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Self-Assembly of Noncyclic Bis-D- and L-tripeptides into Higher Order Tubular Constructs: Design, Synthesis, and X-ray Crystal Superstructure

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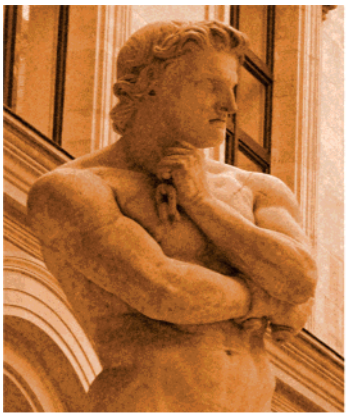

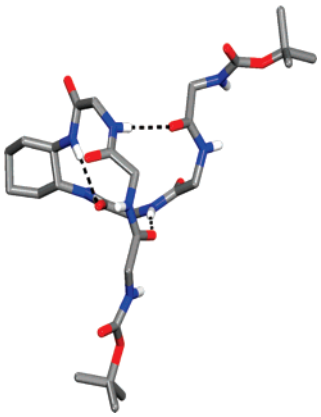

Trans (1*R*,2*R*)-diaminocyclohexane was used as a semirigid vicinal diamine to anchor two *N*-protected tripeptides consisting of L-D-L amino acids as carboxy terminal amides. The bis-tripeptide consisting of L-Ser (OBn)-D-Ser (OBn)-L-Ser (O-*p*-bromobenzyl) Boc afforded X-ray quality crystals containing benzene and chloroform solvent molecules. Analysis of the solid-state structure revealed a highly H-bonded helical open-ended tubular superstructure. The tripeptide strands intertwine like a pair of self-embracing arms, held together by a γ-turn and a 14-membered antiparallel H-bonded macroring spanning the first and third amino acid residues within each strand. Whereas the tripeptide from the *R*,*R* anchor gave beautiful crystals from benzene and chloroform, the analogous construct from the *S*,*S*-anchored diamine gave a gel. Related bis-tripeptides with different amino acids showed extensive intramolecular H-bonding based on NMR titration and dilution experiments.

Introduction

The three-dimensional architecture of proteins and polypeptides is a fundamental topological property that is exploited by nature for molecular recognition, function, and life processes in general.[1] Helical and sheet arrangements are common supramolecular motifs encountered in practically all functional proteins.[2] A better understanding of the underlying principles that govern the architecture of such motifs is a prerequisite for

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(1) Petsko, G. A.; Ringe, D. In *Protein Structure and Function*; Sinauer Associates Inc.: Sunderland, MA, 2004; pp 49−83.
(2) Lesk, A. M. In *Introduction to Protein Architecture, The Structural Biology of Proteins*; Oxford University Press: Oxford, 2000.

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probing the origin of many physical, biophysical, and biomedical phenomena related to specific diseases.[3]

The simulation of ordered supramolecular assemblies using short oligopeptides has been a challenging area of intensive research in recent years.[4,5] Moreover, the advent of nanotechnology has instigated creative ways to construct well-defined three-dimensional oligopeptide architectures.[6] For example, the insightful and scholarly contributions of Ghadiri and co-workers[7] have laid a strong foundation for the construction of tubular assemblies consisting of cyclic D- and L-oligopeptides with wide-ranging applications.[8] Although synthetic helical structures arising from short peptidic units are of common occurrence,[9] the design and synthesis of β-sheets as models for β-stranded peptide sequences presents a different challenge.[10] To this end, stabilization of β-sheets by a network of intermolecular H-bonds has been achieved with the incorporation of rigid templates.[11] Inclusion of noncoded amino acids within a tripeptide such as Boc-Leu-Aib-β-AlaOMe has led to a self-assembled β-sheet type or helical structures.[12] Further modifications have produced helical assemblies that were reported to form polydispersed nanorods.[13] However, such self-assembled motifs have invariably incorporated the helicogenic noncoded amino acid Aib, known for its helix-promoting character.[14] The higher order autoassembly of uncharged, metal free, noncyclic short peptides consisting of natural amino acids (and their D-counterparts) into tubular superstructures is a relatively unexplored area.[15]

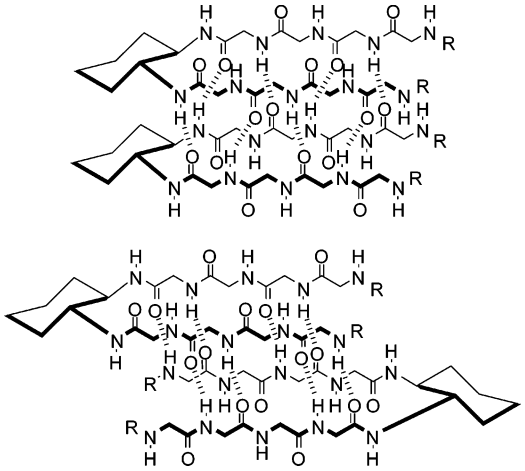


FIGURE 1. Top: Head-to-head parallel β-sheet array. Bottom: Head-to-tail antiparallel β-sheet array. Partial structure with side chains removed for clarity.

We report herein on the design and synthesis of a tubular superconstruct that is formed from the self-assembly of *noncyclic* bis-tripeptides anchored on a semirigid *trans*-1,2-diaminocyclohexane spacer unit. The sequential attachment of alternating L- and D-amino acids to *trans*-(1*R*,2*R*)-diaminocyclohexane (DACH)[16] can potentially lead to two types of idealized H-bonded arrays. A head-to-head orientation can produce a β-sheet resulting from a parallel H-bonding alignment (Figure 1, top). A head-to-tail deployment of the anchoring DACH units on the other hand leads to an antiparallel alignment encompassing interstrand 10-membered H-bonded rings (Figure 1, bottom). The bis-amide of (1*R*,2*R*)-DACH with palmitic acid is reported to produce a helical gel structure in which the anchoring DACH units are slightly staggered in a head-to-head arrangement.[17]

Results and Discussion

Initial studies involving the successive coupling of L- and D-CbzAlaOH to (*R*,*R*)-DACH **1** gave a series of bis-peptides **2**−**5** (Scheme 1). Although the bis-dipeptide **3** and the bis-tripeptide and **4** were soluble in $CHCl_3$, the tetrapeptide **5** formed a gel. Removal of the *N*-Cbz group by hydrogenolysis afforded the free amine **6**, which was converted to the corresponding *N*-Boc and *N*-Ac derivatives **7** and **8**, respectively. ^{1}H NMR dilution experiments in $CDCl_3$ with peptides **2**−**5**, **7**, and **8** showed little if any NH signal change over the concentration range of 10 to 0.6 mM. Titration with increasing amounts of

(3) See for example, Alzheimers disease: (a) Rochet, J. C.; Lansbury, P. T. *Curr. Opin. Struct. Biol.* **2000**, *10*, 60−68. (b) Baumeister, R.; Eimer, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 2978−2982. Huntington's disease: (c) Perutz, M. F. *Curr. Opin. Struct. Biol.* **1996**, *6*, 848−858. (d) MacDonald, M. E.; Gusella, J. F. *Curr. Opin. Neurobiol.* **1996**, *6*, 638−643. Prion protein disease: (e) Prusiner, S. B. *Science* **1997**, *278*, 245−251. (f) Ng, S. B. L.; Doig, A. J. *Chem. Soc. Rev.* **1997**, *26*, 425−432.

(4) See for example: (a) Betz, S. F.; Liebman, P. A.; DeGrado, W. F. *Biochemistry* **1997**, *36*, 2450−2458. (b) Nautiyal, S.; Woolfson, D. N.; King, D. S.; Alber, T. *Biochemistry* **1995**, *34*, 11645−11651. (c) Olofsson, S.; Johansson, G.; Baltzer, L. *J. Chem. Soc., Perkin Trans. 2* **1995**, *11*, 2047−2056. (d) Ghadiri, R.; Soares, C.; Choi, C. *J. Am. Chem. Soc.* **1992**, *114*, 825−831.

(5) For selected reviews, see: (a) Sanford, A. R.; Gong, B. *Curr. Org. Chem.* **2003**, *7*, 1649−1659. (b) Cheng, R. P.; Gellman, S. H.; De Grado, W. F. *Chem. Rev.* **2001**, *101*, 3219−3232. (c) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893-4012. (d) Cubberley, M.; Iverson, B. L. *Curr. Opin. Chem. Biol.* **2001**, *5*, 650−653.

(6) (a) Hartgerink, J. D.; Clark, T. D.; Ghadiri, M. R. *Chem.—Eur. J.* **1998**, *4*, 1367−1372. (b) Ghadiri, M. R. *Adv. Mater* **1995**, *7*, 675−677.

(7) (a) Ghadiri, M. R.; Granja, J. R.; Milligan, R. A.; Mckee, D. E.; Khazanovich, N. *Nature* **1993**, *366*, 324−327. (b) Hartgerink, J. D.; Granja, J. R.; Milligan, R. A.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 43−50. (c) Bong, D. T.; Clark, T. D.; Granja, J. R.; Ghadiri, M. R. *Angew. Chem., Int. Ed.* **2001**, *46*, 988−1011. (d) Clark, T. D.; Buehler, L. K.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 651−656.

(8) (a) Rosenthal-Aizman, K.; Svensson, G.; Unden, A. *J. Am. Chem. Soc.* **2004**, *126*, 3372−3373. (b) Amorin, M.; Castedo, L.; Granja, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 2844−2845. (c) Seebach, D.; Mathews, J. L.; Meden, A.; Wessels, T.; Baerlocher, C.; McCusker, L. B. *Helv. Chim. Acta* **1997**, *80*, 173−182.

(9) Hodgson, D. R.; Sanderson, J. *Chem. Soc. Rev.* **2004**, *33*, 422−430.

(10) For a recent review, see: Longhlin, W. A.; Tyndall, J. D. A.; Glenn, M. P.; Fairlie, V *Chem. Rev.* **2004**, *104*, 6085−6118.

(11) For selected references, see: (a) Schrader, T.; Kirsten, C. *Chem. Commun.* **1996**, 2089−2090. (b) Kelly, J. W.; Lashuel, H. L.; La Brenz, S. R.; Woo, L.; Serpell, L. C. *J. Am. Chem. Soc.* **2000**, *122*, 5262−5277. (c) Nowick, J. S.; Chung, D. M.; Maitra, K.; Maitra, S.; Stigen, K.; Sun, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7654−7661.

(12) (a) Das, A. K.; Haldar, D.; Hegde, R. P.; Shamala, N.; Banerjee, A. *Chem. Commun.* **2005**, 1836−1838. (b) Banerjee, A.; Maji, S. K.; Drew, M. G. B.; Haldar, D.; Banerjee, A. *Tetrahedron Lett.* **2003**, *44*, 335, 699−702. (c) Haldar, D.; Maji, S. K.; Drew, M. G. B.; Banerjee, A.; Banerjee, A. *Tetrahedron Lett.* **2002**, *43*, 5465−5468.

(13) (a) Haldar, D.; Banerjee, A.; Drew, M. G. B.; Das, A. K.; Banerjee, A. *Chem. Commun* **2003**, 1406−1407. (b) Ray, S.; Haldar, D.; Drew, G. D. B.; Banerjee, A. *Org. Lett.* **2004**, *6*, 4463−4465.

