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Synthesis and Structural Characterization of Homochiral Homo-oligomers of Parent *cis*- and *trans*-Furanoid-β-Amino Acids

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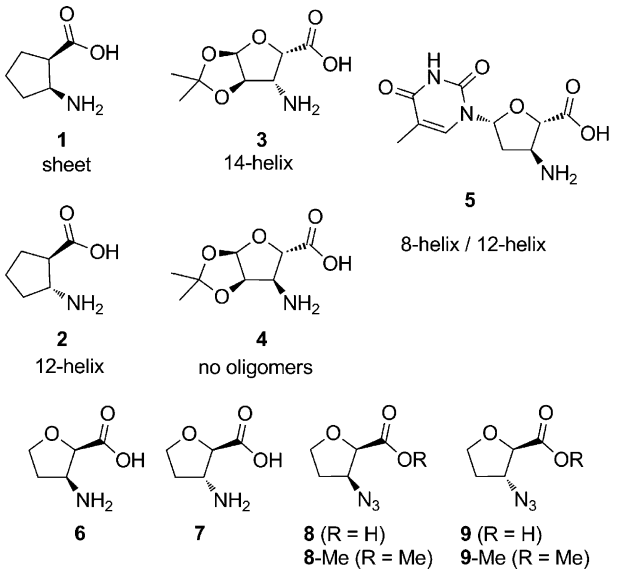
Abstract: The synthesis of homochiral homo-oligomers of *cis*- and *trans*-3-aminotetrahydrofuran-2-carboxylic acids (parent *cis*- and *trans*-furanoid-β-amino acids, referred to as "*cis*-/*trans*-FAA") has been carried out to understand their secondary structures and their dependence on the ring heteroatom. The oligomers of two diastereomers have been shown to have a distinct left-handed helicity. The *cis*-FAA homo-oligomers show a 14-helix structure, in contrast to the homo-oligomers of *cis*-ACPC, which adopt a sheet like structure. The *trans*-FAA homo-oligomers were found to adopt a 12-helix structure, the same trend found in *trans*-ACPC homo-oligomers. With the help of ab initio calculations, the structural features of *cis*-ACPC and *cis*-FAA hexamers were compared. We believe that the more compact packing of the *cis*-FAA hexapeptide should be due to a more favorable interaction between the ring and the backbone amide hydrogen.

Keywords: ab initio calculations · amino acids · density functional calculations · secondary structures · peptides

Introduction

In recent years, several approaches have been put forward to address the mimicking of the secondary structures of the peptides on the one hand and the in vitro stability of synthetic peptides for medicinal applications on the other.[1] The groups of Seebach and Gellman have introduced β-peptides as expeditious tools in this context.[2] The homo- and heterooligomeric β-peptides have been shown to adopt diverse secondary structures (helices, sheets, and turns) and form interesting molecular architectures by self assembly.[3] The homo-oligomers derived from the conformationally constrained (through ring annulations at the C_α–C_β bond) β-amino acids have been the subject of extensive structural investigations.[4–7] The nature of the secondary structure of their homo-oligomers seems to depend mainly upon 1) the relative stereochemistry of the amine and acid groups, 2) ring atoms, and 3) the ring size. For example, the homo-oligomers constructed by the *trans*-2-aminocyclopentane carboxylic acid (*trans*-ACPC) form a stable 12-helix,[5c] whereas the homo-oligomers derived from the *cis*-2-aminocyclopentane carboxylic acid (*cis*-ACPC) form a sheet-like structure.[5d] Interestingly, the homo-oligomers of the *cis*-furanoid-β-amino acid **3** adopt a stable 14-membered helix (Scheme 1),[7a] unlike the sheet structure formed by *cis*-ACPC homo-oligomers.[5d] This difference has been attributed to the rigid conformation of the furanose ring in **3** because of the 1,2-acetonide group. The synthesis of the corresponding *trans*-β-aminofuranose acid **4** has been reported,[7i] however no information about the corresponding homo-olig-



Scheme 1. Five-membered-ring constrained β-amino acids and the secondary structures reported for the corresponding homo-oligomers and the simple *cis*-/*trans*-furanoid-β-amino acids.

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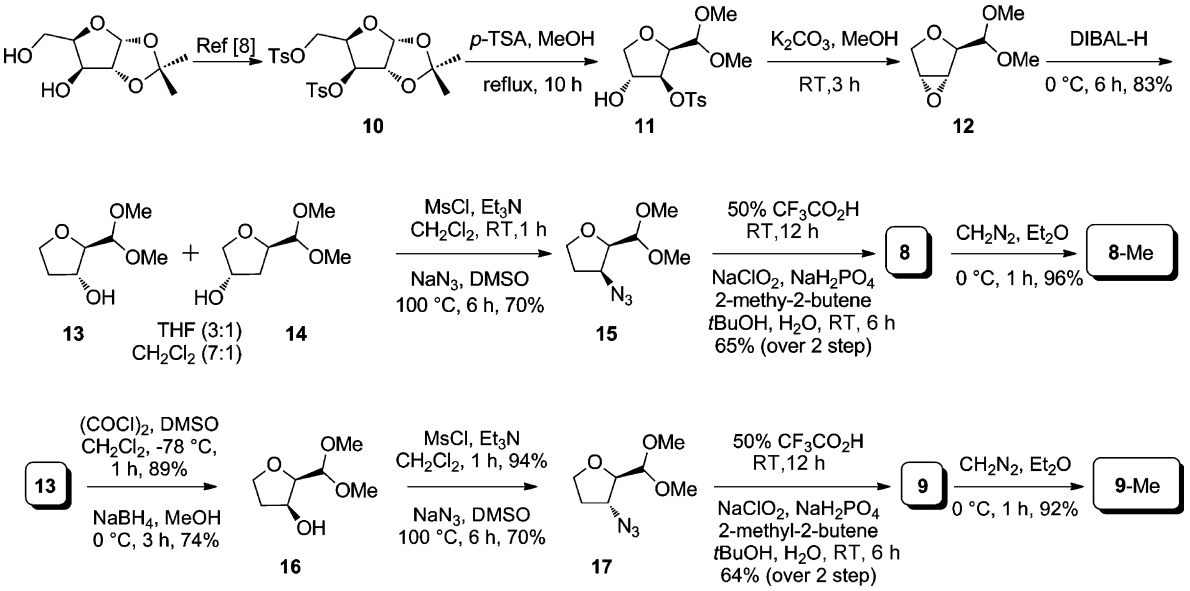


Scheme 2. Synthesis of *cis*-/*trans*-β-FAA monomers **8**/**8**-Me, and **9**/**9**-Me.

omers has been documented. Very recently, Cosstick and co-workers have documented the synthesis of the oligomers of nucleic acid derived furanoid-β-amino acid **5** and showed that they adopt an unusual 8-membered helix,[7d] which has partly been attributed to the β^4-carbon substituent. Interestingly, for the same tetramer, Chandrasekhar's group had reported a 12-helix solution structure.[7e]

