/γ-peptide decamer **15** (5% (v/v) CD_3OH) in $CDCl_3$. (b) Schematic of hydrogen-bonding and solvent-exposed amide protons in the α/γ-peptide 12/10-helix. Red circles indicate amide protons expected to exhibit the largest chemical-shift change upon DMSO addition.

Overall, our data suggest that α/γ-peptides containing AMCP, such as hexamer **9**, octamer **12**, and decamer **15** display a modest tendency to adopt 12/10-helical secondary structure. However, this folding propensity is not strong enough to prevent these oligomers from exploring other conformations, even in a nonpolar solvent such as $CDCl_3$.

CONCLUSIONS

We have presented the enantioselective synthesis of a new type of cyclic γ-amino acid, AMCP, and an evaluation of the conformational behavior of α/γ-peptides that contain AMCP residues. Despite the presence of a conformational constraint within these new residues, arising from incorporation of the Cα−Cβ bond into a cyclopentane ring, α/γ-peptides containing AMCP do not display a strong propensity to adopt a specific secondary structure. NMR data suggest that 12/10-helical conformations are moderately populated by these α/γ-peptides in nonpolar solvents and that other conformations are significantly populated as well. We suspect that the lack of a substituent at Cγ of the AMCP backbone causes this new γ residue to be quite flexible in spite of the Cα−Cβ ring constraint. Consistent with this proposal is our previous report on α/γ-peptides in which the γ residues are derived from **II**, which lacks a substituent at Cγ. Crystallographic data showed that this class of α/γ-peptides can accommodate two different helical conformations.[3d] Further support for the proposed correlation between unsubstituted backbone carbons within a γ-amino acid and flexibility in oligomers that contain the corresponding γ residue is found in the broad conformational diversity evident in crystal structures of oligomers generated from gabapentin, which is disubstituted at Cβ but lacks substituents at Cα and Cγ.[12] It is well-known among conventional peptides that glycine residues, which lack a side chain, are inherently more flexible than other α-amino acid residues.

The NMR evidence for partial folding of α/γ-peptides **9**, **12**, and **15**, including dispersion of amide and HCα resonances, patterns of inter-residue NOEs, and H-bond patterns implicated by NH chemical shifts and DMSO titration results, are comparable to observations reported for a different set of α/γ-peptides by Sharma and Kunwar.[11] NOE-restrained dynamics analysis of these alternative α/γ-peptides, however, seems to suggest a more robust propensity for 12/10-helical secondary structure than we detect for AMCP-containing α/γ-peptides. The difference between the previous conformational conclusions[11] and those we draw here may arise because of differences in γ-residue substitution (the previous series contained γ residues bearing a single, bulky substituent at Cγ), differences in the observed NOE patterns (discussed above), differences in treatment of the NMR data (e.g., variations in the distance ranges assigned to varying NOE intensities for NOE-restrained dynamics calculations), or some combination of these factors.

Fülöp and co-workers have proposed that controlling both ϕ and ψ dihedral angles is critical for manipulating helical secondary structure among α/β-peptides.[13] Our study of AMCP-containing α/γ-peptides suggests an analogous importance for ϕ and ψ dihedral angles in oligomers that contain γ-amino acid residues. Thus, using a ring to constrain one backbone bond within a γ residue may not be sufficient to encode a strong and specific folding propensity.[1]

EXPERIMENTAL METHODS

General Methods. Solvents and reagents were used as received unless otherwise indicated. CH_2Cl_2 and tetrahydrofuran were distilled from CaH_2 and sodium-benzophenone ketyl, respectively. Flash column chromatography was performed on silica gel (40−63 mm mesh). Thin-layer chromatography (TLC) was performed on glass-backed plates with fluorescent indicator. Visualization was carried out with $KMnO_4$ as a general stain and phosphomolybic acid for α/γ-peptides **8**, **9**, **12**, **13**, and **15**, which stain weakly in other conditions ($KMnO_4$, *p*-anisaldehyde, ceric ammonium molybdate, and ceric ammonium sulfate).

HPLC analysis of chiral compounds was carried out on an analytical HPLC system using columns with chiral stationary phases (columns and conditions are indicated in the Supporting Information). One-dimensional ^{1}H NMR spectra were recorded on 300 MHz spectrometers, and results are reported in parts per million (ppm, δ) relative to tetramethylsilane. First-order ^{1}H NMR splitting patterns were assigned on the basis of their appearance as singlet (s), doublet (d), triplet (t), or quartet (q). Resonances that could not be interpreted were designated multiplet (m) or broad (b). One-dimensional ^{13}C NMR spectra were recorded on a 300 MHz spectrometer (@ 75 MHz). For some compounds, higher-field 500 MHz spectrometers were utilized to obtain ^{13}C spectra (indicated on spectra). ^{13}C NMR chemical shifts are reported in the text to ±0.1 ppm, rounded from values to two decimal places obtained from spectra included in the Supporting Information. Two-dimensional ^{1}H−^{1}H NMR COSY, TOCSY, and ROESY experiments were carried out on a 600 MHz spectrometer. High-resolution mass spectra (HRMS) were measured using a an electrospray ionization spectrometer (TOF detector). Optical rotations were measured using a 1 mL cell with a 0.5 dm path length on a digital polarimeter (Na lamp) and are reported as follows: $[\alpha]^{rt}_D$ (*c* in grams per 100 mL). Images of crystal and NMR structures shown throughout the manuscript and the Supporting Information were prepared in MacPymol.[14]

Synthetic Procedures. *1-Cyclopentene-1-carboxaldehyde.* 1-Cyclopentene-1-carboxaldehyde is a known compound characterized previously in the literature.[15] We prepared it for use according to the following a two-step procedure. We note that because of its propensity

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for coevaporation even in low-boiling solvents our yields were reduced following the oxidation step. We isolated 1-cyclopentene-1-carboxaldehyde as a solution of known weight percent in ether/pentane and quantified it by ^{1}H NMR using 1,4-dioxane as an internal standard. To a stirring 0.5 M solution of methyl-1-cyclopentane-1-carboxylate (4.84 mL, 39.6 mmol, 1.0 equiv) in anhydrous hexanes at −78 °C (80 mL) was added DIBAL-H via syringe (1.0 M solution in hexanes; 80 mL, 80.0 mmol, 2.0 equiv) in four 20 mL aliquots over a period of 15 min under a N_2 atmosphere. The reaction was warmed to 0 °C (ice bath) and stirred for 1.5 h. The reaction was quenched with 50 mL of ice cold Rochelle's salt (saturated Na/K tartrate) and allowed to stir at 0 °C open to air. The reaction became a gray−white gelatinous suspension that solubilized over the course of 30 min to 1 h with stirring at room temperature open to air. The mixture was poured into a 1 L separatory funnel containing 200 mL of diethyl ether and 200 mL of distilled H_2O. The layers were separated, and the aqueous layer was extracted twice more with 200 mL of diethyl ether. The organic layers were combined, dried over $MgSO_4$, and concentrated to afford a pale clear oil that was purified via silica gel column chromatography, eluting with 3:1 hexanes/EtOAc. 1-Cyclopentene-1-methanol product was isolated as a clear oil (3.50 g, 90% yield). For the purposes of scaled-up amino acid synthesis, this reaction was often done in multiple passes. ^{1}H 1D NMR in $CDCl_3$ agree with literature values.[14a] ^{1}H NMR literature (300 MHz, $CDCl_3$):[15a] δ 5.62−5.59 (m, 1H), δ 4.18 (m, 2H), δ 2.39−2.27 (m, 4H), 1.96−1.86 (m, 2H), 1.46 (s, 1H). ^{1}H NMR observed (300 MHz, $CDCl_3$): δ 5.62 (app. quintet, 1H, J = 1.8 Hz), δ 4.18 (m, 2H), δ 2.42−2.26 (m, 4H), 1.92 (quintet, 2H, J = 7.5 Hz), 1.08 (broad s, 1H).