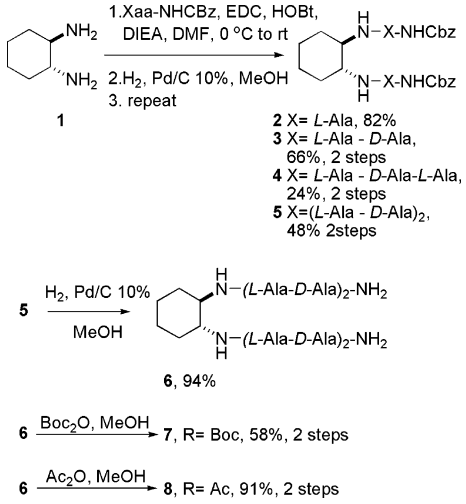
(14) (a) Balaram, P. *Curr. Opin. Struct. Biol.* **1992**, *2*, 845−851. (b) Karle, I. I.; Gurunath, R. B.; Prasad, S.; Kaul, R.; Rao, R. B.; Balaram, P. *J. Am. Chem. Soc.* **1995**, *117*, 9632−9637.

(15) See for example: (a) Srinivasulu, G.; Kumar, S. K.; Sharma, G. V. M.; Kunwar, A. C. *J. Org. Chem.* **2006**, *71*, 8395−8400. (b) Barsby, T.; Warabi, K.; Sørensen, D.; Zimmerman, W. T.; Kelly, M. T.; Andersen, R. J. *J. Org. Chem.* **2006**, *71*, 6031−6037. (c) Görbitz, C. H. *Chem. Commun.* **2006**, 2332−2334. (d) Ray, S.; Haldar, D.; Drew, M. G. B.; Banerjee, A. *Org. Lett.* **2004**, *6*, 4463−4465. (e) For a recent review, see: Moriuchi, T.; Hirao, T. *Chem. Soc. Rev.* **2004**, *33*, 294−301. (f) Görbitz, C. H. *Chem.—Eur. J.* **2001**, *7*, 2332−2334.

(16) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161−3195.

(17) Hanabusa, K.; Yamada, M.; Kimura, M.; Shirai, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1949−1950.

SCHEME 1. Synthetic Scheme for the Alanine Derivatives



DMSO-d_6 also suggested a relatively stable, H-bonded structure as judged from the minimal NH shifts.[18]

In an effort to obtain solids suitable for X-ray crystallographic analysis, we varied the nature of the amino acids (Scheme 2). Thus, *N*-Boc mono-, di-, tri-, and tetrapeptides **9**−**12**, consisting of L- and D-*O*-benzyl serines, afforded microcrystalline products with fully engaged H-bonded structures as indicated by ^{1}H NMR titration experiments.[18] Ultimately, the bis-tripeptide analogue L-Ser (OBn)-D-Ser (OBn)-L-Ser (OPBB) Boc **13**, (OPBB = *p*-bromobenzyl ether) afforded X-ray quality crystals from a mixture of benzene and $CHCl_3$.[19] Much to our surprise (and delight), the crystallographic data revealed that neither of the hypothetical linear β-sheet motifs shown in Figure 1 were actually formed. Instead, the crystal structure, consisting of two symmetry independent conformers **A** and **B** differing slightly in the positions of some side chains, revealed an array of tubular constructs arranged in a parallel spatial alignment separated by benzene and $CHCl_3$ molecules (Figure 2, left).

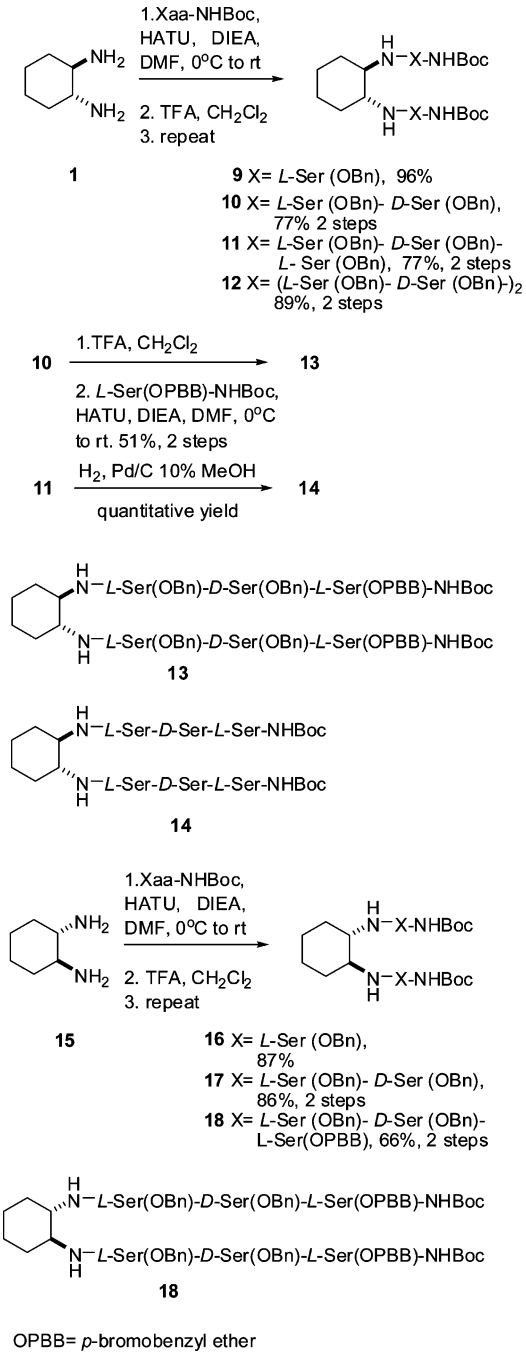
Individual DACH−bis-tripeptide units had in fact self-assembled by engaging in intra- and intermolecular H-bonds, thus forming a supramolecular helical continuum along the vertical axis of the tubular motif (Figure 2, right). The manner in which a carboxy-linked anchored bis-peptide **13** accommodates both intra- and intermolecular H-bonded interactions to achieve the observed helical superstructure is intriguing and, to the best of our knowledge, unprecedented.

Thus, each tripeptide strand assumes a 31° turn at the $i + 1/i + 2$ juncture to expose partially extended strands that cross "over and under" each other in left- and right-handed directions akin to a pair of self-embracing arms reminiscent of Foyatier's Spartacus (Figure 3). Three intramolecular H-bonds consisting of a γ-turn and a 14-membered antiparallel H-bonded ring, spanning the first and third amino acid residues within each strand, can be observed (Figure 3, red dotted line).

In the conformer **A** (Figure 3), the "upper" strand (N10 → N16, Figure 3) is rotated (N10−C10−C11−N11, 32.8(5)°) in a way that brings its first residue at a hydrogen-bonded distance to the first residue of the "lower" strand (N10···O20, 2.903(4) Å). A further turn (C10−C11−N11−C12, −104.6(4)°) is induced by an intramolecular hydrogen bond between the second residue (N11) and the third residue from the lower strand (N11···O24, 2.935(4) Å). The conformation of the upper strand (N14−C14−C15−N16,157.7(3)°,C14−C15−N16−C16,−158.0(3)°) is then aligned so that the carbonyl group of the third residue accepts a hydrogen bond from the second residue of the lower strand (N21···O14, 2.800(4) Å). A similar conformation with the same intramolecular hydrogen bond pattern between the two tripeptide strands is observed for the second conformer **B**.[18]

This type of folding pattern allows further interstrand H-bonding with a classical antiparallel arrangement between

SCHEME 2. Synthetic Scheme for the Serine Derivatives



(18) For details, see Supporting Information.

(19) For selected examples of benzene inclusion in supramolecular complexes, see: (a) Hanessian, S.; Saladino, R.; Margarita, R.; Simard, M.; *Chem.−Eur. J.* **1999**, *5*, 2169−2183. (b) Endo, K.; Sawaki, T.; Koyanagi, M.; Kobayashi, K.; Matuda, H.; Ayama, Y. *J. Am. Chem. Soc.* **1995**, *117*, 8341−8352. (c) Collet, A. *Tetrahedron* **1987**, *43*, 5725−5729. (d) Cerrini, S.; Giglio, E.; Mazza, F.; Pavel, N. Y. *Acta Crystallogr., Sect. B* **1979**, *35*, 2605−2609.

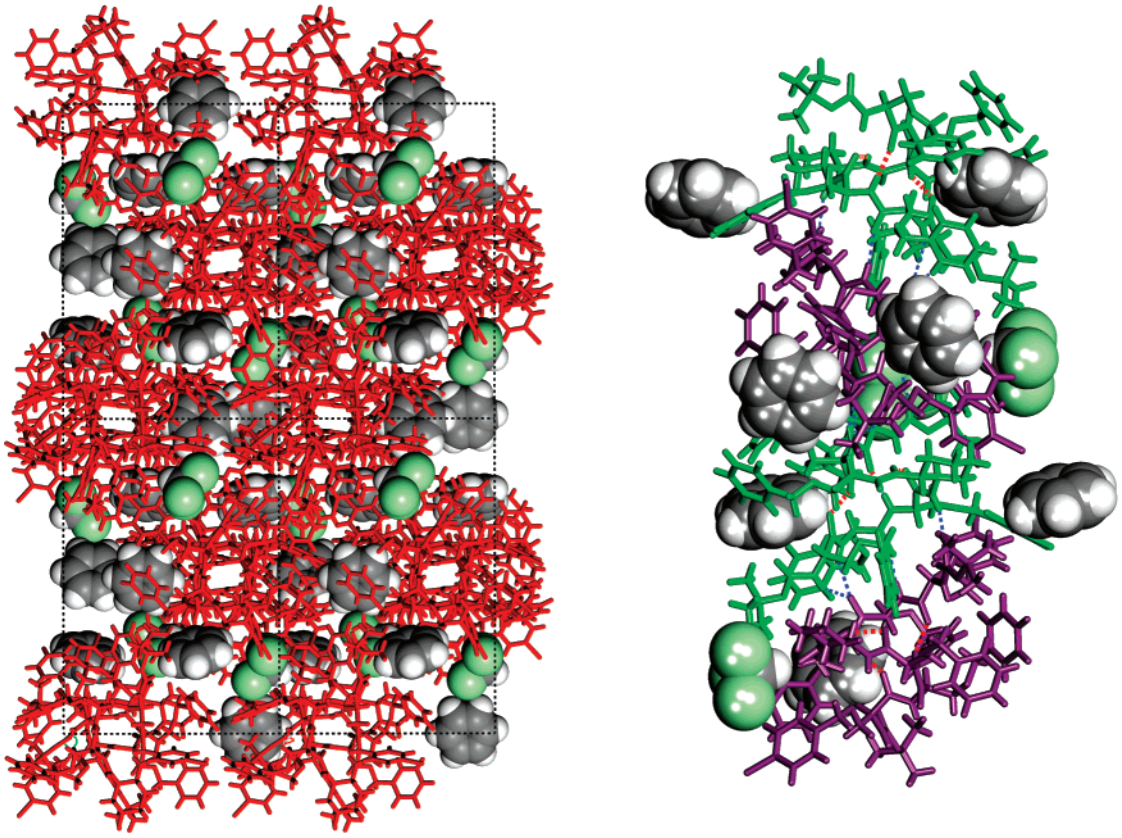


FIGURE 2. Left: View along the *c*-axis of a 2 × 2 × 2 array of unit cells of the packing in structure of DACH−bis-tripeptide **13** displayed in red with the included $CHCl_3$ and benzene molecules shown as sphere of van der Waals radii. Right: View of one column along the *a*-axis showing the stacking of alternating DACH−bis-tripeptide **13** conformers **A** (green) and **B** (purple) with the included $CHCl_3$ and benzene molecules shown as sphere of van der Waals radii.