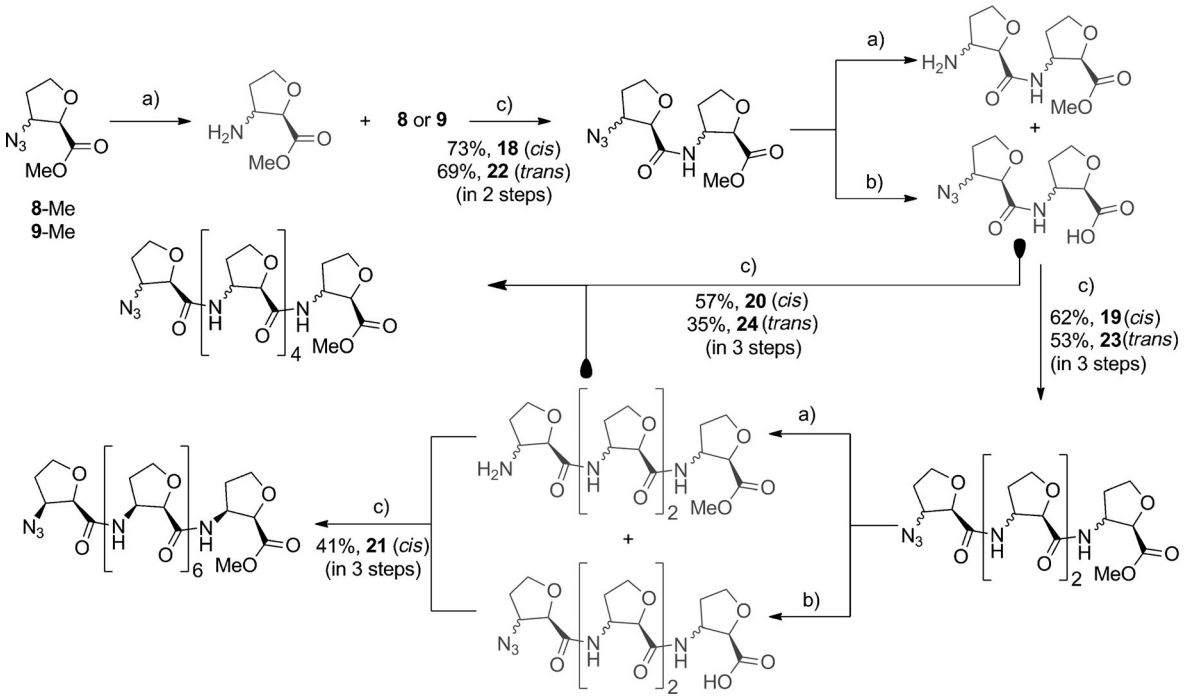
From the structures of the furanoid-β-amino acids reported, it is clear that each β-FAA has its own unique structural elements. What is presently blocking a systematic analysis of the β-FAAs and the prediction of their secondary structures is the absence of a basis of comparison, such as the parent furanoid-β-amino acids **6** and **7** proposed herein. The structural analysis of the homo-oligomers of **6** and **7** has the potential to provide considerable insight into the influence of the ring heteroatom along with setting a basis for comparison between the homo-oligomers of FAAs. In this report, we document the synthesis of the homo-oligomers of **6** and **7** and reveal their secondary structures in solution. With the help of ab initio calculations, we reason that the homo-oligomers of *cis*-FAAs favor a 14-helix structure over a sheet-like structure (reported for the *cis*-ACP oligomers) due to a more favorable contact between the backbone and the ring.

Results and Discussion

The synthesis of the monomeric building blocks began with acid-mediated ring transposition from the known ditosylate **10** to procure the dimethylacetal **11** in quantitative yields. The treatment of dimethylacetal with potassium carbonate in methanol provided the oxirane **12**.[8] The regiochemistry of the opening of epoxide **12** with diisobutylaluminum hydride (DIBAL-H) was found to be solvent dependent. As shown in Scheme 2, in CH_2Cl_2 the regioselectivity towards the opening at C(3) was high and **13**/**14** were obtained in a 7:1 ratio. The free hydroxyl group of **13** was converted to the corresponding mesylate and subjected to the nucleophilic displacement with azide to obtain the azidoacetal **15** in 70% yield. The acetal group in **15** was deprotected by employing 50% TFA at 0°C to room temperature and the resultant crude aldehyde was oxidized to acid **8** by treating with sodium chlorite and sodium dihydrogen phosphate in *t*BuOH and water in the presence of 2-methyl-2-butene as a scavenger. Treatment of acid **8** with diazomethane in CH_2Cl_2/ether at 0°C gave the methyl ester **8**-Me. To prepare the *trans*-FAA, the free C(3)-OH of **13** was oxidized under Swern conditions and the resulting ketone was reduced with sodium borohydride in MeOH to procure **16**. Compound **16** was transformed to the corresponding acid **9** and ester **9**-Me by following a similar reaction sequence as used in the synthesis of **8**/**8**-Me from **15**.

The synthesis of corresponding homo-oligomers was achieved in two steps (Scheme 3). In the first step, the reduction of the azide group was carried out by employing Raney nickel in EtOH under a hydrogen atmosphere at room temperature to obtain the corresponding amine, which was coupled immediately with the acid by using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and hydroxybenzotriazole (HOBt), diisopropylethylamine (DIPEA) in CH_2Cl_2 at room temperature to afford the homo-oligomers in 35–73% yield. In case of the *trans*-β-FAA oligomers, we could only prepare the hexamer. The synthesis of the octamer was hampered by the poor solubility of the coupling partners.

For a preliminary understanding of the secondary structures across the series **18**–**21**, their CD data were recorded in methanol and trifluoroethanol at 200 μmol concentra-



Scheme 3. Reagents and conditions: a) Raney Ni, H_2, RT, EtOH, 2 h; b) NaOH (aq), dioxane, RT, 1 h; c) EDCI, HOBt, DIEA, CH_2Cl_2, 24–40 h, RT.

tions. As shown in Figure 1 i) a), the CD spectra of *cis*-dimer **18** did not show any significant ellipticity. The CD spectrum of *cis*-tetramer **19** displays a shallow minimum at about 219 nm and a maximum at about 193 nm. The hexamer **20** and the octamer **21** have a CD pattern similar to that of **19**, except that both the minimum and maximum are slightly redshifted (220 and 195 nm) and more intense for **21**. The pattern observed for *cis*-FAA oligomers indicates a left-handed 14-helix (slightly redshifted) and is in agreement with the data reported for the *cis*-FAA **3** oligomers. The CD spectrum of **20** in trifluoroethanol (Figure 1 i) b)) shows the two minima at about 221 and 214 nm, a maximum at about 193 nm, and zero crossing at about 211 nm. In the CD spectrum of **21** in trifluoroethanol, the minimum at about 214 nm, maximum at about 193 nm, and zero crossing at about 211 nm revealed that **21** adopted a robust 14-helix structure.

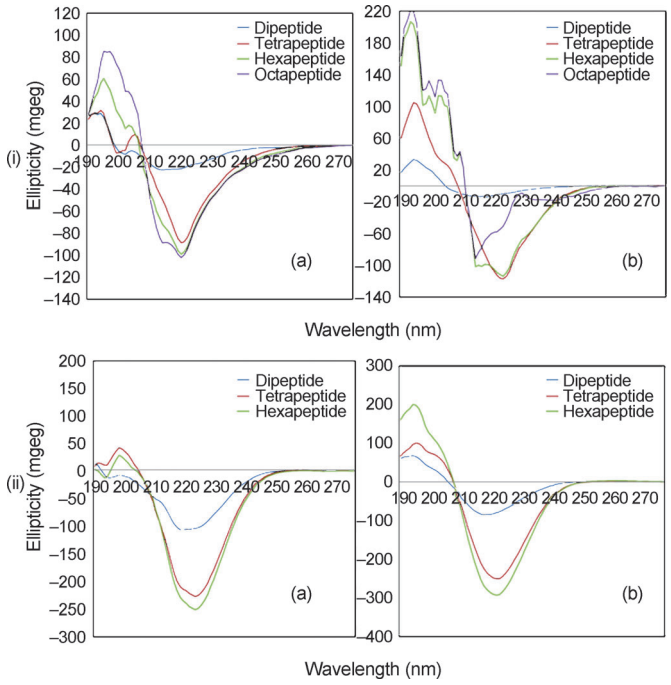


Figure 1. The CD spectral graph of i) *cis*-β-FAA oligomers a) in MeOH b) in TFE and ii) *trans*-β-FAA oligomer a) in MeOH b) in TFE.

The CD spectra of *trans*-dimer **22**, *trans*-tetramer **23** and *trans*-hexamer **24** in methanol showed maxima at 198 nm, zero crossing at 207 nm, and minima at 222 nm (Figure 1 ii) a)). This CD pattern suggests a left-handed 12-helix and is similar to the *trans*-ACPC **2** homo-oligomers and also cyclic-pyrrolidine-based *trans*-β-amino acid homo-oligomers. The CD spectra of *trans*-FAA (**22**–**24**) showed a similar pattern in trifluroethanol as in methanol.