To a stirring suspension of pyridinium chlorochromate (PCC) (13.2 g, 61.4 mmol, 1.2 equiv) in 50 mL of distilled CH_2Cl_2 with ∼3 g of 4 Å molecular sieves at 0 °C (ice bath) was added 1-hydroxymethyl-1-cyclopentene (5.02 g, 51.2 mmol, 1.0 equiv) as a solution in 25 mL of distilled CH_2Cl_2 dropwise over 20 min via an addition funnel under a N_2 atmosphere. The reaction was allowed to stir for ∼6 h as it warmed to rt and was monitored via TLC (3:1 hexanes/EtOAc, $KMnO_4$ stain). The reaction was stirred for 4 h at rt, at which point additional PCC (2.6 g, 12.1 mmol, 0.25 eqiuv) was added. The reaction was monitored by TLC as described and was complete (loss of alcohol starting material spot) after 1 h following addition of more PCC. The reaction was diluted with 50 mL of diethyl ether and filtered through a plug of silica. Fifty milliliters of additional diethyl ether was used to wash the silica plug. The filtrate was filtered a second time as described above (the plug was washed as above). The filtrate was concentrated carefully to yield a malodorous, pale-yellow/green oil. The crude material was purified via silica gel column chromatography, eluting with 13% (v/v) diethyl ether in pentane. The product was isolated as a colorless solution of approximately 88 wt % 1-cyclopenete-1-carboxaldehyde in ether/pentane (solution quantified by ^{1}H NMR with 1,4-dioxane as an internal standard; 1.19 g in solution, 24% yield). Significant yield was lost despite extra care in concentrating the product (ice in rotovap bath). For the purposes of scaled-up amino acid synthesis, this reaction was often done in multiple passes. ^{1}H 1D NMR of 1-cyclopenete-1-carboxaldehyde in $CDCl_3$ agree with literature values.[15b] ^{1}H NMR literature (300 MHz, $CDCl_3$):[14b] δ 9.80 (s, 1H), δ 6.88−6.86 (m, 1H), δ 2.63−2.59 (m, 2H), δ 2.55−2.51 (m, 2H), δ 2.01 (app. t, 1H, J = 7.5 Hz), δ 1.98 (app. t, 1H, J = 7.5 Hz). ^{1}H NMR observed (300 MHz, $CDCl_3$): δ 9.80 (s, 1H), 6.89−6.86 (m, 1H), δ 2.65−2.58 (m, 2H), δ 2.55−2.50 (m, 2H), δ 2.00 (app. quintet, 2H, J = 7.6 Hz). Note that this last resonance would occur from the superposition of the two triplets (δ 2.01, 1.98) reported in the cited reference given their identical three-bond J coupling constants.

*(1R,2R)-1-(Hydroxymethyl)-2-(nitromethyl) Cyclopentane (**1**).* S-(−)-α,α-Diphenylpyrrolidnemethanol trimethylsilyl ether (2.0 g, 6.0 mmol, 0.2 equiv) was dissolved in EtOH. 2,4,6-Collidine (617 μL, 4.7 mmol, 0.15 equiv) was added followed by benzoic (189 mg, 1.6 mmol, 0.05 equiv), and the solution was stirred about 5−10 min until all species dissolved. 1-Cyclopentene-1-carboxaldehyde was added (2.98 g, 31 mmol, 1.0 equiv), and the solution was stirred at room temperature as it slowly took on a yellow−orange color. Nitromethane (3.0 equiv) was added in a single portion, and the solution immediately turned a deep green color. The total reaction volume was ∼62 mL (0.5 M in 1-cyclopentene-1-carboxaldehyde). The reaction was sealed with a septum and stirred at room temperature for 2 h.

The solution was diluted with an equivalent volume of MeOH and cooled to 0 °C in an ice bath. $NaBH_4$ (1.76 g, 46.5 mmol, 1.5 equiv) was added slowly over a period of 15 min, causing the reaction to bubble vigorously. The solution was stirred at 0 °C for an additional 15−30 min or until all bubbling subsided. The reaction was quenched at 0 °C via slow addition of an equal volume of saturated (aq) NH_4Cl and stirred for ∼30 min. The mixture was stirred until all precipitate dissolved and was then allowed to warm to room temperature. The reaction mixture was then diluted in a separatory funnel with brine and extracted five times with Et_2O. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to afford a yellow−orange oil. The crude material was purified via flash column chromatography on silica gel, eluting with a gradient of EtOAC in hexanes (hexanes/EtOAC (v/v) 20:1 to 3:1) to afford pure nitroalcohol **1** as a clear, pale-yellow oil (4.93 g, > 95% yield). R_f (3:1 (v/v) hexanes/EtOAc) = 0.07. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.45 (ABX, J_{AX} = 6.0 Hz, J_{BX} = 9.0 Hz, J_{AB} = 12.0 Hz, ν_{AB} = 83.4 Hz, 2H), 3.61 (ABX, J_{AX} = 5.4 Hz, J_{BX} = 6 0.9 Hz, J_{AB} = 10.3 Hz, ν_{AB} = 831.2 Hz, 2H), 2.47 (sextet, J = 6.0 Hz, 1H), 1.93 (sextet, J = 6.6 Hz, 1H), 1.85 (m, 2H), 1.66 (quintet, J = 7.5 Hz, 2H), 1.43 (quintet, J = 6.3 Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 80.3, 66.2, 45.4, 41.8, 31.1, 29.1, 24.3. Calcd [M + Na^+] observed for $C_7H_{13}NO_3Na^+$, 182.08; found, 182.00. $[\alpha]_D^{rt}$ −15.8° (c 0.6).