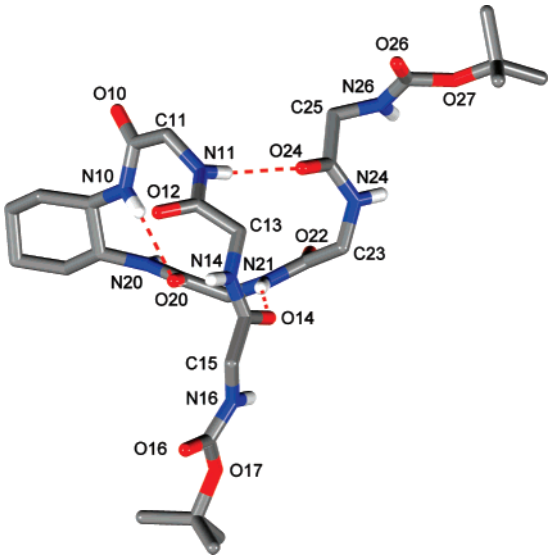


FIGURE 3. X-ray structure of an individual (1*R*,2*R*)-DACH−bis-tripeptide **13** showing intramolecularly H-bonded strands that cross over each other like a pair of self-embracing arms. Side chains and hydrogen atoms (except those attached to nitrogen) have been omitted for clarity. Two distinct but similar conformations **A** and **B** are observed in the crystal; only one is shown.

opposing peptide strands from the different conformers (Figure 4, left, blue hashed lines). The amide carbonyl of the second residue in the upper strand in conformer **A** (O12) is engaged in a bifurcated intermolecular hydrogen bond involving the NH group in the terminal *N*-Boc (N46···O12, 2.845(5) Å) and the amide group nitrogen of the third residue (N44···O12, 2.990-(4) Å) of the DACH tripeptide unit **B**. This last intermolecular hydrogen bond, together with the intramolecular H-bond N31···O44, results in the turn of the terminal *N*-Boc in **B** (C42−C43−N43−C44, 83.1(4)°). The link between the two consecutive conformers **A** and **B** is completed by two additional hydrogen bonds involving the first and second residues of **A** with the third residue and the carbonyl group of the terminal *N*-Boc group, respectively, in conformer **B** (N14···O42, 2.869-(4) Å, N40···O16, 3.094(5) Å). A similar hydrogen bond pattern is observed between the lower strand of conformer **A** (N20 → N26) and that in conformer **B** (N30 → N36).[18]

The combination of intra- and intermolecular H-bond networks results in a helical head-to-tail arrangement of alternating DACH−bis-tripeptide units **A** and **B** assembled in a tubular shape with an average outer diameter of 18 Å (Figure 4, right). The hydrophobic aromatic side chains that are oriented toward the outer periphery do not appear to be within van der Waals contact.

The superstructure contains concave regions surrounded by hydrophobic benzyl and Boc groups (Figure 4, right, arrows). These large cavities are occupied by benzene and $CHCl_3$ solvent molecules, while the internal hydrophilic regions are solvent-free.[19] The benzene molecules occupying the hydrophobic cavities are deployed almost in parallel and perpendicular

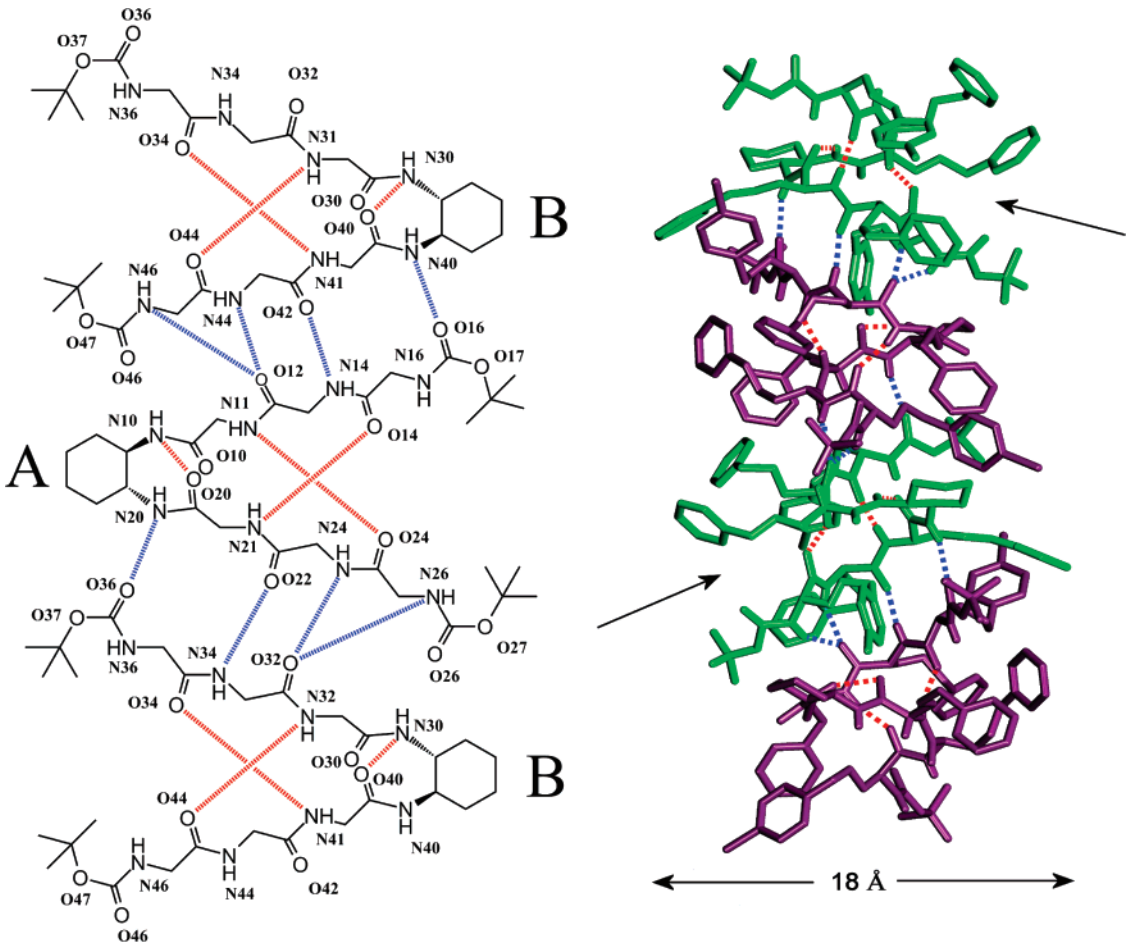


FIGURE 4. Left: H-bonded arrangement of three DACH−bis-tripeptide units in **13** with intra- (red) and inter- (blue) H-bonds (*c*-axis vertical). Side chains are not shown for clarity. Right: Four consecutive DACH−bis-tripeptide units **13** with side chains along the *b*-axis, showing two different conformers **A** (green) and **B** (purple). Arrows indicate concave regions occupied by benzene molecules as in Figure 2. Hydrogen atoms not involved in H-bonds have been omitted for clarity.

orientations relative to the crystallographic *c*-axis (Figure 2, left). Together with the remaining $CHCl_3$ molecules, they line up the sides of the densely packed tube-shaped motifs in a symmetry-related pattern coinciding with the locations of hydrophobic side chains.[20] The inner diameter of the central core is 2.5 Å (Figure 5). Although structure **13** is one of several ensembles in the crystals, it represents the overall three-dimensional topology of the system as a whole.

^{1}H NMR dilution experiments with **13** revealed the existence of relatively stable H-bonded structures within the concentration range of 0.4 to 4.0 mM. Titrations with increasing amounts of DMSO-d_6 in $CDCl_3$ showed minimal if any chemical shift differences of the NH resonances.[18]

Finally, hydrogenolysis of the benzyl ether groups in **11** led to **14** as an amorphous solid which gave a nicely resolved ^{1}H NMR spectrum in pyridine-d_5. Addition of incremental amounts of DMSO-d_6 only slightly shifted the NH resonances.[18] A 20-fold equivalent of CD_3OD per NH group in pyridine-d_5 resulted in only a 20% exchange over a period of 24 h at rt. This suggests the existence of a H-bonded structure of **14** in pyridine-d_5.

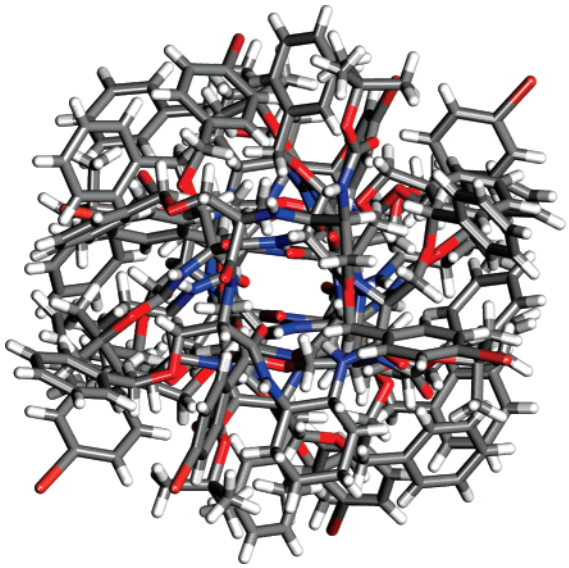


FIGURE 5. Top view along the *c*-axis of one column of DACH−bis-tripeptide **13** showing the internal hydrophilic cavity with an inner diameter of 2.5 Å.

We also prepared the diastereomeric bis-tripeptide **18** with an (*S*,*S*)-DACH anchor (Scheme 2). Although titration experi-

(20) Crystal data for bis-tripeptide **13**·3(C_6H_6)·$CHCl_3$: $C_{171}H_{207}Br_HC1_3N_{16}O_{32}$, FW = 3424.52, orthorhombic, space group $P2_12_12_1$, a = 18.146(3) Å, b = 26.468 Å, c = 35.413(3) Å, V = 17009 Å^3, Z = 4, d_{calc} = 1.377 g cm^{-3}. For details, see Supporting Information.