The 2D NMR of the homo-oligomers was recorded in $CDCl_3$ (except for **24** for which [D_6]DMSO was used). For all the oligomers, the amide protons are well-resolved and displayed a downfield shift ($\delta = 6.8$–8.5 ppm) that suggested their involvement in hydrogen bonding. The N–H chemical shifts are concentration independent, which indicates that this downfield shift is due to internal structure rather than molecular aggregation. Further, the solvent titration studies (by adding the [D_6]DMSO up to 33 % v/v, see Figures SI1–SI9 of the Supporting Information) and variable-temperature experiments (from 0–50 °C by 5 °C intervals (see Figures SI1–SI9 of the Supporting Information) support the in-

tramolecular hydrogen bonding present in these oligomers. In the ^{1}H NMR spectrum of the tetramer **19**, the observed $^3J(\mathrm{NH}-\mathrm{C_\beta H}) = 7.1$–$9.4$ Hz for all the amide protons indicates an antiperiplanar arrangement of NH and $C_\beta H$ protons and $\varphi = 138 \pm 2°$ (C(O)-*N*-C_β-C_α, see Table SI1, Supporting Information for complete details). NOESY data of **19** (Figure SI10 in the Supporting Information) reveal some inter-residue medium to long range NOE signals between $C_\alpha H_{(i)} \rightarrow NH_{(i+1)}$, $NH_{(i+2)} \rightarrow C_\alpha H_{(i+3)}$ and $NH_{(i+2)} \rightarrow MeO_2C$). In the case of the hexapeptide **20**, several inter-residue NOEs $NH_{(i+1)} \rightarrow C_\beta H_{(i+3)}$, $NH_{(i+2)} \rightarrow C_\beta H_{(i+4)}$, $NH_{(i+3)} \rightarrow C_\beta H_{(i+5)}$ were observed that confirmed a 14-helix (Figure 2).

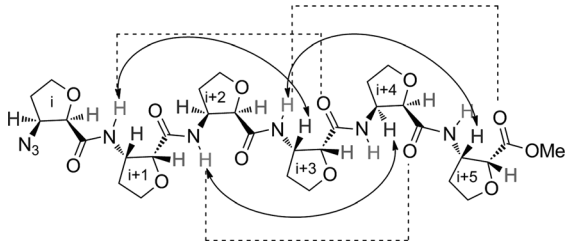


Figure 2. Observed NOEs for *cis*-FAA oligomer **20**.

Due to the overlapping $C_\beta H$ protons, the NOEs between $C_\beta H$ and $C_\alpha H$ could not be assigned. The observed long range NOEs between $NH_{(i+1)} \rightarrow C_\beta H_{(i+3)}$, $NH_{(i+2)} \rightarrow C_\beta H_{(i+4)}$, $NH_{(i+2)} \rightarrow C_\alpha H_{(i+4)}$, $NH_{(i+3)} \rightarrow C_\beta H_{(i+5)}$, $NH_{(i+3)} \rightarrow C_\alpha H_{(i+5)}$, and $NH_{(i+4)} \rightarrow C_\beta H_{(i+6)}$, supported the 14-helix structure proposed from the CD data of octamer **21** (Figure SI11 in the Supporting Information).

The presence of a 12-helix structure in a solution of *trans*-β-FAA oligomer **23** was confirmed with the help of the observed inter-residue NOEs (Figure SI12 in the Supporting Information) Due to the overlapping of two of the five amide protons in the ^{1}H NMR spectra of **24**, interpretation of some of the observed long-range NOEs is complicated. The important inter-residue NOEs observed in the NOESY of the *trans*-hexamer **24** which supported a left-handed 12-helix are given in Figure SI.13 (in the Supporting Information). The dihedral angles $(\varphi) = 135°$ and $(\theta) = 52 \pm 2°$ calculated from the observed $^3J(\mathrm{NH\text{-}C_\beta H}) > 7.6$ Hz and $^3J(\mathrm{C_\alpha H\text{-}C_\beta H}) < 5.0$ Hz are in support of the 12-helix structure. We now turn to the theoretical results

Computational results: The model structures for the ACPC hexamers, both *cis* and *trans* isomers, were built on the basis of previous structural studies. The same caps were used as in the experiment, namely an azide group and a methyl ester. A set of geometries was obtained by varying the dihedral angles of the backbone. To generate suitable starting structures, preliminary optimizations with varying dihedral angles were carried out with the RM1 semiempirical method, as implemented in the MOPAC quantum chemistry program package.[9] The structures thus obtained were then optimized at the B3LYP/6-31G* level of theory.[10] The minima of *cis*-ACPC hexamers were used as starting estimates for the *cis*-FAA structures by introducing an O atom in each building block in place of a CH_2 fragment. This was followed by optimization at the same level of theory. We adopted this procedure to maximize the conformational similarity between the two different hexapeptides, which allows for a comparison on a relatively equal footing, while avoiding an extensive minima search. This would be prohibitive due to the system size, even if semiempirical methods were to be used. Alternatively, one could opt for the use of molecular mechanics (MM). Although recent efforts have been made in obtaining reliable MM parameters for the description of β-peptides, such as in the case of ACPC,[11] there is no consistent set available for both molecules considered in this study. In a final set of calculations, density-fitted local second order Møller–Plesset theory (DF-LMP2)[12a] single points were carried out on each structure, including solvent effects through the COSMO model.[13] Two dielectric constant values were used for each conformer, $\varepsilon = 26.14$ (trifluoroethanol) and $\varepsilon = 80.10$ (water). The basis set used was the Dunning cc-pVTZ basis,[12b] with diffuse functions added to the non-hydrogen atoms.[14] This basis will be hereafter referred to as aug′-cc-pVTZ. In the local calculations, Pipek–Mezey orbitals[15] were used in combination with the NPA domain selection criteria,[16] with TNPA = 0.03. The implementation details of DF-LMP2 in combination with the COSMO model will be published elsewhere.[17] All calculations were carried out with a development version of the software package Molpro 2010.2.[18]

Both the β-sheet and the 14-helix structures for the *cis*-ACPC and *cis*-β-FAA hexamers were optimized in the gas phase, and by using a continuum description of trifluoroethanol and water. In Figure 3 we present a superposition of the optimized *cis*-FAA geometries. The allylic hydrogen atoms were removed for a better visualization.

We will start by discussing the optimized 14-helix structures. A comparison of the *cis*-ACPC and the *cis*-FAA structures shows that the differences are relatively subtle. A first observation would be that the *cis*-ACPC hexapeptide shows a hydrogen bond between the methyl ester cap carbonyl group and the i-3 residue, which is absent in the *cis*-FAA case. This is due to the fact that the ester group in the *cis*-ACPC oligomer presents an eclipsed conformation, instead of a gauche conformation as is observed in the *cis*-FAA oligomer. It is relatively difficult to judge whether this is an effect directly linked to the substitution in the ring or an artifact from our optimization approach. One would need a more complete study of the conformational landscape, using more than a single structure for each conformer. We would also like to note that such changes in the terminal ends can easily happen due to the conformational flexibility in these regions, but should have a rather small effect in the relative conformational energies. Comparing the remaining hydrogen bond distances and angles, we see only small changes (hydrogen bonds vary by about 0.05 Å, well within the mean square root deviation). In conclusion, there are no structural features that would support the idea of enhanced hydrogen