*(1R,2R)-2-((tert-Butoxycarbonyl)amino)methyl)-1-cylopentane-carboxylic Acid (**2**).* Nitroalcohol **1** (3.36 g, 21.1 mmol, 1.0 equiv) was taken up in MeOH that had been presaturated with N_2 for 30 min, and the solution was transferred to a high-pressure flask. A catalytic amount (spatula tip, ∼50 mg) of Raney-Ni was added, and the flask was sealed with a pressure gauge and three-way valve. The flask was evacuated with an aspirator and filled with H_2 at 20 psi three times. The flask was brought up to 40 psi H_2 and stirred vigorously at room temperature for 18 h. The pressure was vented into a fume hood, and the reaction mixture was filtered through a plug of Celite topped with a small layer of silica. The filtrate was carefully concentrated via rotovap to remove MeOH with minimal heating (significant product was lost due to coevaporation with MeOH, even in a cooled rotovap bath) to yield an oily residue ((1*R*,2*R*)-1-(hydroxymethyl)-2-(amino-methyl)-cyclopentane; 1.68 g, 62% yield), which was carried forward without any additional purification. The oily residue was taken up in distilled dichloromethane (100 mL), and the solution was transferred to a round-bottomed flask. *i*-Pr_2EtN (4.53 mL, 26 mmol, 2.0 equiv) was added followed by Boc_2O (4.26 g, 19.5 mmol, 1.5 equiv). The flask was flushed with N_2, sealed with a septum, and stirred at room temperature for 3−5 h. Reaction completion was determined via TLC using ninhydrin stain. The solution was diluted 3-fold with EtOAc and washed once with saturated (aq) $NaHSO_4$, washed once with brine (50 mL each wash), dried over anhydrous Na_2SO4, filtered, and concentrated to afford a pale-orange−-yellow oil. The *N*-Boc amino alcohol product ((1*R*,2*R*)-1-(hydroxymethyl)-2-((*tert*-butoxycarbonyl)amino)methyl)-cyclopentane) was isolated as a clear, colorless oil following column chromatography of the crude reaction product, eluting with 1:1 EtOAc/hexanes (2.11 g, 71% yield). R_f (1:1 (v/v) hexanes/EtOAc) = 0.44. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.17 (broad, 1H), 3.57 (ABX, J_{AX} = 4.9 Hz, J_{BX} = 6.8 Hz, J_{AB} = 10.0 Hz, ν_{AB} = 51.1 Hz, 2H), 3.11 (ABX, unresolved, 2H), 2.40 (broad, 1H), 1.80 (m, 4H), 1.59 (m, 2H), 1.44 (s, 9H), 1.30 (m, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 156.7, 79.3, 66.7, 45.8, 45.4, 43.6, 31.4, 29.7, 28.6, 24.6. Calcd [M + Na^+] for $C_{12}H_{23}NO_3Na^+$, 252.1571; found, 252.1578. $[\alpha]_D^{rt}$ −2.8° (c 4.8).

The *N*-Boc amino alcohol product ((1*R*,2*R*)-1-(hydroxymethyl)-2-((*tert*-butoxycarbonyl)amino)methyl)-cyclopentane) (2.11 g, 9.2 mmol, 1.0 equiv) was dissolved in acetone (∼50 mL) and cooled to 0 °C in an ice bath. Jones' reagent (27.6 mL, 13.8 mmol, 1.5 equiv; see below) was added dropwise via an addition funnel with vigorous stirring. The reaction mixture was stirred at 0 °C for 30 min and then

allowed to gradually warm to room temperature as it stirred for ~18 h. The reaction was quenched with an equal volume of *i*-PrOH, and the resulting mixture stirred for about 1 h until the mixture became a deep green solution. The solution was acidified with 1 N HCl and extracted exhaustively with dichloromethane (10 times) until product was not observed via TLC (bromocresol green stain). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to afford a yellow−green crude oil. The crude carboxylic acid was purified via column chromatography, eluting with EtOAc in hexanes (1:1 v/v) to afford Boc-amino acid **2** as an amorphous solid (1.39 g, 66% yield). TLC was visualized with bromocresol green (the carboxylic acid product appears as yellow spot on blue/green background). R_f (1:1 (v/v) hexanes/EtOAc) = 0.32. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.14 (broad, 1H), 6.47 and 4.92 (NH peak split because of *N*-Boc rotamers; broad, 1H total), 3.20 (m, 2H), 2.43 (m, 1H), 2.32 (m, 1H), 1.90 (broad, 3H), 1.69 (sextet, J = 6.3 Hz, 2H), 1.44 (shoulder at 1.46 because of *N*-Boc rotamers; s, 9H total), 1.34 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 181.1, (158.1, 156.8 − split because of *N*-Boc rotamers), 100.7, (80.8, 79.7 − split because of *N*-Boc rotamers), (48.8, 48.0 − split because of *N*-Boc rotamers), (46.3, 44.5 − split because of *N*-Boc rotamers), (31.0, 30.1 − split because of *N*-Boc rotamers), 30.6, 28.6, 24.9. Calcd [M − H$^-$] for $C_{12}H_{20}NO_4^-$, 242.1397; found, 242.1389. $[\alpha]_D^{rt}$ −21.8° (*c* 3.8).

Jones' Reagent Preparation. Sodium dichromate dihydrate (29.8 g, 100 mmol, 1.0 equiv) was weighed into a flask cooled to 0 °C. H_2SO_4 (21.6 mL, 400 mmol, 4.0 equiv) was added slowly to the flask at 0 °C. The solution was diluted to a volume of 200 mL with distilled H_2O to afford a 0.5 M solution of $H_2Cr_2O_7$.

*Dipeptide (**3**).* *N*-Boc-amino acid **2** (180 mg, 0.74 mmol, 1.0 equiv) was dissolved in distilled dichloromethane (5 mL). *i*-Pr_2NEt (387 μL, 2.2 mmol, 3.0 equiv) was added followed by HOBt (120 mg, 0.89 mmol, 1.2 equiv) and EDCI (170 mg, 0.89 mmol, 1.2 equiv). The reaction was stirred for 15 min at room temperature, at which point D-alanine benzyl ester tosylate salt was added (260 mg, 0.74 mmol, 1.0 equiv). The coupling reaction was stirred for 24 h at room temperature. The reaction was diluted with EtOAc (50 mL) and washed with 1 N (aq) $NaHSO_4$, saturated (aq) $NaHCO_3$, and brine (25 mL each). The acidic aqueous washes were extracted twice with dichloromethane (25 mL each), and the same was done for the combined basic/brine washes. All organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to afford crude semisolid material. Dipeptide **3** was isolated via flash column chromatography on silica gel, eluting with a gradient of EtOAc in hexanes to afford a white solid (300 mg isolated, 51% yield). Small diastereomeric impurities (inseparable) appeared to be present in ^{1}H NMR spectrum. We were able to crystallize a small quantity of **3** and obtain diffraction-quality crystals. Crystallographic characterization of dipeptide **3** is detailed in the Supporting Information. The ^{1}H spectrum shown for **3** in the Supporting Information is from a crystal and a small amount of retained mother liquor that was dried on high vacuum and redissolved in $CDCl_3$. R_f (2.5% (v/v) MeOH in CH_2Cl_2) = 0.16. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H), 5.16 (ABq, J_{AB} = 13.8 Hz, ν_{AB} = 25.1 Hz, 2H), 4.88 (broad, 1H), 4.59 (quintet, J = 8.7 Hz, 1H), 3.54 (m, 1H), 2.90 (m, 1H), 2.29 (quartet, J = 8.7 Hz, 1H), 2.05 (broad, 2H), 1.89−1.52 (broad, 6H), 1.45 (d, J = 7.5 Hz, 3H), 1.44 (s, 9H), 1.33 (broad, 1H). Calcd [M + Na$^+$] for $C_{22}H_{32}N_2O_5Na^+$, 427.2204; found, 427.2206.