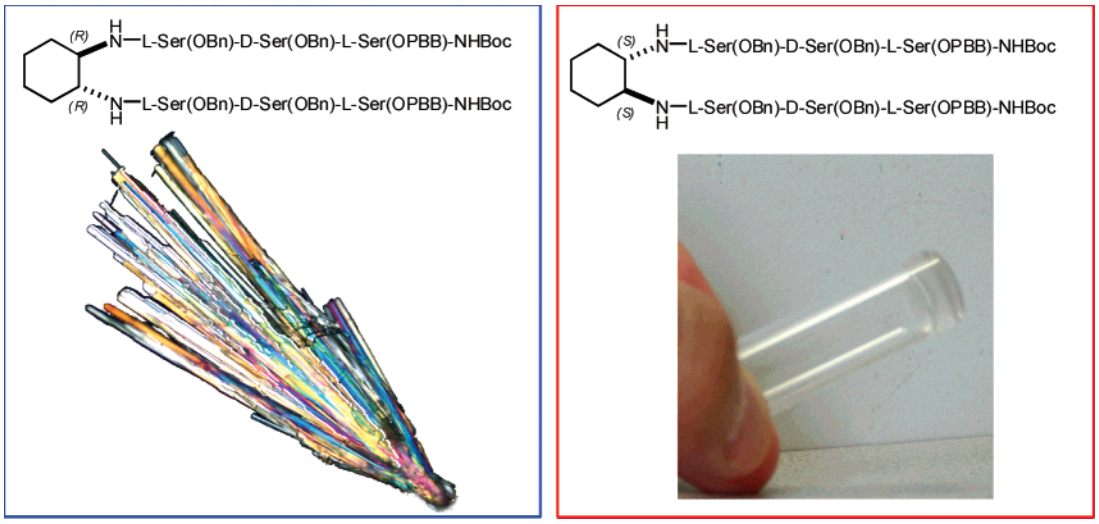
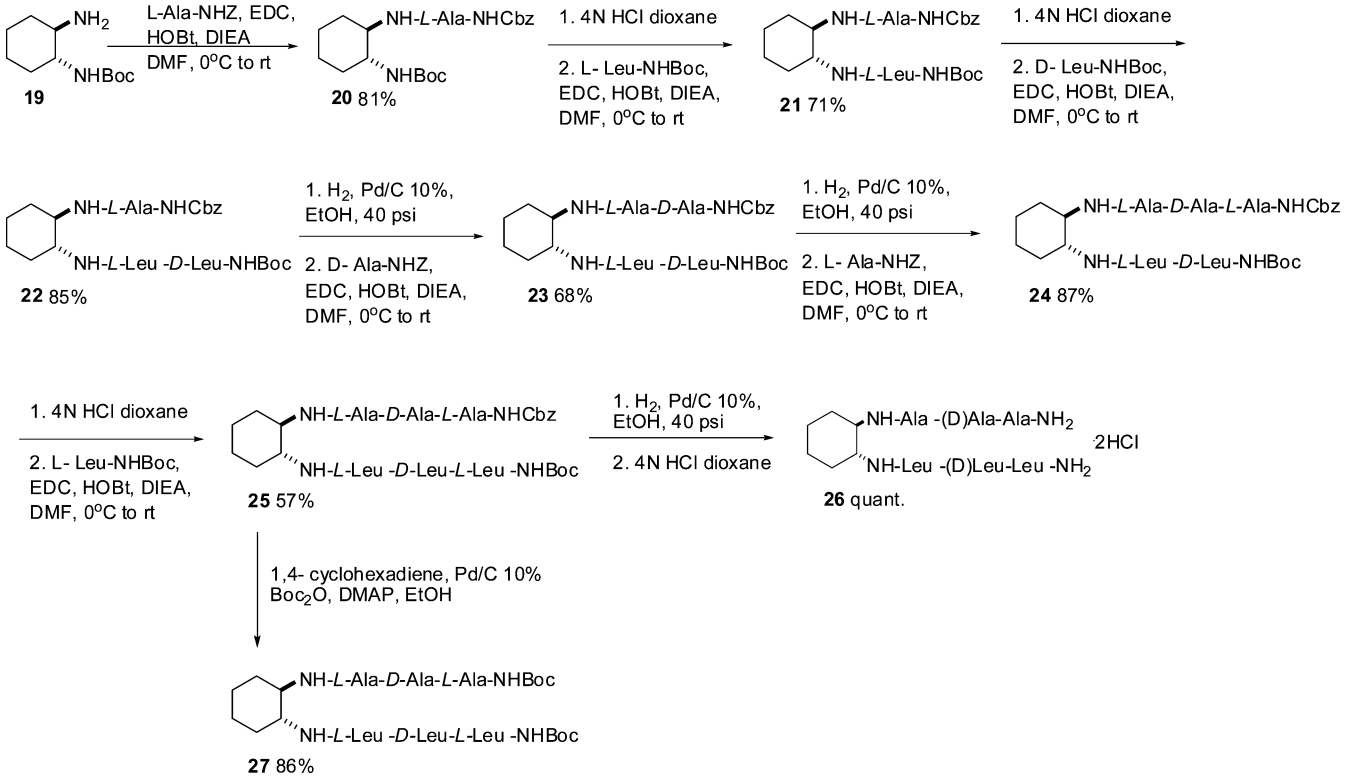


FIGURE 6. Left: crystals of **13** exhibiting birefringence under polarized light. Right: gel form of **18** from a benzene solution.

SCHEME 3. Synthetic Scheme for the Unsymmetrical Ala−Leu Derivatives



ments revealed a behavior almost identical to that of **13**,[18] its solubility properties were markedly different. Whereas beautifully crystalline **13** was freely soluble in benzene, **18** afforded a gel upon heating and cooling from the same solvent (Figure 6).

We next studied the synthesis of the analogous bis-tripeptides comprising D-Ala and L-Ala on one strand in combination with D-Leu and L-Leu on the other strand (Scheme 3). We hoped that these unsymmetrical constructs would provide information regarding possible conformationally distinct secondary structures in solution as revealed by 2D NMR.

Starting with the mono-*N*-Boc derivative of *trans*-(1*R*,2*R*)-diaminocyclohexane **19**[21] and following the standard coupling with *N*-Cbz Ala-OH, **20** was obtained in excellent yields. Deprotection of the *N*-Boc group and coupling with *N*-Boc Leu-OH afforded the bis-monopeptide **21**, which was sequentially deprotected and coupled as above to give the bis-peptides **23**−**25**. Finally, cleavage of the *N*-Cbz and *N*-Boc groups from **25** gave the tripeptide **26**, isolated as the bis-hydrochloride salt. Alternatively, hydrogenolysis of the *N*-Cbz group in **25** followed by protection of the resulting free amine as the Boc derivative afforded the intended bis-*N*-Boc tripeptide **27** as an amorphous solid. Numerous attempts to grow crystals from the Ala−Leu tripeptide series were not successful. Titration with DMSO-d_6 in $CDCl_3$ showed minimal if any chemical shift differences of

(21) Uppadine, L. H.; Keene, F. R.; Beer, P. D. *J. Chem. Soc., Dalton Trans.* **2001**, 2188−2198.

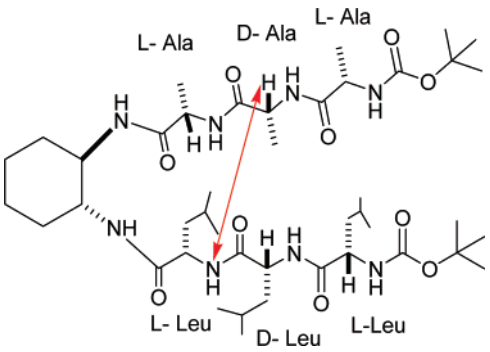


FIGURE 7. Representations of the interstrand cross-talk between D-Ala α-proton and L-LeuNH (red arrow) in **27**.

the NH resonances. Several NOESY and ROESY spectra of **27** at different temperatures (268 and 318 K) and mixing times (0.5, 0.7, 0.8, and 1.2 s) were recorded.[18] In spite of the observation of more than 30 NOESY cross-peaks, most were not significant and indicative of an ordered H-bonded structure. Nevertheless, an nOe was observed between the D-Ala α-proton in one strand and the first L-Leu NH of the other, indicating relative proximity in space (Figure 7).

Unfortunately, other across strand interactions could not be observed, thus precluding the unambiguous assignment of a definitive secondary structure for the Ala−Leu derivative **27** in solution as in the case of **13** in the solid state.

The helical superstructure of **13** in the solid state is reminiscent of the structure of the antibacterial peptide gramicidin A,[22] which consists of a sequence of seven alternating D- and L-amino acids. Dimerization of gramicidin A affords a head-to-head, so-called *β*-helical, motif.[23,24] Valinomycin is a cyclic dodecadepsipeptide that contains D- and L-valine residues among others which, like gramicidin A, is involved in cation transport across membranes.[25] The structure of polytheonamide A, a 48 amino acid residue cytotoxic polypeptide consisting of alternating D- and L-*tert*-butyl leucines among others, has been recently elucidated by NMR techniques.[26] It is only the second naturally occurring noncyclic polypeptide to harbor D− and L-amino acid sequences after gramicidin A. The structure−activity relationship among helix-forming *β*-amino acid oligomers as mimics of host-defense peptides has been studied by Gellman and coworkers.[27]

Conclusions

In conclusion, we have shown that even a minimal noncyclic tripeptide consisting of L- and D-amino acids as **13** can adopt energetically favorable conformations in the solid state when anchored to a C_2-symmetrical turn motif such as DACH. As a result of a unique H-bonding network between the strands of the tripeptides, tube-shaped supramolecular assemblies are formed reminiscent of cyclic peptide nanotubes[7] and other nonpeptidic columnar aggregates.[28] Thus, the need to further exploit the chemistry of short open-ended D- and L-oligopeptides in relation to structure and function is warranted.[29]

Experimental Section

(1*R*,2*R*)-*N*,*N*′-Bis(L-Ala-NHCbz)diaminocyclohexane (2). To an ice-chilled solution of **1** (200 mg, 1.75 mmol) in 49 mL of DMF were added (L) *N*-Cbz-alanine (937 mg, 4.20 mmol), HOBt (708 mg, 5.25 mmol), EDC (1.0 g, 5.25 mmol), and DIEA (1.8 mL, 10.5 mmol). The reaction mixture was stirred for 1 h at 0 °C and 36 h at room temperature. DMF was then removed under reduced pressure, and the residue was dissolved in 28 mL of dichloromethane. Water (28 mL) was then added to the solution, and the phases were separated. The organic layer was washed successively with a saturated aqueous solution of $NaHCO_3$, aq 1 N HCl, and brine, then dried (Na_2SO_4) and evaporated to dryness. The resulting crude was purified by flash column chromatography on silica gel (elution with AcOEt), and the desired product was obtained as a white solid (750 mg, 82%): $[\alpha]_D$ +2 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.28−7.20 (m, 10H), 6.94 (br s, 2H), 6.13 (d, J = 7.7 Hz, 2H), 5.12−5.09 (d, J = 12.3 Hz, 2H), 4.91−4.88 (d, J = 12.3 Hz, 2H), 4.17−4.13 (m, 2H), 3.68 (br s, 2H), 1.94 (br s, 2H), 1.68 (br s, 2H), 1.28−1.23 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 173.6, 156.8, 136.7, 128.8 (2), 128.4, 67.3, 53.8, 51.0, 32.5, 25.1, 18.5; FT-IR (neat) ν (cm^{-1}) 3421, 3325, 1708, 1678, 1524, 1509; MS (FAB) *m*/*e* 525 [M + H]$^+$; HRMS (FAB) for $C_{28}H_{37}N_4O_6$ calcd 525.27131; found 525.27366.

(1*R*,2*R*)-*N*,*N*′-Bis(L-Ala-D-Ala-NHCbz)diaminocyclohexane (3). Compound **2** (500 mg, 0.95 mmol) was dissolved in methanol (9.5 mL) and hydrogenated (1 atm) in the presence of 10% Pd/C for 16 h at room temperature. After removal of the catalyst by filtration through Celite, the solvent was evaporated under vacuum, affording the corresponding free diamine as a white solid. This material was then coupled with (D) *N*-Cbz-alanine under the same conditions described for the synthesis of **2** (purification by flash chromatography on silica gel elution with AcOEt/MeOH 9/1), affording the desired product as a white solid (344 mg, 66% over two steps): $[\alpha]_D$ −14 (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.36−7.27 (m, 12H), 6.95 (br s, 2H), 6.09−6.06 (d, J = 7.5 Hz, 2H), 5.14−5.10 (d, J = 12.2 Hz, 2H), 5.05−5.01 (d, J = 12.2 Hz, 2H), 4.41−4.30 (m, 4H), 3.70 (br s, 2H), 1.94 (br s, 2H), 1.70 (br s, 2H), 1.40−1.24 (m, 16H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 173.5, 172.9, 156.8, 136.5, 128.9, 128.6, 128.4, 67.4, 54.2, 50.9, 49.0, 32.2, 25.0, 18.9, 17.9; FT-IR (neat) ν (cm^{-1}) 3425, 3334, 1713, 1669, 1524, 1508; MS (FAB) *m*/*e* 667 [M + H]$^+$; HRMS (FAB) for $C_{34}H_{47}N_6O_8$ calcd 667.34553; found 667.34590.