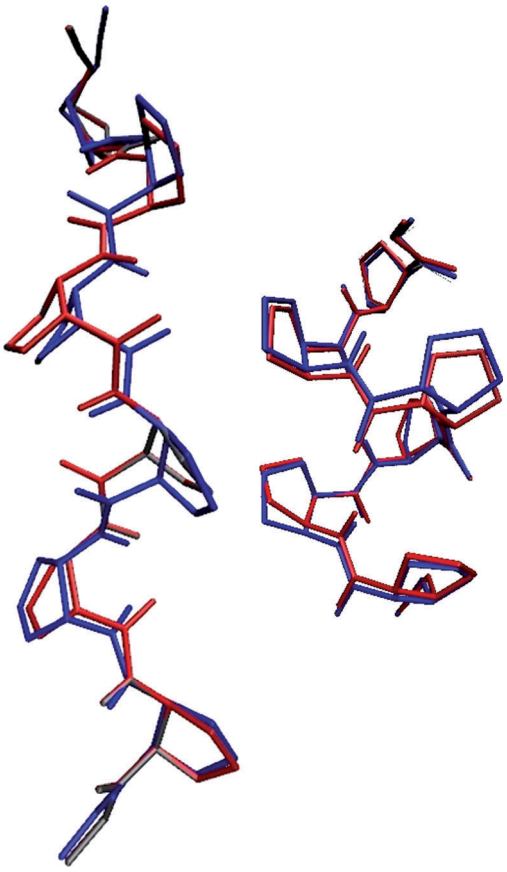


Figure 3. Superimposed optimized structures for the *cis*-FAA β-sheet (left) and *cis*-FAA 14-helix (right) under different solvent descriptions. The structures are color coded distinguishing gas phase (blue) from trifluoroethanol (red), and water (gray).

bonding in the *cis*-FAA case. However, there is a visible difference in the tightness of the loop. Comparing the distances between the backbone amide hydrogen and the ring oxygen (*cis*-FAA) or carbon (*cis*-ACPC) the distances in the former case are found to be much shorter. In the 14-helix *cis*-FAA the hydrogen is 2.1–2.2 Å away from the oxygen. In the *cis*-ACPC the distance between the ring carbon and the hydrogen is 2.5–2.6 Å. The reasons behind this difference are straightforward. By replacing a CH_2 group with an oxygen atom, one reduces steric effects and also introduces a favorable electrostatic interaction between the latter and the amide hydrogen. We have also calculated the solvent-accessible surface area (SASA) for the 14-helix structures. This shows that the *cis*-FAA 14-helix exhibits an accessible area 6% smaller than *cis*-ACPC. This would mean that the former structure is more compact. This is in line with our observation above. The loop in the *cis*-FAA can be made much tighter as a repulsive interaction between the backbone and the ring has been removed. A closer look into the backbone average dihedral angles for the 14-helix geometries reveals that the *cis*-ACPC hexapeptide can be characterized by the following angles: $\varphi = -138.66°$, $\theta = 46.10°$, and $\psi = -124.06°$. The *cis*-FAA hexapeptide average angles are, in turn, $\varphi = -145.86°$, $\theta = 38.70°$, and $\psi = -114.06°$. The ψ dihedral angles are usually taken as the determining parameters for the backbone structure.[19] We observe that the *cis*-FAA 14-helix presents a smaller ψ. This is in agreement with the SASA ratio, which supports the idea of tighter packing in the *cis*-FAA hexapeptide.

The β-sheet structures are kept almost unchanged from one case to the other. Aside from a distortion in the rings, the angles are perfectly comparable. This is mostly expected, since an unstrained conformation should only weakly depend on substitutions in the ring.

The relative energies for the *cis*-ACPC and *cis*-FAA hexapeptides are displayed in Table 1. The values are given as the energy difference E(14-helix)$-E$(β-sheet), so that positive values indicate a larger stabilizing force for the β-sheet, whereas negative values indicate that the 14-helix conformation is more stable. In this case, we also look at the results obtained from including an approximate solvent description. In the case of trifluoroethanol and water, the COSMO model was used both in the optimization step as well as in the DF-LMP2 calculation. In agreement with previous experimental[5d] and theoretical studies,[3b] the *cis*-ACPC hexapeptide has a preference for the β-sheet conformation. The DF-LMP2 energy differences between the latter and the 14-helix range between 3.8 kcal mol^{-1} in water and 6.0 kcal mol^{-1} in the gas phase. However, in the case of *cis*-FAA, the ordering is inverted. In the gas phase, as well as in the two solvents considered, the 14-helix conformer is more stable. The relative energies are almost unchanged in going from trifluoroethanol to water. Although we do not take into account the explicit structure of the solvent around the oligopeptide, this is already an indication that the energetic ordering should only be marginally affected by the solvent in use. The largest difference is in the *cis*-FAA case, on going from the gas phase to trifluoroethanol (9 kcal mol^{-1}).

Table 1. Relative energy differences (in kcal mol^{-1}) between the β-sheet and 14-helix conformers computed at the DF-LMP2/aug′-cc-pVTZ level of theory (E(14-helix)$-E$(β-sheet)). The structures were optimized with B3LYP/6-31G*. The COSMO model was used to approximate solvent effects for both single point and optimization runs. The DFT energies are given in parenthesis, for comparison.

	cis-ACPC	*cis*-FAA
gas phase	6.0 (17.1)	−16.7 (−4.3)
trifluoroethanol	3.3 (12.8)	−7.7 (1.4)
water	3.4 (12.3)	−8.6 (2.3)

Comparing now the *cis*-FAA to the *cis*-ACPC, the differences in the relative energies are quite pronounced. In total, there is a shift of 10–23 kcal mol^{-1}. Although the hydrogen-bonding network is one of the main structural features in the 14-helix, changes in these bonds could not explain such a difference. Each bond should contribute only 2–5 kcal mol^{-1}, and since we do not observe significant changes in distances/angles, it would be difficult to sum their contributions to such a large value. A destabilization of the β-sheet

is also unlikely. There are no unfavorable contacts linked to the ring oxygen. We argue that this effect can only be explained by a reduced strain in the 14-helix, as discussed above in connection to the SASA values.

The B3LYP/6-31G* relative energies have also been included in Table 1. At this lower level of theory, the 14-helix is strongly disfavored, with the *cis*-FAA hexapeptide even becoming less stable than the β-sheet conformation in both solvents. The reason behind the discrepancy between DF-LMP2 and B3LYP is easy to understand. The DFT method is unable to correctly describe dispersion interactions, which are of utmost importance to the stability of the helix. Although the method is relatively suitable for obtaining qualitative structures of β-oligopeptides, one should be cautious about comparing the energetics of such systems at the DFT level. This is particularly true when comparing packed to extended conformers.

Conclusion

To summarize, the homo-oligomers of two diastereomeric FAAs have shown distinct left-handed helicity in which the *cis*-FAA oligomers were showing 14-helix structures, which is in contrast to the *cis*-ACPC, which adopt a sheet-like structure. We observe that *trans*-FAA adopted a 12-helix structure, like the *trans*-ACPC oligomers. The similar secondary structures observed for the oligomers of *cis*-FAAs **6** and **3** reveal that a rigid conformation in the monomer may not be sufficient premise for the noticed 14-helical conformation, instead of sheet-like structure, of *cis*-ACPC homo-oligomers. By comparing the structural features of *cis*-ACPC and *cis*-FAA hexamers, we observe no marked change in the hydrogen bond strength, but the overall conformation of the *cis*-FAA is seen to be more compact, favoring close dispersion contacts. This is evidenced in comparing DFT with DF-LMP2 results, in which the former lack the description of van der Waals forces. The more compact packing of the *cis*-FAA hexapeptide should be due to a more favorable interaction between the ring and the backbone fold, primarily in the amide hydrogen pointing towards the ring. The replacement of CH_2 with oxygen removes steric repulsion and introduces an electrostatic interaction which allows for a tighter fold.