The X-ray crystal structure of **3** revealed the configuration at C1 and C2 of cyclopentyl ring of AMCP to be (R,R). These stereocenters would have been set in the asymmetric conjugate addition of nitromethane to 1-cyclopentene-1-carboxaldehyde. Thus, we propose that the crystal structure of dipeptide **3** reveals the configuration of the sole observed product of the reaction sequence to produce nitroalcohol **1** to also be (R,R).

*Boc-NH-AMCP-OBn (**4**).* Boc-NH-AMCP-OH (**2**) (1g, 4.1 mmol, 1.0 equiv) was dissolved in 20 mL of DMF (*N*,*N*-dimethylformamide). Cs_2CO_3 (1.34 g, 4.1 mmol, 1.0 equiv) was added, and the reaction mixture was was stirred rapidly at room temperature. Benzyl bromide (487 μL, 4.9 mmol, 1.2 equiv) was added, the reaction flask was sealed with a septum, and the reaction mixture was stirred vigorously for 18 h at room temperature. The reaction mixture was then diluted with EtOAc (~100 mL) and transferred to a separatory funnel. DMF was removed by washing five times with 50 mL of H_2O. Each H_2O wash was back-extracted four times with 50 mL of Et_2O. All organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to a pale-yellow oil. The crude material was purified to a clear colorless oil via column chromatography on silica, eluting with 3:1 hexanes/EtOAC. R_f (3:1 hexanes: EtOAC) = 0.27. The product was isolated in >95% yield (colorless oil, 1.37 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (m, 5H), 5.13 (ABq, J_{AB} = 12.4 Hz, ν_{AB} = 13.5 Hz, 2H), 4.78 (broad, 1H), 3.151 (m, 2H), 2.50 (q, J = 7.5 Hz, 1H), 2.33 (sextet, J = 7.2 Hz, 1H), 1.89 (m, 3H), 1.68 (m, 2H), 1.43 (s, 9H), 1.31 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 1761, 156.2, 136.3, 128.8, 128.4, 128.3, 79.3, 66.6, 48.4, 45.1, 44.3, 30.7, 30.5, 28.6, 25.0. Calcd [M + Na$^+$] for $C_{19}H_{27}NO_4Na^+$, 356.1833; found, 356.1830. $[\alpha]_D^{rt}$ −15.3°.

General Procedures for α/γ-Peptide Synthesis. General Procedure A: Benzyl Deprotection. Peptide was dissolved in MeOH (~20 mL/mmol peptide) that had been saturated with bubbling N_2 for 30 min prior to reaction. A catalytic quantity (spatula tip) of 10 wt % (dry) Pd/C (wet) was added to the solution, and the reaction flask was flushed with N_2 and sealed with a septum. The flask was evacuated on an aspirator and back-filled from an H_2 balloon three times. The flask was equipped with a H_2 balloon, and the reaction was stirred for 5 h at room temperature. Following observation of the loss of a benzyl signal from the crude ^{1}H NMR spectrum of the reaction mixture (~5 h; samples were filtered to remove catalyst), the mixture was filtered at once through a pad of Celite topped with a thin layer of silica. The filtrate was evaporated to yield peptide acid fragments as white foams, typically in >95% yield on the basis of the mass of the isolated crude material. This material was taken forward into coupling reactions without further purification in all cases.

General Procedure B: N-Boc Deprotection. Peptide was dissolved in minimal 1,4-dioxane. Five to ten milliliters of a solution of 4 N HCl in 1,4-dioxane (or approximately 15 equiv HCl relative to peptide) was added to the solution, and the reaction flask was sealed with a septum. The reaction was stirred for 3 to 4 h at room temperature. Following loss of the *N*-Boc signal from the crude ^{1}H NMR spectrum of an aliquot of the reaction mixture, the reaction flask was evacuated on an aspirator for 30 min to remove dissolved HCl. 1,4-Dioxane was removed via rotovap to yield dipeptide HCl salts, typically in >95% yield on the basis of the mass of the crude isolated material. This material was taken forward into coupling reactions without further purification in all cases.

*Boc-HN-^{D}Ala-AMCP-OBn (**5**).* Benzyl ester **4** (Boc-HN-AMCP-OBn; 1.37 g, 0.41 mmol, 1.0 equiv) was Boc-deprotected according to general procedure B in >95% yield to give H_2N-AMCP-OBn·HCl, which was carried forward without further purification. Boc-HN-^{D}Ala-OH (776 mg, 4.1 mmol, 1.0 equiv) was dissolved in 10 mL of distilled CH_2Cl_2. *i*-Pr_2EtN (4.29 mL, 24.6 mmol, 6.0 equiv) was added followed by HOBt (665 mg, 4.92 mmol, 1.2 equiv) and EDCI (942 mg, 4.92 mmol, 1.2 equiv). The solution was stirred for 5 min. H_2N-AMCP-OBn·HCl was then added, and the solution was stirred overnight at room temperature. The solution was diluted 4-fold with EtOAc and washed twice each (25 mL each wash) with 1 M aqueous $NaHSO_4$, then saturated (aq) $NaHCO_3$, then brine. Each aqueous layer was extracted twice with 25 mL of CH_2Cl_2. All organic layers were combined, dried over $MgSO_4$, filtered, and evaporated to afford a crude solid. The product was purified via column chromatography eluting with 1:1 (v/v) EtOAc/hexanes to give an amorphous solid. R_f (1:1 EtOAc/hexanes) = 0.18. 1.275 g isolated, 77% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (m, 5H), 6.50 (broad, 1H), 5.14 (s, 2H), 4.93 (broad, 1H), 45 (m, 1H), 3.32 (m, 2H), 2.51 (q, J = 8.9 Hz, 1H), 2.34 (sextet, J = 7.7 Hz, 1H), 1.99 (m, 1H), 1.89 (m, 2H), 1.64 (quintet, J = 6.9 Hz), 1.44 (s, 9H), 1.34 (m, 1H), 1.28 (J = 6.9 Hz, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 176.3, 172.9, 169.6, 136.2, 128.9, 128.5, 128.4, 66.7, 48.7, 44.0, 43.5, 30.8, 30.5, 28.6, 25.0, 18.8. Calcd [M + Na$^+$] for $C_{22}H_{32}N_2O_5Na^+$, 427.2204; found, 427.2210.