(1*R*,2*R*)-*N*,*N*′-Bis(L-Ala-D-Ala-L-Ala-NHCbz)diaminocyclohexane (4). The title compound was obtained starting from **3** (250 mg, 0.37 mmol) and following the procedures described for the

(22) (a) Wallace, B. A.; Ravikumar, K. *Science* **1988**, *241*, 182−187. (b) Langs, D. A. *Science* **1988**, *241*, 188−191. (c) Ketchen, R. R.; Hu, W.; Cross, T. A. *Science* **1993**, *261*, 1457−1460. (d) Burkhart, B. M.; Li, N.; Langs, D. A.; Pangborn, W. A.; Duax, W. L. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 12950−12955.

(23) For relevant articles, see: (a) Åkerfelt, K.; Lear, L. D.; Wasserman, Z. R.; Chung, L. A.; De Grado, W. F. *Acc. Chem. Res.* **1993**, *26*, 191−197. (b) Gokel, G. W.; Mukhopadhyay, A. *Chem. Soc. Rev.* **2001**, *30*, 274−286.

(24) For a study of tartaric acid−gramicidin hybrids, see for example: (a) Stankovic, C. J.; Heinemann, S. H.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 3702−3704. (b) Xiao, J.; Weisblum, B.; Wipf, P. *J. Am. Chem. Soc.* **2005**, *127*, 5742−5743.

(25) Streinrauf, L. K.; Hamilton, J. A.; Sabesan, M. N. *J. Am. Chem. Soc.* **1982**, *104*, 4085−4091.

(26) Hamada,T.; Matsunaga, S.; Yano, G.; Fusetani, N. *J. Am. Chem. Soc.* **2005**, *127*, 110−118.

(27) (a) Sadowsky, J. D.; Murray, J. K.; Tomita, Y.; Gellman, S. H. *ChemBioChem* **2007**, *8*, 903−916. (b) Price, J. L.; Horne, W. S.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 6376−6377. (c) Horne, W. S.; Price, J. L.; Keck, J. L.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 4178−4180. (d) Sadowsky, J. D.; Fairlie, W. D.; Hadley, E. B.; Lee, H.-S.; Umezawa, N.; Nikolovska-Coleska, Z.; Wang, S.; Huang, D. C. S.; Tomita, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 139−154. (e) Porter, F. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11516−11529.

(28) For helical cation-promoted oligomeric, open-ended heterocycles, see: Petitjean, A.; Cuccia, A, L. A.; Lehn, J.-M.; Nierengarten, H.; Schmutz, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1195−1198.

(29) Keizer, H. M.; Sijbesma, R. P. *Chem. Soc. Rev.* **2005**, *34*, 226−234.

synthesis of **3** from **2** (i.e., coupling with (L) *N*-Cbz-alanine and purification by flash chromatography on silica gel). Elution with AcOEt/MeOH 9/1 gave **4** as a white solid (72 mg, 24%, over two steps): $[\alpha]_D$ −3 (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.70 (br s, 2H), 7.36−7.28 (m, 12H), 6.65 (br s, 2H), 5.24−5.20 (d, J = 12.1 Hz, 2H), 5.15−5.12 (d, J = 8.7 Hz, 2H), 5.08−5.04 (d, J = 12.1 Hz, 2H), 4.67−4.63 (m, 2H), 4.43−4.40 (m, 2H), 4.32−4.28 (m, 2H), 3.51 (br s, 2H), 1.81−1.78 (m, 2H), 1.55 (m, 2H), 1.35 (d, J = 6.7 Hz, 6H), 1.24−1.22 (m, 16H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 173.7, 173.4, 172.7, 156.9, 136.5, 128.9, 128.8, 128.7, 67.6, 53.4, 50.7, 49.0 (2), 32.5, 25.0, 18.4 (2), 17.9; FT-IR (neat) ν (cm^{-1}) 3414, 3314, 1714, 1670, 1539, 1507; MS (FAB) *m*/*e* 810 $[M + H]^+$; HRMS (FAB) for $C_{40}H_{57}N_8O_{10}$ calcd 809.41976; found 809.42151.

(1*R*,2*R*)-*N*,*N*′-Bis(L-Ala-D-Ala-L-Ala-D-Ala-NHCbz)diaminocyclohexane (5). The title compound was obtained starting from **4** (680 mg, 0.84 mmol) and following the procedures described for the synthesis of **3**. Coupling with (D) *N*-Cbz-alanine and purification by flash chromatography on silica gel (elution with AcOEt/MeOH 4/1) gave **5** as a white solid (380 mg, 48%, over two steps): $[\alpha]_D$ −24 (*c* 0.125, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.64 (br s, 2H), 7.34−7.31 (m, 12H), 7.22 (br s, 2H), 6.84 (br s, 2H), 6.23 (d, J = 6.0 Hz, 2H), 5.16−5.13 (d, J = 12.2 Hz, 2H), 5.08−5.05 (d, J = 12.2 Hz, 2H), 4.55−4.40 (m, 8H), 3.66 (m, 2H), 1.77−1.75 (m, 2H), 1.69−1.66 (m, 2H), 1.36−1.15 (m, 28H); ^{13}C NMR (CD_3OD, 100 MHz) δ (ppm) 174.8, 173.9, 173.8, 173.6, 157.4, 137.2, 128.5, 128.0, 127.7, 66.6, 52.9, 51.3, 50.0, 49.8, 49.7, 31.9, 24.7, 17.1, 16.7, 16.4, 16.3; FT-IR (neat) ν (cm^{-1}) 3306, 1662, 1530; MS (FAB) *m*/*e* 951 $[M]^+$; HRMS (FAB) for $C_{46}H_{67}N_{10}O_{12}$ calcd 951.49399; found 951.49100.

(1*R*,2*R*)-*N*,*N*′-Bis(L-Ala-D-Ala-L-Ala-D-Ala-NH$_2$)diaminocyclohexane (6). The title compound was obtained starting from **5** (300 mg, 0.31 mmol), following the procedures for the deprotection of **2**. Hydrogenolysis and filtration through Celite afforded **6** as a white solid (225 mg, 94%). The crude product was used in the next step without any further purification: $[\alpha]_D$ −9 (*c* 0.55, MeOH); ^{1}H NMR (CD_3OD, 300 MHz) δ (ppm) 4.32−4.18 (m, 6H), 3.67 (br s, 2H), 3.47−3.40 (t, J = 6.8 Hz, 2H), 1.92 (br s, 2H), 1.74 (br s, 2H), 1.37−1.25 (m, 28H); ^{13}C NMR (CD_3OD, 75 MHz) δ (ppm) 177.4, 174.1, 173.7 (2), 53.1, 50.2, 49.8, 49.7, 49.5, 32.0, 24.8, 20.2, 17.2, 16.9, 16.4; MS (FAB) *m*/*e* 705 $[M + Na]^+$, 683 $[M + H]^+$; HRMS (FAB) for $C_{30}H_{55}N_{10}O_8$ calcd 683.42043; found 683.42077.

(1*R*,2*R*)-*N*,*N*′-Bis(L-Ala-D-Ala-L-Ala-D-Ala-NHBoc)diaminocyclohexane (7). Boc_2O (19 mg, 0.088 mmol) was added to a stirred solution of diamine **6** (15 mg, 0.022 mmol) in methanol (1 mL). The reaction mixture was stirred at room temperature for 60 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (AcOEt/MeOH 9/1) to give the desired product as a white solid (11 mg, 58%, over two steps): $[\alpha]_D$ −5 (*c* 0.55, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.63 (br s, 2H), 7.49 (br s, 2H), 7.23 (br s, 2H), 7.11 (br s, 2H), 5.79 (br s, 2H), 4.53−4.43 (m, 6H), 4.24−4.22 (m, 2H), 3.67 (m, 2H), 1.92 (br s, 2H), 1.75 (br s, 2H), 1.46 (s, 18H), 1.49−1.25 (m, 28H); ^{13}C NMR (CD_3OD, 100 MHz) δ (ppm) 175.0, 173.9, 173.8, 173.7, 156.7, 79.5, 53.0, 50.9, 50.1, 49.9, 49.5, 31.9, 27.7, 24.7, 17.1, 17.0, 16.6, 16.4; FT-IR (neat) ν (cm^{-1}) 3309, 1664, 1534, 1509; MS (FAB) *m*/*e* 905 $[M + Na]^+$, 882 $[M]^+$, 782 $[M - Boc]^+$, 683 $[M - 2Boc]^+$; HRMS (FAB) for $C_{40}H_{71}N_{10}O_{12}$ calcd 883.52529; found 883.52250.

(1*R*,2*R*)-*N*,*N*′-Bis(L-Ala-D-Ala-L-Ala-D-Ala-NHAc)diaminocyclohexane (8). Acetic anhydride (10 μL, 0.076 mmol) was added to a stirred solution of diamine **6** (10 mg, 0.015 mmol) in methanol (500 μL). The reaction mixture was stirred at room temperature for 48 h. The solvents were removed under reduced pressure, and the residue was triturated with ether, the white solid filtered and dried under vacuum. The desired product was obtained as a white solid (10 mg, 91% over two steps): $[\alpha]_D$ −8 (*c* 0.1, MeOH); ^{1}H NMR (CD_3OD, 400 MHz) δ (ppm) 4.31−4.26 (m, 8H), 3.74−3.71 (m, 2H), 1.99 (s, 6H), 1.91 (br s, 2H), 1.74 (br s, 2H), 1.40−1.35 (m, 28H); ^{13}C NMR (CD_3OD, 100 MHz) δ (ppm) 174.5, 173.9, 173.8, 173.6, 172.3, 52.9, 50.1, 49.9, 49.8, 49.7, 31.9, 24.7, 21.4, 17.1, 16.7, 16.5, 16.4; FT-IR (neat) ν (cm^{-1}) 3302, 1656, 1541, 1523; MS (FAB) *m*/*e* 790 $[M + Na]^+$, 768 $[M + H]^+$.

(1*R*,2*R*)-*N*,*N*′-Bis(L-Ser(OBn)-NHBoc)diaminocyclohexane (9). To an ice-chilled solution of **1** (300 mg, 2.63 mmol) in 13 mL of DMF were added (L) *N*-Boc-serine (OBn) (1.86 g, 6.31 mmol), HATU (2.4 g, 6.31 mmol), and DIEA (2.75 mL, 15.78 mmol). The reaction mixture was stirred for 1 h at 0 °C and 48 h at room temperature. Water (50 mL) and EtOAc (50 mL) were added and the layers separated. The organic phase was washed successively with water, a saturated solution of $NaHCO_3$, brine, then dried on Na_2SO_4 and evaporated to dryness. The solid obtained was purified by flash column chromatography on silica gel (elution with AcOEt/hexanes 1/1), affording the desired product as a white solid (1.12 g, 96%): $[\alpha]_D$ +6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.24−7.19 (m, 10H), 6.75 (d, J = 6.3 Hz, 2H), 5.45 (br s, 2H), 4.49−4.46 (d, J = 12.1 Hz, 2H), 4.41−4.38 (d, J = 12.1 Hz, 2H), 4.20 (br s, 2H), 3.75 (br s, 2H), 3.59 (br s, 2H), 3.52−3.48 (dd, J = 9.3, 5.4 Hz, 2H) 1.92 (br s, 2H), 1.65 (d, J = 7.6 Hz, 2H), 1.37 (s, 18H), 1.25−1.22 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.9, 156.0, 138.0, 128.5, 128.1, 127.9, 80.3, 73.5, 69.8, 54.4, 54.1, 32.3, 28.6, 24.9; FT-IR (neat) ν (cm^{-1}) 3416, 1710, 1668, 1528, 1496; MS (FAB) *m*/*e* 669 $[M + H]^+$, 569 $[M - Boc]^+$, 469 $[M - 2Boc]^+$; HRMS (FAB) for $C_{36}H_{53}N_4O_8$ calcd 669.38634; found 669.38370.