Experimental Section

3,4-Epoxy-5-(*R-trans*)-dimethoxymethyltetrahydrofuran (12): A solution of ditosyl compound **10** (200 g, 400 mmol) was dissolved in MeOH (1.6 L) and treated with a catalytic amount of *p*-toluene sulfonic acid (6.4 g, 10.0 mmol) and heated to reflux for 24 h. After completion, the reaction mixture was cooled to 0 °C and added the potassium carbonate (138.4 g, 1.0 mol) and stirred at RT for 2 h. The reaction mixture was filtered (Celite), neutralized (1 N HCl) and concentrated under reduced pressure. The crude product was extracted with EtOAc and the ethyl acetate layer was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by silica gel column chromatography to give **12** (50 g, 78 % in two steps). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 4.28$ (d, $J = 4.5$ Hz, 1H), 4.08 (d, $J = 4.5$ Hz, 1H), 3.97 (d, $J = 10.3$ Hz, 1H), 3.83 (d, $J = 10.3$ Hz, 1H), 3.82 (d, $J = 3.0$, 0.8 Hz, 1H), 3.78 (dd, $J = 3.0$, 0.8 Hz, 1H), 3.46 (s, 3H), 3.44 ppm (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): $\delta = 54.8$ (q), 55.8 (q), 56.0 (d), 56.3 (d), 67.5 (t), 77.4 (d), 104.6 ppm (d); MS (ESI): *m*/*z* (%): 183.1 (100) [$M^+ + Na$]; elemental analysis calcd (%) for $C_7H_{12}O_4$: C 51.49, H 7.55; found: C 51.73, H 7.53.

Reduction of 3,4-epoxy-5-(*R-trans*)-dimethoxymethyltetrahydrofuran (12): At 0 °C, diisobutylaluminium hydride (250 mL, 2.5 M solution in toluene, 625 mmol) was added to a solution of **12** (50 g, 212.5 mmol) in dry CH_2Cl_2 (800 mL) and the reaction mixture was stirred until compound **12** was consumed. The reaction mixture was cooled to −10 °C and quenched by adding MeOH (30 mL) and saturated sodium potassium tartrate. The resulting suspension was filtered, dried (Na_2SO_4) and concentrated. The crude product was subjected to chromatographic purification (25 % ethyl acetate in petroleum ether) to yield **13** (37.5 g, 74 %) and the regioisomer **14** (4.6 g, 9 %) as colorless oils.

(2*R*,3*R*)-2-(Dimethoxymethyl)tetrahydrofuran-3-ol (13): $[\alpha]_D^{25} = -28.8$ ($c = 2.0$ in MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 4.27$ (dt, $J = 5.5$, 2.5 Hz, 1H), 4.15 (d, $J = 5.7$ Hz, 1H), 3.87 (dd, $J = 8.2$, 5.7 Hz, 2H), 3.67 (dd, $J = 5.7$, 3.5 Hz, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 2.03 (ddd, $J = 12.8$, 8.1, 6.9 Hz, 1H), 1.81 ppm (dddd, $J = 12.8$, 9.4, 5.7, 3.7 Hz, 1H). MS (ESI): *m*/*z* (%): 131 (100) [$M^+ - OCH_3$]; elemental analysis calcd (%) for $C_7H_{14}O_4$: C 51.84, H 8.70; found: C 51.69, H 8.61.

(3*S*,5*R*)-5-(Dimethoxymethyl)tetrahydrofuran-3-ol (14): $[\alpha]_D^{25} = -1.9$ ($c = 1.5$, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 4.42$ (ddd, $J = 5.8$, 3.8, 1.8 Hz, 1H), 4.17 (d, $J = 6.7$ Hz, 1H), 3.86 (dd, $J = 6.7$, 3.8 Hz, 2H), 3.70 (dd, $J = 9.6$, 3.9 Hz, 1H), 3.36 (s, 6H), 1.94–1.86 ppm (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): $\delta = 36.3$ (t), 53.9 (q), 55.0 (q), 71.6 (d), 75.5 (t), 77.1 (d), 105.6 ppm (d); MS (ESI): *m*/*z* (%): 185.07 (100) [$M^+ + Na$]; elemental analysis calcd (%) for $C_7H_{14}O_4$: C 51.84, H 8.70; found: C 51.73, H 8.54.

(2*R*,3*S*)-3-Azido-2-(dimethoxymethyl)tetrahydrofuran (15): A solution of **13** (5.0 g, 38.83 mmol) and Et_3N (9.8 mL, 69.37 mol) in CH_2Cl_2 (50 mL) was treated with mesyl chloride (3.0 mL, 37.61 mol) at 0 °C and stirred for 1 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and quenched with cold water and then washed with water and brine. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the intermediate mesylate (6.96 g, 94 %) as a liquid. A portion of the mesylate was purified by column chromatography for the analytical data. Otherwise the crude mesylate was directly subjected to azidation reaction. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 5.18$–5.10 (m, 1H), 4.23 (dd, $J = 4.2$, 1.0 Hz, 1H), 4.05–3.96 (m, 2H), 3.86 (ddd, $J = 8.3$, 7.8, 1.3 Hz, 1H), 3.42 (s, 3H), 3.40 (s, 3H), 2.99 (s, 3H), 2.22–2.12 ppm (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): $\delta = 33.8$ (t), 37.6 (q) 54.6 (q), 56.3 (q), 67.2 (t), 82.0 (d), 83.6 (d), 103.8 ppm (d); MS (ESI): *m*/*z* (%): 263.1 (100) [$M^+ + Na$].

The mesylate (6.9 g, 28.27 mmol) was dissolved in dry DMSO (180 mL) and sodium azide (5.6 g, 86.15 mmol) was added. The contents were stirred at 100 °C for 12 h. The reaction mixture was diluted with EtOAc (450 mL), washed with water (3 × 80 mL). The organic extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10→20 % EtOAc in petroleum ether) to obtain **15** (4.03 g, 75 %) as a colorless oil. $[\alpha]_D^{25} = +46.8$ ($c = 1$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 4.47$ (d, $J = 7.5$ Hz, 1H), 4.10 (ddd, $J = 5.6$, 3.9, 1.7 Hz, 1H), 4.04–3.92 (m, 1H), 3.88 (dd, $J = 8.6$, 4.2 Hz, 1H), 3.76 (dd, $J = 7.5$, 3.9 Hz, 1H), 3.44 (s, 3H), 3.43 (s, 3H), 2.29–2.00 ppm (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): $\delta = 32.4$ (t), 53.5 (q), 55.0 (q), 62.7 (d), 66.7 (t), 80.7 (d), 103.2 ppm (d); IR ($CHCl_3$): $\tilde{\nu} = 3352$, 2939, 2888, 2833, 2514, 2105, 1634, 1445, 1401, 1333, 1274, 1192, 1144, 1083, 1018, 977, 959, 931, 873, 757, 666 cm^{-1}; MS (ESI): *m*/*z* (%): 210.1 (100) [$M^+ + Na$], 226.0 (65) [$M^+ + K$], 188.2 (45) [$M^+ + 1$]; elemental analysis calcd (%) for $C_7H_{13}N_3O_3$: C 44.91, H 7.00, N 22.45; found: C 44.83, H 6.89, N 22.39.

(2*R*,3*S*)-3-Azidotetrahydrofuran-2-carboxylic acid (8): A suspension of azido-acetal **15** (15 g, 80.13 mmol) in trifluoroacetic acid (50 %, 150 mL) was stirred at RT for 12 h. The reaction mixture was cooled to 0 °C CH_2Cl_2 (200 mL) and then neutralized with sodium bicarbonate and ex-

tracted with CH_2Cl_2 (3×200 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting crude aldehyde was used directly for the next step without any further purification.