*Boc-HN-(^{D}Ala-AMCP)$_2$-OBn (**8**).* Two 405 mg (1.0 mmol, 1.0 equiv) portions of α/γ-peptide dimer **5** were deprotected orthogonally according to general procedure A and general procedure B to yield an

α/γ-dipeptide acid **6** and α/γ-dipeptide amine HCl salt **7**, both in >95% yield. α/γ-Dipeptide acid **6** (1.0 mmol, 1.0 equiv) was dissolved in DMF (2.5 mL). *i*-Pr_2EtN (1.045 mL, 6.0 mmol, 6.0 equiv) was added followed by HOBt (162 mg, 1.2 mmol, 1.2 equiv) and EDCI (230 mg, 1.2 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 15 min, at which point a solution of α/γ-dipeptide amine HCl salt **7** (1.0 mmol, 1.0 equiv) in DMF was added (2.5 mL). The reaction flask was sealed with a septum, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted 10-fold with EtOAc and washed (25 mL each wash) twice each with 1 M aqueous $NaHSO_4$, then saturated (aq) $NaHCO_3$, then brine. Each aqueous layer was extracted twice with 25 mL of CH_2Cl_2. All organic layers were combined, dried over $MgSO_4$, filtered, and evaporated to afford a crude solid. The product was purified via column chromatography eluting with a gradient of 3:1 hexanes/EtOAc to 1:3 hexanes/EtOAc. The product eluted when the column was flushed with neat EtOAc. R_f (2.5% (v/v) MeOH in CH_2Cl_2) = 0.20. Tetramer **8** was isolated as a white solid (530 mg, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 5H), 7.24 (broad, 1H), 7.17 (broad, 1H), 679 (broad, 1H), 5.13 (*J* = 7.2 Hz, 1H), 5.07 (ABq, J_{AB} = 13.7 Hz, ν_{AB} = 9.9 Hz, 2H), 4.29 (quintet, *J* = 7.5 Hz, 1H), 4.06 (quintet, *J* = 6.9 Hz, 1H), 3.28 (broad, 3H), 3.11 (broad, 1H), 2.48 (q, *J* = 7.8 Hz, 1H), 2.30 (sextet, *J* = 8.1 Hz, 1H), 2.19 (broad, 2H), 1.96−1.52 (broad, 11H), 1.36 (s, 9H), 1.31 (m, 2H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.23 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 177.0, 176.3, 174.1, 173.9, 156.0, 136.2, 128.8, 128.4, 128.2, 80.3, 66.7, 50.7, 49.6, 49.0, 48. 6, 44.7, 44.1, 43.4, 43.0, 31.1, 30.8, 30.5, 28.5, 25.8, 25.0, 18.3, 18.1. Calcd [M + H^+] for $C_{32}H_{48}N_4O_7H^+$, 601.3596; found, 601.3591.

*Boc-HN-(^{D}Ala-AMCP)$_3$-OBn (**9**).* A 0.33 mmol portion of α/γ-peptide dimer **5** was deprotected according to general procedure A (to yield **6**), and a 0.33 mmol portion of α/γ-peptide tetramer **8** was deprotected according general procedure B. α/γ-Dipeptide acid **6** (0.33 mmol, 1.0 equiv) was dissolved in 2.5 mL of DMF. *i*-Pr_2EtN (348 μL, 2 mmol, 6.0 equiv) was added followed by HOBt (54 mg, 0.4 mmol, 1.2 equiv) and EDCI (77 mg, 0.4 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 15 min, at which point a solution of N-deprotected **8** in 2.5 mL of DMF was added. The reaction flask was sealed with a septum, and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was diluted 10-fold with EtOAc and washed (25 mL each wash) twice each with 1 M aqueous $NaHSO_4$, then saturated (aq) $NaHCO_3$, then brine. Each aqueous layer was extracted twice with 25 mL of CH_2Cl_2. All organic layers were combined, dried over $MgSO_4$, filtered, and evaporated to afford a crude solid. The product was purified via column chromatography eluting with a gradient of 1:1 hexanes/EtOAc to neat EtOAc. R_f (neat EtOAc) = 0.32. Hexamer **9** was isolated as a white solid (200 mg, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, *J* = 6.9 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.54 (d, *J* = 6.6 Hz, 1H), 7.34 (broad, 1H), 7.29 (m, 5H), 6.56 (broad, 1H), 5.07 (ABq, J_{AB} = 13.1 Hz, ν_{AB} = 7.7 Hz, 2H), 5.02 (d, *J* = 3 Hz, 1H), 4.26 (quintet, *J* = 7.5 Hz, 1H), 4.21 (quintet, J = 7.5 Hz, 1H), 4.13 (quintet, *J* = 5.0 Hz, 1H), 3.55−3.29 (broad, 3H), 3.22−2.98 (broad, 3H), 2.48 (q, *J* = 8.1 Hz), 2.22 (broad, 5H), 1.80 (broad, 11H), 1.59 (broad, 7H), 1.36 (s, 9H), 1.32 (m, 2H), 1.28 (d, *J* = 9.9 Hz, 3H), 1.25 (d, *J* = 9.9 Hz, 3H), 1.16 (d, *J* = 9.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.0, 177.9, 176.2, 174.5, 174.5, 173.8, 155.8, 135.8, 128.7, 128.3, 128.1, 80.1, 66.7, 50.4, 50.3, 49.6, 49.2, 49.1, 48.7, 44.4, 44.3, 44.1, 44.0, 43.0, 43.03, 31.6, 31.4, 31.2, 31.1, 30.7, 30.3, 28.3, 26.6, 26.1, 24.8, 18.1, 17.3, 16.9. Calcd [M + Na^+] for $C_{42}H_{64}N_6O_9Na^+$, 819.4627; found, 819.4606.