(1*R*,2*R*)-*N*,*N*′-Bis(L-Ser(OBn)-D-Ser(OBn)-NHBoc)diaminocyclohexane (10). Compound **9** (1.6 g, 2.39 mmol) was dissolved in 10 mL of dichloromethane, trifluoroacetic acid (10 mL) was then added, and the resulting solution was stirred at room temperature for 2 h. The solvents were removed under reduced pressure, and the residue was coevaporated with toluene, then dried overnight under vacuum. The solid obtained was used without any further purification in the ensuing coupling to (D) *N*-Boc-serine (OBn) under the same conditions described for the synthesis of **9** (purification by flash column chromatography on silica gel, eluting with AcOEt/hexanes 3/2), affording the desired product as a white solid (1.88 g, 77% over two steps): $[\alpha]_D$ −46 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.32−7.20 (m, 22H), 6.73 (br s, 2H), 6.18 (br s, 2H), 4.71 (br s, 2H), 4.55−4.39 (m, 10H), 4.06−3.96 (m, 2H), 3.96−3.92 (m, 2H), 3.69−3.56 (m, 4H), 3.56−3.46 (br s, 2H), 1.86 (br s, 2H), 1.59 (br s, 2H), 1.45 (s, 18H), 1.07 (br s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.0, 170.3, 156.3, 138.1, 137.9, 128.9, 128.8, 128.7, 128.5, 128.1, 127.9, 80.5, 73.6, 72.9, 70.7, 68.3, 55.3, 54.2, 52.6, 32.0, 28.8, 24.8; FT-IR (neat) ν (cm^{-1}) 3334, 1668, 1538, 1497; MS (FAB) *m*/*e* 1023 $[M]^+$, 923 $[M - Boc]^+$, 823 $[M - 2Boc]^+$; HRMS (ESI) for $C_{56}H_{75}N_6O_{12}$ (MH^+) calcd 1023.54375; found 1023.54210.

(1*R*,2*R*)-*N*,*N*′-Bis(L-Ser(OBn)-D-Ser(OBn)-L-Ser(OBn)-NHBoc)diaminocyclohexane (11). The title compound was obtained starting from **10** (1.5 g, 1.47 mmol) following the general procedures for the synthesis of **10** from **9** (i.e., coupling with (L) *N*-Boc-serine (OBn) and purification by flash column chromatography on silica gel). Elution with AcOEt/hexanes 2/1 gave **11** as a white solid (1.56 g, 77% over two steps: $[\alpha]_D$ −7.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.57 (br s, 2H), 7.41 (d, J = 6.9 Hz, 2H), 7.28−7.22 (m, 30H), 6.85 (br s, 2H), 5.72 (d, J = 6.9 Hz, 2H), 4.76−4.74 (m, 2H), 4.63−4.60 (m, 2H), 4.51−4.38 (m, 14H), 3.83−3.79 (m, 6H), 3.62−3.52 (m, 8H), 1.89 (d, J = 9.6 Hz, 2H), 1.61−1.58 (m, 2H), 1.43 (s, 18H), 1.16−1.10 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.3, 170.3, 170.2, 155.9, 138.0 (2), 137.9, 128.9, 128.8, 128.6, 128.5, 128.2, 128.1 (2), 128.0, 127.9, 80.3, 73.5, 73.3, 70.4, 69.9 (2), 69.2, 54.4, 54.2, 53.9, 53.0, 32.0, 28.7, 24.9; FT-IR (neat) ν (cm^{-1}) 3332, 1666, 1496; MS (FAB) *m*/*e* 1377 $[M]^+$, 1277 $[M - Boc]^+$, 1177 $[M - 2Boc]^+$; HRMS (ESI) for $C_{76}H_{97}N_8O_{16}$ (MH^+) calcd 1377.70171; found 1377.69973.

(1*R*,2*R*)-*N*,*N*′-Bis(L-Ser(OBn)-D-Ser(OBn)-L-Ser(OBn)-D-Ser(OBn)-NHBoc)diaminocyclohexane (12). The title compound was obtained starting from **11** (500 mg, 0.36 mmol) following the general procedures for the synthesis of **10** (i.e., coupling with (D) *N*-Boc-serine (OBn) and purification by flash column chromatography on silica gel). Elution with AcOEt/hexanes 3/1 gave **12** as a white solid (560 mg, 89% over two steps): $[\alpha]_D$ −2 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.69 (br s, 2H), 7.57 (br s, 2H), 7.42−7.18 (m, 40H), 7.15 (br s, 2H), 6.93 (br s, 2H), 5.70 (br s, 2H), 4.77 (br s, 2H), 4.71−4.55 (m, 4H), 4.53−4.31 (m, 18H), 3.89−3.70 (m, 8H), 3.68−3.49 (m, 10H), 1.86 (br s, 2H), 1.59 (br s, 2H), 1.49−1.32 (m, 20H), 1.20−1.04 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.0, 170.7, 170.3, 170.2, 156.1, 138.1, 138.0 (2), 137.9, 128.8 (2), 128.7 (2), 128.5 (2), 128.2 (2), 128.1 (2), 128.0, 127.9, 80.6, 73.5 (2), 73.2, 70.2, 69.7, 69.5 (2), 69.1, 54.8, 53.9 (2), 53.5, 53.1, 32.1, 28.7, 24.9; FT-IR (neat) ν (cm^{-1}) 3327, 1667, 1497; MS (FAB) *m*/*e* 1754 $[M + Na]^+$, 1732 $[M]^+$, 1632 $[M - Boc]^+$, 1532 $[M - 2Boc]^+$; HRMS (ESI) for $C_{96}H_{119}N_{10}O_{20}$ (MH^+) calcd 1731.85966; found 1731.85850.

(1*R*,2*R*)-*N*,*N*′-Bis(L-Ser(OBn)-D-Ser(OBn)-L-Ser(OPBB)-NHBoc)diaminocyclohexane (13). The title compound was obtained starting from **10** (100 mg, 0.098 mmol) and following the general procedures for the synthesis of **10** (i.e., coupling with (L) *N*-Boc-serine (OPBB) and purification by flash column chromatography on silica gel). Elution with AcOEt/hexanes 2/1 gave **13** as a white crystalline solid (76 mg, 51% over two steps): crystallization from 1:1 benzene/$CHCl_3$ (hexanes atmosphere); $[\alpha]_D$ −5 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.58 (d, J = 6.2 Hz, 2H), 7.48−7.38 (m, 6H), 7.38−7.23 (m, 20H), 7.21−7.13 (m, 4H), 6.82 (d, J = 6.3 Hz, 2H), 5.74 (d, J = 6.8 Hz, 2H), 4.85−4.74 (m, 2H), 4.70−4.58 (m, 2H), 4.54−4.40 (m, 14H), 3.93−3.74 (m, 6H), 3.70−3.46 (m, 8H), 1.99−1.85 (m, 2H), 1.75−1.62 (m, 2H), 1.46 (s, 18H), 1.22−1.09 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.3, 170.3 (2), 155.9, 137.9 (2), 137.1, 131.9, 129.7, 128.8, 128.2, 128.1, 127.9 (2), 127.6, 122.0, 80.5, 73.5, 73.3, 72.7, 70.5, 69.9, 69.1, 54.4, 54.2, 53.9, 53.0, 32.1, 28.7, 24.9; FT-IR (neat) ν (cm^{-1}) 3334, 1669, 1537; MS (FAB) *m*/*e* 1536 $[M + H]^+$, 1535 $[M]^+$, 1435 $[M - Boc]^+$; HRMS (ESI) for $C_{79}H_{95}Br_2N_8O_{16}$ (MH^+) calcd 1533.52273; found 1533.52085.

(1*R*,2*R*)-*N*,*N*′-Bis(L-Ser-D-Ser-L-Ser-NHBoc)diaminocyclohexane (14). Compound **11** (100 mg, 0.098 mmol) was dissolved in methanol (10 mL) and hydrogenated (60 psi) in the presence of 10% Pd/C (40 mg) for 16 h at room temperature. After removal of the catalyst by filtration through Celite, the solvent was evaporated under vacuum, affording the title compound as a white solid (64 mg, quantitative yield): $[\alpha]_D$ −3 (*c* 1.4, MeOH); ^{1}H NMR (pyridine-d_5, 400 MHz) δ (ppm) 9.18 (d, J = 7.0 Hz, 2H), 8.76 (d, J = 7.4 Hz, 2H), 8.38 (br s, 2H), 8.02 (d, J = 7.4 Hz, 2H), 6.25 (br s, 6H), 5.20 (d, J = 5.3 Hz, 2H), 5.16−5.09 (m, 2H), 5.01 (d, J = 6.6 Hz, 2H), 4.54−4.51 (m, 2H), 4.50−4.48 (m, 2H), 4.47 (d, J = 4.58 Hz, 2H), 4.45 (d, J = 5.0 Hz, 2H), 4.31−4.24 (m, 4H), 4.18 (d, J_1 = 4.7 Hz, 1H), 4.16 (d, J = 4.7 Hz, 1H), 4.02−3.95 (m, 2H), 1.99−1.89 (m, 2H), 1.47 (s, 18H), 1.41−1.30 (m, 4H), 0.98−0.88 (m, 2H); ^{13}C NMR (pyridine-d_5, 100 MHz) δ (ppm) 172.5, 171.5, 171.0, 156.4, 78.9, 63.3, 62.6, 62.2., 57.8, 56.8, 56.3, 53.7, 31.9, 28.2, 24.6; FT-IR (neat) ν (cm^{-1}) 3308, 1655, 1529; MS (ESI) *m*/*e* 859 $[M + Na]^+$, 837 $[M + H]^+$, 737 $[M - Boc + H]^+$; HRMS (ESI) for $C_{34}H_{61}N_8O_{16}$ (MH^+) calcd 837.42000; found 837.41958.

(1*S*,2*S*)-*N*,*N*′-Bis(L-Ser(OBn)-NHBoc)diaminocyclohexane (16). The title compound was obtained starting from **15** (207 mg, 1.81 mmol) following the procedures for the preparation of **9** from **1** (i.e., coupling with (L) *N*-Boc-serine (OBn) and purification by flash column chromatography on silica gel). Elution with hexanes/AcOEt 60/40 gave **16** as a white solid (1.04 g, 87%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.43−7.30 (m, 10H), 6.92 (d, J = 6.4 Hz, 2H), 5.67 (d, J = 6.4 Hz, 2H), 4.55 (app s, 4H), 4.38−4.25 (m, 2H), 3.94 (d, J = 6.8 Hz, 2H), 3.80−3.68 (m, 2H), 3.60−3.49 (m, 2H), 2.00−1.85 (m, 2H), 1.82−1.69 (m, 2H), 1.50 (s, 18H), 1.32−1.10 (m, 4H); MS (ESI) *m*/*e* 669 $[M + H]^+$, 569 $[M - Boc + H]^+$.