NaH_2PO_4·$2H_2O$ (2.24 g, 16.03 mmol dissolved in 15 mL water, pH 7) was added to a cooled solution of the above aldehyde and 2-methyl-2-butene (84.3 g, 1.20 mol) in *t*BuOH and H_2O (2:1, 75 mL). Sodium chlorite (80%, 27.18 g, 240.4 mmol) was added slowly and the resulting mixture was stirred at RT for 10 h. After the reaction was completed, solid $NaHCO_3$ was added. The reaction mixture was extracted with CH_2Cl_2 (2×100 mL) and the CH_2Cl_2 layer was discarded. The aqueous layer was neutralized with concd HCl and extracted with CH_2Cl_2 (3×200 mL). The combined organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (silica gel 20→90% EtOAc in petroleum ether) to procure acid **8** (12.6 g, 73% over 2 steps) as a colorless oil. $[\alpha]_D^{25}=+70.5$ ($c=1.5$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=8.69$ (s br, 1H), 4.54 (d, $J=5.1$ Hz, 1H), 4.38 (ddd, $J=7.7$, 5.2, 2.6 Hz, 1H), 4.42–3.99 (m, 2H), 2.33–2.11 ppm (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3+CCl_4$): $\delta=31.1$ (t), 62.8 (d), 67.6 (t), 78.0 (d), 172.4 ppm (s); IR ($CHCl_3$): $\tilde{\nu}=2960$, 2560, 2115, 1746, 1483, 1330, 1272, 1113, 1085, 1026, 967, 937, 871, 789, 759, 698, 665 cm^{-1}; MS (ESI): *m*/*z* (%): 180.1 (100) [M^++Na], 196.3 (53) [M^++K], 158.1 (32) [M^++1]; elemental analysis calcd (%) for $C_5H_7N_3O_3$: C 38.22, H 4.49, N 26.74; found: C 38.31, H 4.41, N 26.58.

(2*R*,3*S*)-Methyl 3-azidotetrahydrofuran-2-carboxylate (8-Me): At 0°C, a solution of acid **8** (6.0 g, 38.2 mmol) in CH_2Cl_2 (50 mL) and was treated with a solution of diazomethane in ether (300 mL) until the color of the diazomethane persisted. The solution was kept standing for 2 h and treated with few drops of acetic acid to quench the residual diazomethane. The solvent was removed and the residue was purified by silica gel column chromatography (silica gel 15→25% EtOAc in petroleum ether) to afford **8**-Me (6.27 g, 96%) as colorless syrup. $[\alpha]_D^{25}=+10.4$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=4.49$ (d, $J=5.3$ Hz, 1H), 4.38 (ddd, $J=8.2$, 5.3, 2.8 Hz, 1H), 4.13 (dt, $J=9.6$, 7.2 Hz, 1H), 3.97 (ddd, $J=12.7$, 8.2, 4.5 Hz, 1H), 3.79 (s, 3H), 2.34–2.10 ppm (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3+CCl_4$): $\delta=31.5$ (t), 51.5 (q), 62.6 (d), 67.1 (t), 79.8 (d), 168.8 (s); IR ($CHCl_3$): $\tilde{\nu}=3359$, 2956, 2894, 2560, 2112, 1760, 1439, 1326, 1268, 1113, 1033, 1013, 924, 869, 795, 745 cm^{-1}; MS (ESI): *m*/*z* (%): 194.1 (100) [M^++Na], 233.0 (35) [M^++K]; elemental analysis calcd (%) for $C_6H_9N_3O_3$: C 42.10, H 5.30, N 24.55; found: C 42.19, H 5.37, N 24.49.

(2*R*,3*R*)-3-Azidotetrahydrofuran-2-carboxylic acid (17): In a flame-dried, two necked, round-bottom flask (1 L) was dissolved oxalyl chloride (32 mL, 372 mmol) under N_2 atmosphere in dry CH_2Cl_2 (600 mL). After the solution was cooled to −78°C, dry DMSO (35.0 mL, 492 mmol) was added dropwise with stirring for 15 min. To this, a solution of alcohol **13** (20 g, 121.2 mmol) in dry CH_2Cl_2 (150 mL) was added dropwise and stirred for 30 min at the same temperature and treated with Et_3N (103.2 mL, 185 mmol) and stirred for an additional 30 min at −78°C. The reaction mixture was partitioned between CH_2Cl_2 and water, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. Combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude product by column chromatography (15% ethyl acetate in petroleum ether) afforded ketone as a colorless oil which was used for next step without any purification.

At −15°C, a solution of the crude ketone in methanol (500 mL) was treated with $NaBH_4$ (13.04 g, 370.0 mmol) in portions with a 10 min interval. After completing the additions, stirring was continued for another 1 h at 0°C. The contents were concentrated and dissolved in ethyl acetate (500 mL). The ethyl acetate solution was washed with water and brine, then dried (Na_2SO_4) and concentrated to get syrup like compound **16**, which was used directly for the next step.

At 0°C, a solution of the crude alcohol **16** and Et_3N (51.6 mL, 370.0 mmol) in CH_2Cl_2 (400 mL) was treated with mesyl chloride (10.48 mL, 135.6 mmol) and stirred for 3 h at RT. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with cold water and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford crude mesylated compound. The crude product was divided into four parts and used directly for the next step.

A solution of the above crude mesylate in DMSO (100 mL) was treated with sodium azide (6.0 g, 92.5 mmol) and the contents were stirred at 100°C for 5 h. The reaction mixtures were cooled to RT and diluted with EtOAc (500 mL), washed with water (3×100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10→20% EtOAc in petroleum ether) to obtain **17** (12.12 g, 48%, from **13**) as a colorless oil. $[\alpha]_D^{25}=-18.2$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=4.25$ (d, $J=4.9$ Hz, 1H), 4.10 (dd, $J=7.5$, 3.8 Hz, 1H), 4.01–3.92 (m, 1H), 3.88 (ddd, $J=11.2$, 8.4, 7.5 Hz, 2H), 3.43 (s, 3H), 3.42 (s, 3H), 2.15 (ddd, $J=15.9$, 13.1, 7.5 Hz, 1H), 1.89 ppm (dddd, $J=13.1$, 11.1, 4.5, 4.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3+CCl_4$): $\delta=32.5$ (t), 54.4 (q), 56.0 (q), 61.9 (d), 67.5 (t), 83.4 (d), 104.3 ppm (d); IR ($CHCl_3$): $\tilde{\nu}=3400$, 3083, 3015, 2937, 2866, 2835, 2110, 1588, 1494, 1462, 1443, 1408, 1306, 1226, 1186, 1129, 986, 930, 843, 814, 756, 666 cm^{-1}; MS (ESI): *m*/*z* (%): 210.1 (100) [M^++Na], 226.0 (39) [M^++K], 188.2 (19) [M^++1]; elemental analysis calcd (%) for $C_7H_{13}N_3O_3$: C 44.91, H 7.00, N 22.45; found: C 44.83, H 7.12, N 22.17.

(2*R*,3*R*)-3-Azidotetrahydrofuran-2-carboxylic acid (9): Compound **9** was prepared by using the procedure used for the preparation of compound **8**. $[\alpha]_D^{25}=-91.8$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=8.99$ (s br, 1H), 4.42 (d, $J=2.8$ Hz, 1H), 4.38 (dt, $J=6.1$, 3.1 Hz, 1H), 4.20–3.98 (m, 2H), 2.31–2.14 (m, 1H), 2.10–2.95 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3+CCl_4$): $\delta=31.6$ (t), 64.4 (d), 68.4 (t), 81.5 (d), 174.9 ppm (s); IR ($CHCl_3$): $\tilde{\nu}=3020$, 2400, 2107, 1602, 1519, 1475, 1432, 1217, 1094, 929, 771, 666 cm^{-1}; MS (ESI): *m*/*z* (%): 180.1 (100) [M^++Na]; elemental analysis calcd (%) for $C_5H_7N_3O_3$: C 38.22, H 4.49, N 26.74; found: C 38.31, H 4.41, N 26.47.