*Boc-HN-(^{D}Ala-AMCP)$_4$-OBn (**12**).* Two 0.33 mmol portions of α/γ-peptide tetramer **8** were deprotected orthogonally according to general procedure A and general procedure B to yield α/γ-tetrapeptide acid **10** and α/γ-tetrapeptide amine HCl salt **11**, respectively, with both reactions proceeding in >95% yield. Tetrapeptide acid **10** (0.33 mmol, 1.0 equiv) was dissolved in 2.5 mL of DMF. *i*-Pr_2EtN (348 μL, 2 mmol, 6.0 equiv) was added followed by HOBt (54 mg, 0.4 mmol, 1.2 equiv) and EDCI (77 mg, 0.4 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 15 min, at which point a solution of α/γ-tetrapeptide amine HCl salt **11** in DMF (2.5 mL) was added. The reaction flask was sealed with a septum, and the reaction mixture was stirred at room temperature for 72 h. The reaction mixture was diluted 10-fold with EtOAc and washed twice each with 1 M aqueous $NaHSO_4$, then saturated (aq) $NaHCO_3$, then brine. Each aqueous layer was extracted twice with 25 mL of CH_2Cl_2. All organic layers were combined, dried over $MgSO_4$, filtered, and evaporated to afford a crude solid. The product was purified via column chromatography, eluting with a gradient of 1 (v/v) to 5% MeOH in CH_2Cl_2. R_f (5% MeOH) = 0.14. Octamer **12** was isolated as a white solid (190 mg, 58% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.74 (d, *J* = 6.3 Hz, 1H), 8.37 (d, *J* = 6.3 Hz, 1H), 7.96 (d, *J* = 4.8 Hz, 1H), 7.60 (broad, 2H), 7.45 (d, *J* = 6.0 Hz, 1H), 7.36 (m, 5H), 6.60 (broad, 1H), 5.13 (ABq, J_{AB} = 11.0 Hz, ν_{AB} = 9.1 Hz, 2H), 5.10 (d, *J* = 9.9 Hz, 1H), 4.24 (m, 1H), 4.27 (broad, 3H), 3.54 (broad, 4 H), 3.13 (broad, 4H), 2.54 (q, *J* = 8.4 Hz, 1H), 2.32 (broad, 7H), 1.87 (broad, 15 H), 1.64 (broad, 13H), 1.43 (s, 9H), 1.33 (broad, 10H), 1.26 (d, *J* = 7.8 Hz, 3H), 1.21 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.4, 178.2, 178.1, 176.2, 174.9, 174.7, 174.6, 173.8, 171.2, 155.8, 135.8, 128.7, 128.3, 128.1, 80.1, 66.7, 60.4, 50.4, 50.4, 49.5, 49.3, 48.8, 44.5, 44.4, 44.2, 44.1, 44.0, 43.7, 43.0, 31.7, 31.6, 31.6, 31.5, 31.5, 31.4, 31.2, 30.7, 30.2, 29.7, 28.3, 26.8, 26.7, 26.3, 24.8, 22.7, 21.1, 18.1, 17.2, 17.1, 16.6, 14.2, 14.1. Calcd [M + H^+] for $C_{52}H_{80}N_8O_{11}H^+$, 993.6020; found, 993.6027.

*Compound (**S1**): Boc-HN-(^{D}Phe-AMCP)-OBn.* See the Supporting Information for the synthesis scheme. Benzyl ester **4** (Boc-HN-AMCP-OBn; 1.09 g, 3.3 mmol, 1.0 equiv) was Boc-deprotected according to general procedure B in >95% yield to give H_2N-AMCP-OBn·HCl, which was carried forward without further purification. Boc-HN-^{D}Phe-OH (1.041 g, 3.9 mmol, 1.2 equiv) was dissolved in 10 mL of distilled CH_2Cl_2. *i*-Pr_2EtN (3.5 mL, 19.6 mmol, 6.0 equiv) was added followed by HOBt (530 mg, 3.9 mmol, 1.2 equiv) and EDCI (751 mg, 3.9 mmol, 1.2 equiv). The solution was stirred for 10 min. H_2N-AMCP-OBn·HCl was then added, and the reaction mixture was stirred for 24 h at room temperature. The reaction mixture was diluted 4-fold with EtOAc and washed twice each (25 mL each wash) with 1 M aqueous $NaHSO_4$, then saturated (aq) $NaHCO_3$, then brine. Each aqueous layer was extracted twice with 25 mL of CH_2Cl_2. All organic layers were combined, dried over $MgSO_4$, filtered, and evaporated to afford a crude solid. The product was purified via column chromatography, eluting with a gradient from 1:5 (v/v) to 1:1 EtOAc/hexanes to give dipeptide **S1** as an amorphous solid (1.027 g isolated, 65% yield). R_f (20:1 CH_2Cl_2/MeOH) = 0.49. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (broad m, 10H), 6.13 (broad, 1H), 5.09 (ABq, J_{AB} = 12.0 Hz, ν_{AB} = 16.8 Hz, 2H), 4.96, (broad, 1H), 4.27 (q, *J* = 6.9 Hz, 1H), 3.11 (superimposed ABX patterns, 4H), 2.38 (q, *J* = 8.4 Hz, 1H), 2.19 (sextet, *J* = 7.8 Hz, 1H), 1.85 (m, 3H), 1.62 (broad, 2H), 1.40 (s, 9H), 1.22 (m 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 176.0, 171.4, 137.1, 136.2, 129.5, 128.8, 128.5, 128.3, 127.1, 66.6, 56.2, 48.4, 43.9, 43.1, 38.9, 30.7, 30.3, 28.5, 24.9, 19.0. Calcd [M + Na^+] for $C_{28}H_{36}N_2O_5Na^+$, 503.2517; found, 503.2528.

*Boc-HN-(^{D}Phe-AMCP)$_2$-OBn (**13**).* See the Supporting Information for the synthesis scheme. Two 199 mg (0.42 mmol, 1.0 equiv) portions of α/γ-peptide dimer **S1** (see the Supporting Information for preparation of this dipeptide) were deprotected orthogonally according to general procedure A and general procedure B to yield a α/γ-dipeptide acid **S2** and a α/γ-dipeptide amine HCl salt **S3**, respectively, both in >95% yield. The α/γ-dipeptide acid **S2** (0.42 mmol, 1.0 equiv) was dissolved in 5 mL of CH_2Cl_2. *i*-Pr_2EtN (444 μL, 2.5 mmol, 6.0 equiv) was added followed by HOBt (67 mg, 0.5 mmol, 1.2 equiv) and EDCI (95.4 mg, 0.5 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 15 min, at which point a solution of dipeptide amine HCl salt **S3** in 5 mL of CH_2Cl_2 was added. The reaction flask was sealed with a septum, and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was diluted 4-fold with EtOAc and washed twice each (25 mL each wash) with 1 M aqueous $NaHSO_4$, then saturated (aq) $NaHCO_3$, then brine. Each aqueous layer was extracted twice with 25 mL of CH_2Cl_2. All organic layers were combined, dried over $MgSO_4$, filtered, and evaporated to afford a crude solid. The product was purified via

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column chromatography, eluting with a gradient of 1 (v/v) to 5% MeOH in CH_2Cl_2. R_f (5% (v/v) MeOH in CH_2Cl_2) = 0.30. Tetramer **13** was isolated as an amorphous solid (183.9 mg, 58% yield). Note that small additional peaks in the ^{1}H NMR spectrum are attributed to rotamers, which were not observed in the ^{13}C NMR spectrum. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 15H), 6.81 (broad, 3H), 5.31 (d, J = 8.7 Hz, 1 H), 5.10 (ABq, J_{AB} = 12.3 Hz, ν_{AB} = 14.0 Hz, 2H), 4.64 (q, J = 7.8 Hz, 1H), 4.43 (q, J = 7.2 Hz, 1H), 3.16 (broad, 8H), 2.46 (q, J = 9 Hz, 1H), 2.29 (sextet, J = 6.3 Hz, 1H), 2.13 (broad, 1H), 1.85 (m, 4H), 1.64 (broad, 6H), 1.38 (s, 9H), 1.24 (m, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 176.3, 176.2, 172.6, 172.1, 156.0, 137.5, 137.2, 136.3, 129.5, 128.8, 128.8, 128.8, 128.6, 128.4, 128.2, 127.1, 127.0, 80.5, 56.3, 55.1, 48.6, 48.5, 44.3, 44.1, 44.0, 43.3, 42.1, 38.4, 38.1, 30.7, 30.5, 30.3, 28.5, 25.1, 25.0. Calcd [M + Na^+] for $C_{44}H_{56}N_4O_7Na^+$, 775.4042; found, 775.4057.