(1*S*,2*S*)-*N*,*N*′-Bis(L-Ser(OBn)-D-Ser(OBn)-NHBoc)diaminocyclohexane (17). The title compound was obtained starting from **16** (668 mg, 1.0 mmol) following the procedures for the preparation of **10** from **9** (i.e., deprotection with trifluoroacetic acid in dichloromethane, then coupling with (D) *N*-Boc-serine (OBn) and purification by flash column chromatography on silica gel). Elution with hexanes/AcOEt 20/80 gave **17** as a white fluffy solid (880 mg, 86% on two steps): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.42 (d, J = 6.8 Hz, 2H), 7.37−7.27 (m, 20H), 6.81 (br s, 2H), 5.69 (br s, 2H), 4.62 (d, J = 11.9 Hz, 2H), 4.57−4.45 (m, 8H), 4.41 (br s, 2H), 3.98−3.84 (m, 4H), 3.73−3.65 (m, 2H), 3.65−3.52 (m, 4H), 1.88−1.81 (m, 2H), 1.65 (d, J = 6.8 Hz, 2H), 1.43 (s, 18H), 1.25−1.15 (m, 2H); MS (ESI) *m*/*e* 1023 $[M + H]^+$, 923 $[M - Boc + H]^+$.

(1*S*,2*S*)-*N*,*N*′-Bis(L-Ser(OBn)-D-Ser(OBn)-L-Ser(OPBB)-NHBoc)diaminocyclohexane (18). The title compound was obtained starting from **17** (322 mg, 0.31 mmol) following the procedures for the preparation of **13** from **10** (i.e., deprotection with trifluoroacetic acid in dichloromethane, then coupling with (L) *N*-Boc-serine (OPBB) and purification by flash column chromatography on silica gel). Elution with $CHCl_3$/MeOH 97/3 gave **18** as a glassy solid (317 mg, 66% on two steps): $[\alpha]_D$ −6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.51 (d, J = 6.8 Hz, 2H), 7.44−7.39 (m, 3H), 7.35−7.23 (m, 28H), 7.17−7.13 (m, 4H), 6.85 (d, J = 7.3 Hz, 2H), 5.74 (d, J = 7.3 Hz, 2H), 4.67 (dd, J_1 = 5.4 Hz, J_2 = 8.3 Hz 2H), 4.53−4.39 (m, 14H), 3.91−3.78 (m, 6H), 3.72−3.63 (m, 6H), 3.53 (dd, J_1 = 5.4 Hz, J_2 = 8.3 Hz, 2H), 1.91−1.84 (m, 2H), 1.44 (s, 18H), 1.30−1.22 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.5 (2), 169.4, 155.4, 137.3, 137.1, 136.3, 131.1, 128.9, 128.1, 128.0, 127.5, 127.4 (2), 127.2, 121.2, 79.7, 72.9, 72.8, 72.0, 69.5, 69.1, 68.8, 53.9, 53.2, 52.7, 52.4, 31.7, 27.9, 24.3; FT-IR (neat) ν (cm^{-1}) 3270, 1635, 1553; MS (ESI) *m*/*e* 1536 $[M + H]^+$, 1535 $[M]^+$, 1435 $[M - Boc]^+$; HRMS (ESI) for $C_{79}H_{95}Br_2N_8O_{16}$ (MH^+) calcd 1533.52273; found 1533.52101.

(1*R*,2*R*)-*N*-(L-Ala-NHCbz),*N*′-Boc-diaminocyclohexane (20). Compound **19** (65 mg, 0.3 mmol) was dissolved in 8.4 mL of DMF, the resulting solution ice-chilled, and (L) *N*-Cbz-alanine (160 mg, 0.72 mmol), HOBt (121 mg, 0.9 mmol), EDC (172 mg, 0.9 mmol), and DIEA (313 μL, 1.8 mmol) were added in sequence. The reaction mixture was stirred for 1 h at 0 °C and 36 h at room temperature. DMF was then removed under reduced pressure, and the residue was dissolved in 8.4 mL of dichloromethane. Water (8.4 mL) was then added to the solution, and the two phases were separated. The organic layer was washed successively with a saturated solution of $NaHCO_3$, aq 1 N HCl, and brine, then dried (Na_2SO_4) and evaporated to dryness. The resulting crude material was purified by flash column chromatography on silica gel (eluting with $CHCl_3$/MeOH 96/4), affording the desired product as a pale yellow solid (102 mg, 81%): $[\alpha]_D$ +20 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.42−7.29 (m, 5H), 6.78 (d, J = 6.8 Hz, 1H), 5.55 (d, J = 6.4 Hz, 1H), 5.14 (d, J = 12.2 Hz, 1H), 5.09 (d, J = 12.2 Hz, 1H), 4.81 (d, J = 7.3 Hz, 1H), 4.21 (t, J = 6.8 Hz, 1H), 3.64−3.49 (m, 1H), 3.43−3.27 (m, 1H), 2.10−1.93 (m, 2H), 1.82−1.64 (m, 2H), 1.49−1.35 (m, 12H), 1.34−1.12 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.9, 156.5, 155.3, 136.0, 128.1, 127.7 (2), 79.3, 66.4, 54.6, 53.5, 50.4, 32.1, 31.8, 28.0, 24.6, 24.1, 19.1; FT-IR (neat) ν (cm^{-1}) 3306, 1660, 1530; MS (ESI) *m*/*e* 442 $[M + Na]^+$, 420 $[M + H]^+$, 320 $[M - Boc + H]^+$.

(1*R*,2*R*)-*N*-(L-Ala-NHCbz),*N*′-(L-Leu-NHBoc)diaminocyclohexane (21). Compound **20** (92 mg, 0.219 mmol) was dissolved in a 4 N HCl solution in dioxane (1.1 mL), and the resulting solution was stirred at room temperature until complete consumption of the starting material. The solvent was removed under reduced pressure, and the residue was used in the next coupling step without any further purification. The monoamine chlorohydrate was then dissolved in 6 mL of DMF, the resulting solution was ice-chilled, and (L) *N*-Boc-leucine monohydrate (131 mg, 0.52 mmol), HOBt

(89 mg, 0.66 mmol), EDC (126 mg, 0.66 mmol), and DIEA (230 μL, 1.3 mmol) were added in sequence. The reaction mixture was stirred for 1 h at 0 °C and 36 h at room temperature. DMF was then removed under reduced pressure, and the residue was dissolved in 6 mL of dichloromethane. Water (6 mL) was then added to the solution, and the phases were separated. The organic layer was washed successively with a saturated solution of $NaHCO_3$, aq 1 N HCl, and brine, then dried (Na_2SO_4) and evaporated to dryness. The resulting crude material was then purified by flash column chromatography on silica gel (eluting with $CHCl_3$/MeOH 98/2), affording the desired product as a pale yellow oil (82 mg, 71%, over two steps): $[\alpha]_D$ −24 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz, −5 °C) δ (ppm) 7.40−7.34 (m, 5H), 6.55 (d, J = 7.0 Hz, 1H), 6.48 (d, J = 7.3 Hz, 1H), 5.80 (d, J = 8.3 Hz, 1H), 5.39 (d, J = 8.3 Hz, 1H), 5.18 (d, J = 12.2 Hz, 1H), 4.98 (d, J = 12.2 Hz, 1H), 4.14 (q, J_1 = 7.3 Hz, J_2 = 14.7 Hz, 1H), 4.02−3.95 (m, 1H), 3.69−3.59 (m, 2H), 1.97 (d, J = 11.5 Hz, 2H), 1.92−1.81 (m, 2H), 1.74 (d, J = 6.7 Hz, 2H), 1.65−1.55 (m, 2H), 1.48−1.39 (m, 2H), 1.37−1.31 (m, 12H), 0.90 (dd, J_1 = 3.5 Hz, J_2 = 5.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 173.2, 172.8, 156.0, 155.6, 135.9, 128.1, 127.8 (2), 79.6, 66.6, 53.4, 53.1, 52.6, 50.2, 40.6, 31.8, 31.7, 27.9, 24.3, 24.2, 22.7, 21.4, 17.6; FT-IR (neat) ν (cm^{-1}) 3298, 1712, 1646, 1532; MS (ESI) *m*/*e* 555.4 $[M + Na]^+$, 533.3 $[M + H]^+$, 433.3 $[M - Boc + H]^+$; HRMS (ESI) for $C_{28}H_{45}N_4O_6$ calcd 533.33336; found 533.33243.

(1*R*,2*R*)-*N*-(L-Ala-NHCbz),*N*′-(L-Leu-D-Leu-NHBoc)diaminocyclohexane (22). The title compound was obtained starting from **21** (79 mg, 0.15 mmol) following the procedures for the preparation of **21** from **20** (i.e., coupling with (D) *N*-Boc-leucine and purification by flash column chromatography on silica gel). Elution with $CHCl_3$/MeOH 98/2 gave **22** as a white solid (82 mg, 85%, over two steps): $[\alpha]_D$ −8.3 (*c* 0.6, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.45−7.28 (m, 5H), 7.02−6.85 (m, 2H), 6.75 (d, J = 6.35 Hz, 1H), 6.14 (d, J = 6.8 Hz, 1H), 5.60−5.49 (m, 1H), 5.20 (d, J = 12.2 Hz, 1H), 5.03 (d, J = 12.2 Hz, 1H), 4.44−4.32 (m, 1H), 4.20 (q, J_1 = 6.13 Hz, J_2 = 13.2 Hz, 1H), 4.15−4.06 (m, 1H), 3.70−3.54 (m, 2H), 2.06−1.89 (m, 2H), 1.77−1.66 (m, 3H), 1.64−1.51 (m, 3H), 1.42 (s, 9H), 1.38−1.22 (m, 7H), 0.99−0.78 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 172.8, 172.2, 162.3, 155.9, 155.5, 135.8, 128.2, 127.8 (2), 79.7, 66.7, 53.7, 53.3, 53.0, 51.2, 50.2, 40.2 (2), 31.5, 27.9, 24.3, 24.2 (2), 22.7, 22.6, 21.3 (2), 17.8; FT-IR (neat) ν (cm^{-1}) 3389, 2934, 1694, 1640, 1531, 1455, 1256; MS (ESI) *m*/*e* 667.2 $[M + Na]^+$, 646.2 $[M + H]^+$, 546.3 $[M - Boc + H]^+$.

(1*R*,2*R*)-*N*-(L-Ala-D-Ala-NHCbz),*N*′-(L-Leu-D-Leu-NHBoc)diaminocyclohexane (23). Compound **22** (79 mg, 0.122 mmol) was dissolved in ethanol (1.2 mL) and hydrogenated (40 psi) in the presence of 10% Pd/C (8 mg) for 16 h at room temperature. After removal of the catalyst by filtration through Celite, the solvent was evaporated under vacuum, affording the corresponding free monoamine. The resulting crude material was used without any further purification for the coupling to (D) *N*-Cbz-alanine, as described for the preparation of **20**. Purification by flash column chromatography on silica gel (AcOEt/hexanes gradient elution, from 50/50 to 75/25) afforded the title compound as a white solid (57 mg, 68%, over two steps): $[\alpha]_D$ −30 (*c* 0.6, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz, 0 °C) δ (ppm) 7.43−7.32 (m, 6H), 7.26 (d, J = 6.8 Hz, 1H), 6.85 (d, J = 6.4 Hz, 1H), 6.74 (d, J = 6.35 Hz, 1H), 6.00 (d, J = 6.35 Hz, 1H), 5.38 (d, J = 6.4 Hz, 1H), 5.20 (d, J = 12.2 Hz, 1H), 5.04 (d, J = 12.2 Hz, 1H), 4.55−4.43 (m, 2H), 4.4.0−4.32 (m, 1H), 4.31−4.24 (m, 1H), 3.65−3.54 (m, 2H), 2.07−1.91 (m, 2H), 1.85−1.58 (m, 6H), 1.56−1.50 (m, 2H), 1.45 (s, 9H), 1.38 (d, J = 7 Hz, 3H), 1.33 (d, J = 7 Hz, 3H), 1.30−1.22 (m, 4H), 0.99−0.84 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 174.0, 173.6, 172.9 (2), 156.7, 156.4, 136.6, 128.9, 128.5, 128.4, 80.3, 67.3, 54.4, 54.2, 53.6, 51.9, 51.0, 48.9, 41.9, 41.0, 32.3, 32.1, 28.8, 25.1 (2), 25.0 (2), 23.5, 22.1, 22.6, 19.2, 17.9; FT-IR (neat) ν (cm^{-1}) 3294, 2933, 1644, 1532; MS (ESI) *m*/*e* 738.2 $[M + Na]^+$, 717.2 $[M + H]^+$, 617.2 $[M - Boc + H]^+$; HRMS (ESI) for $C_{37}H_{61}N_6O_8$ calcd 717.45454; found 717.45364.