(2*R*,3*R*)-Methyl 3-azidotetrahydrofuran-2-carboxylate (9-Me): The esterification of acid **9** (6 g, 38.2 mmol) with diazomethane following the procedure used in the preparation of **8**-Me, gave **9**-Me (6 g, 92%) as colorless oil. $[\alpha]_D^{25}=+34.5$ ($c=1.5$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=4.38$ (d, $J=3.0$ Hz, 1H), 4.26 (dd, $J=6.5$, 3.2 Hz, 1H), 4.13 (dd, $J=8.5$, 4.3 Hz, 1H), 4.04–3.96 (m, 1H), 3.77 (s, 3H), 2.28–2.17 (m, 1H), 2.08–1.94 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3+CCl_4$): $\delta=31.5$ (t), 52.5 (q), 64.3 (t), 68.1 (d), 81.7 (d), 170.9 ppm (s); IR ($CHCl_3$): $\tilde{\nu}=3020$, 2974, 2874, 2842, 2112, 1753, 1655, 1598, 1504, 1479, 1463, 1415, 1342, 1215, 1134, 1113, 1028, 928, 889, 866, 756, 668 cm^{-1}; MS (ESI): *m*/*z* (%): 194.1 (100) [M^++Na], 233.0 (31) [M^++K]; elemental analysis calcd (%) for $C_6H_9N_3O_3$: C 42.10, H 5.30, N 24.55; found: C 42.31, H 5.18, N 24.57.

Synthesis of *cis*-dipeptide (18): A solution of azido ester **8**-Me (1 g, 5.84 mmol) in EtOH (20 mL) was stirred under an atmosphere of hydrogen in the presence of Raney nickel (0.5 g,) for 1 h. After the completion of reaction as indicated by TLC, the reaction mixture was filtered through celite and the solvent removed under reduced pressure to obtain crude amine.

A solution of acid **8** (1.0 g, 6.4 mmol), 1-hydroxybenzotriazole (950 mg, 7.0 mmol), and diisopropylethylamine (2.54 mL, 14.6 mmol) in dry CH_2Cl_2 (20 mL) was treated with EDCI·HCl (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) (1.1 g, 7.0 mmol) and stirred for 30 min. After that a solution of crude amine in CH_2Cl_2 (7 mL) was added and reaction mixture was stirred for 24 h at RT. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with brine. The organic phase was dried (Na_2SO_4) and concentrated. The crude product was purified over a silica gel column chromatography (50→60% ethyl acetate in petroleum ether) to obtain the dimer **18** (1.2 g, 73%) as a thick syrup. $[\alpha]_D^{25}=-24.2$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.99$ (d, $J=8.6$ Hz, 1H), 4.89 (ddd, $J=10.6$, 6.2, 4.9 Hz, 1H), 4.47 (d, $J=5.9$ Hz, 1H), 4.43 (dt, $J=4.9$, 1.3 Hz, 1H), 4.33 (d, $J=4.5$ Hz, 1H), 4.15 (dt, $J=8.3$, 6.9 Hz, 1H), 3.99–3.90 (m, 3H), 3.74 (s, 3H), 2.32 (ddt, $J=13.6$, 8.3, 6.9 Hz, 1H), 2.17 (ddt, $J=13.6$, 9.2, 5.2 Hz, 1H), 2.07 (dddd, $J=10.3$, 5.2, 4.1, 1.3 Hz, 1H), 1.96 ppm (dddd, $J=13.6$, 10.3, 5.9, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=32.7$ (t), 32.9 (t), 50.7 (d), 51.9 (d), 62.9 (q), 67.3 (t), 67.7 (t), 78.9 (d), 81.8 (d), 167.9 (s), 170.1 ppm (s); IR ($CHCl_3$): $\tilde{\nu}=3338$, 2956, 2107, 1745, 1667, 1532, 1440, 1266, 1098, 728 cm^{-1}; MS (ESI): *m*/*z* (%): 307.2 (100) [M^++Na], 323.1(32) [M^++K], 285.2 (29) [M^++1], 301 (15) [M^++H_2O−1]; elemental analysis calcd (%) for $C_{11}H_{16}N_4O_5$: C 46.48, H 5.67, N 19.71; found: C 46.39, H 5.58, N 19.63.

Synthesis of *cis*-tetrapeptide (19): To a solution of dimer **18** (500 mg, 1.76 mmol) in EtOH (15 mL) was added Raney nickel (400 mg,) and stirred under an atmosphere of hydrogen for 1 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure.

To a stirred solution of dimer **18** (500 mg, 1.76 mmol) in dioxane/water 9:1 (14 mL), aqueous sodium hydroxide (3.0 mL, 2 M) was added at 0 °C and the reaction mixture was stirred for 1 h at RT. The reaction mixture was neutralized with 2 N HCl and concentrated under reduced pressure. The crude residue was extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure to procure the dimer acid.

At 0 °C a solution of crude *cis*-dimer acid, 1-hydroxybenzotriazole (285 mg, 2.11 mmol) and diisopropylethylamine (0.8 mL, 4.40 mmol) in dry CH_2Cl_2 (15 mL) was treated with 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (330 mg, 2.11 mmol) and stirred for 30 min. To this, a solution of crude amine in CH_2Cl_2 (5 mL) was introduced and the contents stirred at RT for 35 h. The reaction mixture was diluted with dichloromethane (100 mL) and washed with H_2O (20 mL, 3 times). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by the silica gel column chromatography (1→3% methanol in CH_2Cl_2) to obtain the tetramer **19** (560 mg, 62%) as colorless amorphous solid. $[\alpha]_D^{25}=-52.3$ ($c=1.0$, $CHCl_3$); IR ($CHCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.06$ (d, $J=7.5$ Hz, 1H), 7.72 (d, $J=8.2$ Hz, 1H), 7.10 (d, $J=8.9$ Hz, 1H), 4.85–4.73 (m, 3H), 4.49 (d, $J=6.0$ Hz, 1H), 4.43 (dt, $J=6.0$, 4.5, 1.8 Hz, 1H), 4.37 (d, $J=4.5$ Hz, 1H), 4.35 (d, $J=7.3$ Hz, 1H), 4.27 (d, $J=8.2$ Hz, 1H), 4.21 (dd, $J=8.2$, 4.5 Hz, 1H), 4.17 (dd, $J=8.2$, 6.2 Hz, 1H), 4.09 (ddd, $J=10.8$, 8.5, 2.3 Hz, 1H), 4.06 (dd, $J=9.1$, 6.7 Hz, 1H), 3.98 (dd, $J=8.5$, 3.5 Hz, 1H), 3.96–3.90 (m, 3H), 3.86 (d, $J=10.2$, 8.9, 6.2 Hz, 1H), 3.75 (s, 3H), 2.47–2.29 (m, 1H), 2.23–2.15 (m, 1H), 2.13–2.07 (m, 1H), 1.96–1.90 (m, 1H), 1.86–1.79 (m, 1H), 1.67–1.57 ppm (m, 1H); ^{13}C NMR (100 MHz , $CDCl_3$): $\delta=30.9$ (t), 31.8 (t), 32.1 (t), 32.6 (t), 50.4 (d), 51.1 (d), 51.2 (d), 52.3 (d), 63.0 (d), 67.2 (t), 67.6 (t), 67.7 (t), 67.8 (t), 75.8 (d), 77.2 (d), 78.9 (d), 81.9 (d), 168.6 (s), 170.4 (s), 170.5 ppm (s, 2C); $\tilde{\nu}=3383$, 2925, 2113, 1729, 1668, 1520, 1451, 1271, 1219, 1085, 1027, 1007, 759, 728 cm^{-1}; MS (ESI): *m*/*z* (%): 533.5 (100) [M^++Na], 549.5 (31) [M^++K], 511.5 (63) [M^++1]; elemental analysis calcd (%) for $C_{21}H_{30}N_6O_9$: C 49.41, H 5.92, N 16.46; found: C 49.39, H 5.97, N 16.39.