*Boc-HN-(^{D}Ala-AMCP)$_3$-(^{D}Phe-AMCP)$_2$-OBn (**15**).* A 0.11 mmol portion of α/γ-peptide hexamer **9** was deprotected according to general procedure A and a 0.11 mmol portion of α/γ-peptide tetramer **13** was deprotected according general procedure B to yield an α/γ-hexapeptide acid and α/γ-tetrapeptide HCl salt **14**, respectively, with both reactions proceeding in >95% yield. The α/γ-hexapeptide acid (0.11 mmol, 1.0 equiv) was dissolved in 2.5 mL of 4:1 NMP/DMSO. i-Pr_2EtN (0.118 mL, 0.66 mmol, 6.0 equiv) was added followed by Oxyma (20.3 mg, 0.14 mmol, 1.3 equiv) and EDCI (25.3 mg, 0.13 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 15 min, at which point a solution of α/γ-tetrapeptide amine HCl salt **14** in 2.5 mL of 4:1 NMP/DMSO was added. The reaction flask was sealed with a septum, and the reaction mixture was stirred at room temperature for 5 days. The reaction was diluted with EtOAc and transferred to a separatory funnel. NMP/DMSO were removed by washing the diluted reaction five times with 50 mL of H_2O. Each H_2O wash was back-extracted four times with 50 mL of Et_2O. The combined organic layers were washed twice each with 1 M aqueous $NaHSO_4$, then saturated (aq) $NaHCO_3$, then brine. Each aqueous layer was extracted twice with CH_2Cl_2. All organic layers were combined, dried over $MgSO_4$, filtered, and evaporated to afford a crude solid. The product was purified via column chromatography, eluting with a gradient of 1 (v/v) to 10% MeOH in CH_2Cl_2. R_f (5% MeOH) = 0.15. The product was isolated as an amorphous solid (116 mg, 77% yield). ^{1}H NMR (300 MHz, $CDCl_3$ with 5% CD_3OH): δ 8.63 (d, J = 6.3 Hz, 1H), 8.51 (d, J = 7.5 Hz, 1H), 8.19 (d, J = 9.3 Hz, 1H), 8.12 (broad, 2H), 8.03 (d, J = 3.9 Hz, 1H), 7.88 (d, J = 3.9 Hz, 1H), 7.79 (d, J = 6.3 Hz, 1H), 7.25 (m, 15H), 6.97 (broad, 1H), 5.61 (d, J = 9.3 Hz, 1H), 5.09 (ABq, J_{AB} = 11.7 Hz, ν_{AB} = 15.2 Hz, 2H), 4.60 (q, J = 7.5 Hz, 1H), 4.45 (broad, 2H), 4.33 (broad, 1H), 4.18 (broad, 1H), 3.13 (broad, 15H), 2.36 (broad, 8H), 1.77 (broad, 25H), 1.44 (s, 9H), 1.33 (broad, 14H). ^{13}C NMR (125 MHz, $CDCl_3$ with 5% CD_3OH): carbonyl (11 observed, 11 in molecule) and aromatic peaks are listed below because these were diagnostic of decamer **15**. The full ^{13}C NMR spectrum is provided in the Supporting Information. 179.2, 178.7, 178.3, 178.1, 176.2, 175.4, 174.8, 174.6, 174.6, 173.8, 173.0, 156.2, 151.6, 137.8, 137.5, 136.1, 136.0, 129.6, 129.4, 129.5, 129.3, 128.7, 128.6, 128.4, 128.3, 128.1, 126.9, 126.8, 125.7. Calcd [M + H^+] for $C_{74}H_{104}N_{410}O_{13}H^+$, 1365.1; found, 1365.1.

2D NMR Procedures. *Sample Preparation.* NMR samples were prepared by dissolving the α/γ-peptide in $CDCl_3$ (0.03%) TMS. CD_3OH was added to a concentration of 5% (v/v) to the solution of decamer **15** to fully solubilize the α/γ-peptide; the total concentration of this sample was 2 mM. Samples were prepared with 500–600 μL solvent for use in 5 mm NMR tubes. Spectra were referenced to tetramethylsilane. Samples showed the same spectral features after several weeks in solution, without showing visible signs of precipitation. All 2D NMR experiments were preformed on 600 MHz spectrometer. Data were collected at 10, 20, and 24 °C, respectively, for α/γ-peptides **9**, **12**, and **15.** Sample concentrations for all three α/γ-peptides were 2 mM.

gCOSY, TOCSY,[16] *and ROESY.*[17] Standard pulse sequences were used, and data were processed using the spectrometer's software. Assignments and analyses of spectra were performed in the SPARKY program.[18] Spectral windows, f2 resolutions, and mixing times are as follows:

Hexamer **9**: p6492.5 Hz; points in f2 = 1664; TOCSY mixing time = 120 ms; ROESY mixing time = 300 ms

Octamer **12**: 6999.7 Hz; points in f2 = 1792; TOCSY mixing time = 80 ms; ROESY mixing time = 200 ms

Decamer **15**: 8000 Hz; points in f2 = 2048; TOCSY mixing time = 80 ms; ROESY mixing time = 200 ms. Note that the CD_3OH solvent peak was suppressed for this sample, which was essential in allowing for the assignnment of AMCP H_g protons.

Shifted sinebell window functions were applied before Fourier transformation of 2D data. For all samples, gCOSY spectra were obtained in absolute mode with gradient echo coherence selection. TOCSY and ROESY spectra were acquired in the sensitive mode with hypercomplex phase cycling. Data were collected with 1600–2048 points in f2 (above) and 200–600 points in f1. TOCSY experiments employed a standard MLEV-17 spin lock sequence with a spin lock field of 7 to 8 kHz. ROESY experiments utlilized spin-locking fieds of ~3 kHz.

Note on Mixing Times. Our choice of mixing times of 200–300 ms in ROESY experiments was due to the exploratory nature of our study. Medium-range ROESY crosspeaks give the most compelling evidence for helical folding (e.g., between residues i and i + 4 in an α-helix or between residues i and i + 2 in our α/γ-peptides). These ROEs arise from through-space interactions between H atoms that are many bonds apart. Such ROEs are fundamentally slower in their rate of build up than short-range ROEs that arise from H atoms separated by only a few bonds. We can use extended mixing times confidently because the ROESY experiment allows one to identify (and disregard) crosspeaks that arise from spin diffusion or TOCSY artifacts because these crosspeaks would be of the same sign as the diagonal of the 2D spectrum; the true ROESY crosspeaks that we seek are opposite in sign relative to the diagonal.