(1*R*,2*R*)-*N*-(L-Ala-D-Ala-L-Ala-NHCbz),*N*′-(L-Leu-D-Leu-NHBoc)diaminocyclohexane (24). The title compound was obtained starting from **23** (89 mg, 0.124 mmol) following the general procedures described for the preparation of **23** from **22** (i.e., coupling with (L) *N*-Cbz-alanine and purification by flash column chromatography on silica gel). Elution with $CHCl_3$/MeOH 95/5 gave **24** as a white solid (85 mg, 87%, over two steps): $[\alpha]_D$ −7 (*c* 0.6, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.52 (d, J = 6.6 Hz, 1H), 7.41−7.30 (m, 5H), 7.27−7.16 (m, 2H), 7.04 (d, J = 8 Hz, 1H), 6.69 (d, J = 6.6 Hz, 1H), 6.26 (d, J = 7.0 Hz, 1H), 5.47 (d, J = 6.6 Hz, 1H), 5.19 (d, J = 11.8 Hz, 1H), 5.11 (d, J = 11.8 Hz, 1H), 4.66−4.51 (m, 2H), 4.47−4.26 (m, 3H), 4.47−4.28 (m, 3H), 3.65−3.40 (m, 2H), 2.00−1.86 (m, 2H), 1.76−1.52 (m, 6H), 1.52−1.38 (m, 12H), 1.37−1.27 (m, 6H), 1.01−0.78 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 174.0, 173.6, 172.9 (2), 156.7, 156.4, 136.6, 128.9, 128.5, 128.4, 80.3, 67.3, 54.4, 54.2, 53.6, 51.9, 51.0, 48.9, 41.9, 41.0, 32.3, 32.1, 28.8, 25.1 (2), 25.0 (2), 23.5, 22.1, 22.6, 19.2, 17.9; FT-IR (neat) ν (cm^{-1}) 3292, 2933, 1654, 1529; MS (ESI) *m*/*e* 810.6 $[M + Na]^+$, 788.5 $[M + H]^+$, 688.5 $[M - Boc + H]^+$.

(1*R*,2*R*)-*N*-(L-Ala-D-Ala-L-Ala-NHCbz),*N*′-(L-Leu-D-Leu-L-Leu-NHBoc)diaminocyclohexane (25). The title compound was obtained starting from **24** (65 mg, 0.08 mmol) following the procedures described for the preparation of **21** from **20** (i.e., coupling with (L) *N*-Boc-leucine monohydrate and purification by flash column chromatography on silica gel). Elution with AcOEt/hexanes gradient elution, from 90/10 to 100% gave **25** as a white solid (42 mg, 57%): $[\alpha]_D$ −6.5 (*c* 0.5, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz, 0 °C) δ (ppm) 7.5 (d, J = 7.0 Hz, 1H), 7.65 (d, J = 7.0 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.41−7.36 (m, 6H), 7.09 (d, J = 7.7 Hz, 1H), 6.84 (d, J = 7.7 Hz, 1H), 6.23 (d, J = 7.4 Hz, 1H), 5.25−5.16 (m, 2H), 5.12 (d, J = 12.0 Hz, 1H), 4.68−4.57 (m, 2H), 4.45−4.37 (m, 2H), 4.36−4.30 (m, 1H), 4.26−4.17 (m, 1H), 3.69−3.58 (m, 1H), 3.57−3.49 (m, 1H), 1.96−1.87 (m, 2H), 1.66−1.58 (m, 6H), 1.57−1.52 (m, 3H), 1.47 (s, 9H), 1.41 (d, J = 6.7 Hz, 3H), 1.35 (d, J = 6.7 Hz, 3H), 1.31 (d, J = 6.7 Hz, 3H), 1.28−1.23 (m, 6H), 0.99−0.94 (m, 7H), 0.93−0.89 (m, 7H), 0.89−0.83 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 173.2, 172.7, 172.6, 172.5, 172.0, 171.7, 156.0, 155.6., 135.9, 128.1, 127.7 (2), 79.4, 66.6, 53.2 (2), 52.6, 52.4, 51.2, 51.0, 50.0, 48.2 (2), 40.8 (2), 40.6, 32.0, 31.6, 29.3 (2), 28.0, 24.4, 24.2, 22.8, 22.7, 22.5, 21.6, 21.4, 21.3, 17.9, 17.6, 17.4; FT-IR (neat) ν (cm^{-1}) 3285, 2927, 1642, 1538; MS (ESI) *m*/*e* 923.7 $[M + Na]^+$, 901.5 $[M + H]^+$, 801.5 $[M - Boc + H]^+$; HRMS (ESI) for $C_{46}H_{77}N_8O_{10}$ $(MH)^+$ calcd 901.57572; found 901.57245.

(1*R*,2*R*)-*N*-(L-Ala-D-Ala-L-Ala-NH_2),*N*′-(L-Leu-D-Leu-L-Leu-NH_2)diaminocyclohexane (26). Compound **25** (28 mg, 0.031 mmol) was dissolved in methanol (2 mL) and hydrogenated (40 psi) in the presence of 10% Pd/C (3 mg) for 16 h at room temperature. After removal of the catalyst by filtration through Celite, the solvent was evaporated under vacuum, affording the corresponding free amine as a white solid. This was then dissolved in 3 mL of a 4 N HCl solution in dioxane and 200 μL of water and stirred at room temperature for 2 h. Evaporation of the solvent under reduced pressure afforded the title compound as a bis-hydrochloride salt in quantitative yield: $[\alpha]_D$ −14 (*c* 0.3, MeOH); ^{1}H NMR (pyridine-d_5, 500 MHz) δ (ppm) 10.16 (d, J = 7.51 Hz, 1H), 9.95 (d, J = 7.3 Hz, 1H), 8.96−8.87 (m, 2H), 8.78 (d, J = 7.2 Hz, 1H), 8.47 (d, J = 7.7 Hz, 1H), 5.96 (br s, 2H), 5.25−5.18 (m, 1H), 5.17−5.10 (m, 2H), 5.10−5.04 (m, 2H), 4.99 (q, J_1 = 7.2 Hz, J_2 = 7.5 Hz, 1H), 4.16−4.00 (m, 2H), 2.28−2.22 (m, 2H), 2.22−2.12 (m, 5H), 2.09−1.98 (m, 5H), 1.96 (d, J = 6.9 Hz, 3H), 1.77 (d, J = 7.1 Hz, 3H), 1.74 (d, J = 7.0 Hz, 3H), 1.49−1.37 (m, 4H), 1.06 (d, J = 6.2 Hz, 3H), 1.03 (d, J = 6.2 Hz, 3H), 1.00 (d, J = 6.2 Hz, 3H), 0.99 (d, J = 6.2 Hz, 3H), 0.95 (d, J = 6.2 Hz, 3H), 0.93 (d, J = 6.2 Hz, 3H); ^{13}C NMR (pyridine-d_5, 100 MHz) δ (ppm) 173.3, 172.7, 172.5 (2), 170.7, 170.4, 53.0, 52.5(2), 52.4,

50.0, 49.7, 49.5, 40.7, 40.6, 40.5, 31.7 (2), 31.6, 24.6 (2), 24.4, 22.9, 22.8, 22.2, 22.1, 21.0, 21.3, 18.0, 17.4, 17.2; FT-IR (neat) ν (cm^{-1}) 3235, 2955, 2929, 1655, 1548; MS (ESI) *m*/*e* 689.4 $[M + Na]^+$, 667.4 $[M + H]^+$; HRMS (ESI) for $C_{33}H_{62}N_8O_6$ $(MH)^+$ calcd 667.48651; found 667.48705.

(1*R*,2*R*)-*N*-(L-Ala-D-Ala-L-Ala-NHBoc),*N*′-(L-Leu-D-Leu-L-Leu-NHCbz)diaminocyclohexane (27). Compound **25** (10 mg, 0.011 mmol) was dissolved in ethanol (0.5 mL). Boc_2O (22 mg), 10% Pd/C (10 mg), DMAP (a spatula tip), and 1,4-cyclohexadiene (20 μL) were added in sequence, and the resulting solution was stirred under argon at room temperature overnight. After removal of the catalyst by filtration through a 45 μm syringe filter, the solvent was evaporated under vacuum, affording the corresponding crude product. This was purified by flash column chromatography on silica gel (AcOEt/hexanes gradient elution, from 65/35 to 100%), affording the title compound as a white solid (8.6 mg, 86%): $[\alpha]_D$ −15 (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz, 45 °C) δ (ppm) 7.49 (d, J = 7.6 Hz, 1H), 7.40−7.32 (m, 1H), 7.20−7.07 (br m, 2H), 6.78 (d, J = 6.1 Hz, 1H), 6.51 (br s, 1H), 5.46 (br s, 1H), 5.26 (br s, 1H), 4.64 (dd, J_1 = 6.4 Hz, J_2 = 13.7 Hz, 1H), 4.58 (dd, J_1 = 10.7 Hz, J_2 = 7.3 Hz, 1H), 4.38 (dd, J_1 = 5.8 Hz, J_2 = 12.2 Hz, 1H), 4.33−4.29 (m, 1H), 4.26 (br s, 1H), 4.23−4.15 (m, 1H), 3.66−3.53 (m, 2H), 2.01 (d, J = 11.9 Hz, 1H), 1.96 (d, J = 10.7 Hz, 1H), 1.76−1.60 (m, 9H), 1.48−1.46 (m, 18H), 1.38 (d, J = 7.0 Hz, 3H), 1.38 (d, J = 7.0 Hz, 3H), 1.36 (d, J = 7.0 Hz, 3H), 1.31 (d, J = 7.0 Hz, 3H), 1.29−1.24 (m, 6H), 0.97−0.94 (m, 8H), 0.93−0.91 (m, 7H), 0.90−0.88 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, 45 °C) δ (ppm) 173.4, 173.0, 172.9, 172.7, 172.3, 172.0, 155.7, 155.6, 79.9 (2), 53.6, 53.3, 52.9, 51.7, 51.5, 50.7, 48.7 48.4, 41.3, 41.0, 40.8, 32.3, 32.1, 31.9, 29.6 (2), 29.3, 28.4, 28.3, 24.8 (2), 24.7 (2), 23.0 (2), 22.8, 22.6, 22.0, 21.9, 21.7,18.1 (2), 17.3; FT-IR (neat) ν (cm^{-1}) 3288, 2930, 1995, 1644, 1548, 1452, 1366, 1250, 1169, 1050; MS (ESI) *m*/*e* 889.3 $[M + Na]^+$, 867.4 $[M + H]^+$; HRMS (ESI) for $C_{43}H_{78}N_8O_{10}$ $(MH)^+$ calcd 867.59137; found 867.59252.

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Supporting Information Available: Complete crystallographic data for compound **13**, ^1H DMSO-d_6 titration experiments, copies of ^1H and ^{13}C spectra for all the new compounds, and 2D spectra for **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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