Sequence Assignment. Chemical-shift assignment was accomplished via sequential procedures.[9] Briefly, the N-terminal Boc NH amide peak was identified for each peptide as the most upfield of the amide chemical shifts (this is due to the increased shielding of a urethane carbonyl versus an amide carbonyl). The resonances of the N-terminal residue were assigned using TOCSY and ROESY crosspeaks (with COSY to assist in cases of ambiguous chemical shifts). The next residue in the sequence was assigned on the basis of a strong NOE (1.8–3.0 Å) crosspeak between the HCα of the N-terminal residue and the NH amide resonance of the next residue. Once the NH peak of the following residue was identified, the above procedure was repeated proceeding from the N-terminus to the C-terminus of each peptide sequence. ^{1}H chemical-shift assignments and structural NOEs for α/γ-peptides **9**, **12**, and **15** are tabulated in the Supporting Information.

Note on NOEs in α/γ-Peptides. Midrange and long-range NOEs between nonadjacent amino acids (between residue i and i + 2 or greater) are typically viewed in α-peptides as crosspeaks that do not arise simply because of proximity in a peptide sequence and are therefore indicative of some type of compact conformation. γ-Amino acids, however, span a significant distance in space in a given α/γ-peptide sequence. For this reason, we define sequential NOEs specifically as the signals between the HCα of residue i and the NH amide proton resonance of residue i + 1. Furthermore, we view signals between γ-residue i and α-residue i + 1 other than the characteristic sequential NOE as indicative of some type of structure, even though the residues are adjacent.

Note on the Selection of ROESY Experiments in This Study. We routinely select ROESY in preference to NOESY for 2D NMR studies of peptidic oligomers between 500 and 1500 Da. In general, molecules in this mass range display attenuated or very weak NOESY spectra, presumably because their rotational correlation times fall into a range such that their product with the Larmor frequency approaches unity; the net effect of this is an NOE value of low or zero magnitude. The buildup of crosspeaks in ROESY, although fundamentally lower in signal-to-noise than for NOESY, always leads to positive signals and is independent of the correlation time/Larmor frequency mathematical

relationship. In addition, ROESY allows for the unique assignment of crosspeaks involving one proton from a diastereotopic methylene unit (spin diffusion effects in NOESY experiments lead to signals to both protons, when only one may in fact be interacting), which is useful given our desire to calculate NMR structures.

Derivation of Distance Restraints from Integration of ROESY Spectra Crosspeaks. Crosspeaks were integrated in the program SPARKY[18] using the Gaussian mode. Integrations were converted into distances using eq 1

$$r_{ij} = r_{\mathrm{ref}} \sqrt[6]{\frac{I_{\mathrm{ref}}}{I_{ij}}} \quad (1)$$

where r_{ij} is the distance between two protons calculated from measured integrations, r_{ref} is the reference distance, I_{ref} is the corrected integration corresponding to the reference distance, and I_{ij} is the integration corrected according to eq 1

$$I_{ij} = I_{\mathrm{measured}}/(n_{\mathrm{Hi}} \times m_{\mathrm{Hj}}) \quad (2)$$

where m and n are the multiplicities of each of the interacting protons i and j. For example, if two methylene protons yield a single crosspeak with three methyl protons, the measured integration is divided by 6, the product of the multiplicities, prior to being entered into eq 1.

Selection of the Reference Distance. The most obvious choice for reference distance was to use the crosspeak between the diastereotopic benzyl ester protons in each peptide. However, the proximity of this crosspeak to the diagonal in the ROESY spectra of α/γ-peptide **9** precluded accurate integration. Because the diagonal is opposite in sign from ROESY crosspeaks by definition, this proximity reduces the value of the benzyl methylene crosspeak. This would give an artificially low integration, resulting in weak NOEs appearing stronger than they actually are. Therefore, to avoid this possible error, we selected the crosspeaks between ^{D}Alanine Hα and methyl Hβ signals for hexamer **9**. The reference distance was calculated to 2.4 Å according to the method of Wuthrich.[9a] I_{ref} was then calculated as the average integration of the three crosspeaks resulting from the ^{D}Alanine Hα and methyl Hβ signals in hexamer **9**, corrected according to eq 2. The diastereotopic methylene crosspeaks of the benzyl groups of octamer **12** and decamer **15** were sufficiently resolved from the diagonal of the ROESY spectrum and were used as distance references with a value of 1.6 Å.

*NMR Structure Calculations for α/γ-Peptides **9**, **12**, and **15**.* The nonsequential NOEs tabulated above were used as distance restraints in simulated annealing/torsional dynamics calculations in the CNS software package (ver. 1.3) for α/γ-peptides **9**, **12**, and **15**.[10] We manually created CNS-formatted topology and parameter files for AMCP. We increased the scale of the dihedral energy term by 20% during both torsional and Cartesian slow-cooling stages that follow the high-temperature annealing stage in the anneal.inp protocol downloaded with CNS. All other parameters were used in the default setting from the anneal.inp protocol downloaded with the CNS software package. For each peptide, we generated 1000 initial structures in the annealing stage and then selected for the 10 lowest-energy structures using the accept.inp protocol, again with increased dihedral energy terms but no other specified selection criteria. The raised energy terms were necessary to prevent the cyclopentyl rings of AMCP residues from being forced into planar conformations. Additionally, it was necessary to place dihedral constraints, measured from the crystal structure of dipeptide **3**, on the ring dihedrals to maintain cyclopentane envelope conformations. This was done while leaving the backbone dihedral about the cyclopentyl ring, ζ, free to float with the rest of the backbone torsion angles during the annealing runs. We note that i to $i + 1$ NOEs are typically thought of as a consequence of peptide sequence, often occurring independently of conformation. However, we consider NOEs across the full distance of a γ residue to the adjacent amino acid to be midrange because these distances would correspond to those found from residue i to residue $i + 2$ in α-peptides. We did not include the strong sequential NOEs, defined earlier, in our calculations. In all cases, the lowest-energy structures selected for analysis following calculations did not display any violations of our distance constraints derived from NMR study.

■ ASSOCIATED CONTENT

Supporting Information

Preparation of **S1**, **S2**, **S3**, and **13**. HPLC trace and description of conjugate addition optimization for nitroalochol **1**. Tabulated 2D NMR data, chemical-shift assignments, and 2D NMR spectra for α/γ-peptides **9**, **12**, and **15**. Statistics and ensembles generate from NMR-restrained molecular dynamics calculations. ^{1}H and ^{13}C NMR spectra for all new compounds. Aggregation control and DMSO titration experiments for α/γ-peptide decamer **15**. Crystallographic report and CIF file for the structure of dipeptide **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gellman@chem.wisc.edu.

Present Address

[†]Department of Chemistry, Yale University, New Haven, Connecticut 06511, United States. E-mail: michael.giuliano@yale.edu.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

In memory of Professor Howard E. Zimmerman, 1926−2012.

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