Synthesis of *cis*-hexapeptide (20): The procedure used for the synthesis of tetrapeptide **19** was followed to prepare the hexapeptide **20**. The amine partner was made by the reduction of the azide group of *cis*-tetramer **19** (100 mg, 0.193 mmol) and the acid partner obtained from ester hydrolysis of *cis*-dimer **18** (60 mg, 0.21 mmol). The resulting crude product after the coupling reaction was purified by column chromatography (5→10% methanol in CH_2Cl_2) to afford the *cis*-hexamer **20** (82 mg, 57%) as colorless amorphous solid. $[\alpha]_D^{25}=-65.3$ ($c=0.5$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.20$ (d, $J=8.4$ Hz, 1H), 8.10 (d, $J=9.5$ Hz, 1H), 7.87 (d, $J=9.7$ Hz, 1H), 7.12 (d, $J=9.6$ Hz, 1H), 6.86 (d, $J=8.6$ Hz, 1H), 5.08–4.98 (m, 3H), 4.94–4.81 (m, 2H), 4.56 (d, $J=7.3$ Hz, 1H), 4.48–4.41 (m, 3H), 4.38 (d, $J=8.9$ Hz, 1H), 4.34 (d, $J=9.3$ Hz, 1H), 4.27 (d, $J=9.0$ Hz, 1H), 4.22 (dd, $J=8.6$, 4.4 Hz, 1H), 4.18–4.05 (m, 5H), 3.99–3.93 (m, 2H), 3.88–3.81 (m, 2H), 3.80 (s, 3H), 3.78–3.71 (m, 2H), 2.39–2.31 (m, 1H), 2.29–2.22 (m, 2H), 2.18–2.01 (m, 7H), 1.99–1.92 ppm (m, 2H); ^{13}C NMR (100 MHz , $CDCl_3$): $\delta=30.6$ (t), 30.9 (t), 30.9 (t), 31.3 (t), 32.0 (t), 32.5 (t), 50.4 (d), 50.7 (d), 50.8 (d), 51.0 (d), 51.2 (d), 52.5 (d), 63.0 (d), 67.4 (t), 67.5 (t), 67.6 (t), 67.7 (t), 67.7 (t), 67.7 (t), 77.0 (d),77.2 (d), 77.4 (d), 77.7 (d, 2C), 79.0 (d), 81.5 (d), 168.8 (s), 169.6 (s), 170.3 (s), 170.4 (s), 170.7 (s), 171.1 ppm (s); IR ($CHCl_3$): $\tilde{\nu}=3324$, 2925, 2846, 2113, 1728, 1665, 1660, 1651, 1520, 1274, 1083, 991, 758, 729 cm^{-1}; MS (ESI): *m*/*z* (%): 759.5 (100 [M^++Na], 775.4 (7) [M^++K], 301.2 (100) [M^+-435]); elemental analysis calcd (%) for $C_{31}H_{44}N_8O_{13}$: C 50.54, H 6.02, N 15.21; found: C 50.59, H 5.99, N 15.27.

Synthesis of *cis*-octapeptide (21): The preparation of octamer **21** was carried out as described for the preparation of *cis*-tetramer **19**. Both the coupling partners were obtained from the *cis*-tetramer **19**. The amine partner made by the reduction of the azide group of tetramer **19** (60 mg, 0.117 mmol) and acid partner obtained from ester hydrolysis of tetramer **19** (60 mg, 0.117 mmol) and coupled to obtain the octamer **21** (46 mg, 41%) as amorphous solid (purification by column chromatography 10→15% methanol in CH_2Cl_2). $R_f=0.25$ (MeOH/CH_2Cl_2 1:9); $[\alpha]_D^{25}=-144$–155 ($c=0.1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.28$ (d, $J=8.5$ Hz, 1H), 8.22 (d, $J=9.8$ Hz, 1H), 8.13 (d, $J=9.6$ Hz, 1H), 8.03 (d, $J=9.7$ Hz, 1H), 7.89 (d, $J=9.9$ Hz, 1H), 7.10 (d, $J=9.7$ Hz, 1H), 6.83 (d, $J=8.6$ Hz, 1H), 5.13–5.01 (m, 5H), 4.94–4.81 (m, 3H), 4.57 (d, $J=7.4$ Hz, 1H), 4.46 (sbr, 2H), 4.44 (d, $J=7.8$ Hz, 1H), 4.39 (d, $J=9.2$ Hz, 1H), 4.35 (d, $J=9.5$ Hz, 1H), 4.25 (dbr, $J=8.6$, 3H), 4.19–4.09 (m, 7H), 4.07 (t, $J=7.7$ Hz, 1H), 3.96 (ddd, $J=12.9$, 7.3, 1.4 Hz, 3H), 3.85 (dd, $J=6.7$, 1.4 Hz, 1H), 3.81 (s, 3H), 3.73–3.65 (m, 4H), 2.38–2.33 (m, 2H), 2.29–2.22 (m, 3H), 2.19–2.12 (m, 5H), 2.10–2.05 (9 m, 5H), 1.96–1.92 ppm (m, 1H); ^{13}C NMR (100 MHz , $CDCl_3$): $\delta=30.0$ (t), 30.2 (t), 30.6 (t), 30.9 (t), 30.9 (t), 31.1 (d), 32.0 (t), 32.5 (t), 50.4 (d), 50.6 (d), 50.8 (d), 51.0 (d), 51.1 (d, 2C), 51.3 (d), 52.5 (d), 63.0 (d), 67.4 (t), 67.5 (t), 67.6 (t), 67.7 (t, 2C), 67.8 (t), 77.2 (d), 77.7 (d, 2C), 77.8 (d), 79.1 (d), 81.4 (d), 168.9 (s), 169.6 (s), 170.2 (s), 170.5 (s), 170.6 (s), 170.8 (s), 171.1 (s), 171.3 ppm (s); IR ($CHCl_3$): $\tilde{\nu}=3324$, 2925, 2854, 2112, 1725, 1717, 1661, 1656, 1653, 1649, 1523, 1459, 1082, 987, 728 cm^{-1}; MS (ESI): *m*/*z* (%): 985.7 (7) [M^++Na], 963.7 (5) [M^++H], 549.4 (100) [M^+−413], 492 (63) [M^+−470]; elemental analysis calcd (%) for $C_{41}H_{58}N_{10}O_{17}$: C 51.14, H 6.07, N 14.55; found: C 51.23, H 6.11, N 14.49.

Synthesis of *trans*-dipeptide (22): The same sequence of procedures as for the preparation of *cis*-FAA dimer **18** were used with the acid **9** (808 mg, 5.14 mmol) and monomer–amine (prepared by the hydrogenolysis of the azide **9**-Me using Raney nickel, 800 mg, 4.67 mmol) to afford *trans*-FAA dimer **22** (915 mg, 69%) as colorless syrup. $[\alpha]_D^{25}=-141.4$ ($c=2.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.88$ (d, $J=6.9$ Hz, 1H), 4.63 (ddd, $J=11.2$, 7.5, 3.8 Hz, 1H), 4.39 (dt, $J=2.9$, 5.9 Hz, 1H), 4.33 (d, $J=3.4$ Hz, 1H), 4.30 (d, $J=2.8$ Hz, 1H), 4.20–4.11 (m, 1H), 4.09–3.98 (m, 3H), 3.77 (s, 3H), 2.40–2.31 (m, 1H), 2.11–1.98 (m, 2H), 1.91–1.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=31.3$ (t), 31.8 (t), 52.1 (d), 53.3 (d), 64.0 (q), 67.6 (t), 67.9 (t), 81.2 (d), 82.8 (d), 169.7 (s), 171.1 ppm (s); IR ($CHCl_3$): $\tilde{\nu}=3341$, 2955, 2890, 2107, 1746, 1667, 1532, 1439, 1267, 1212, 1098, 924, 729 cm^{-1}; MS (ESI): *m*/*z* (%): 307.2 (100) [M^++Na], 323.1(31) [M^++K], 285.2 (30) [M^++1], 301 (14) [M^++H_2O−1]; elemental analysis calcd (%) for $C_{11}H_{16}N_4O_5$: C 46.48, H 5.67, N 19.71; found: C 46.53, H 5.61, N 19.67.

Synthesis of *trans*-tetrapeptide (23): The procedures used in the preparation of *cis*-FAA tetramer **19** were followed. Coupling of the dimer acid (prepared by alkaline hydrolysis of **22**, 400 mg, 1.41 mmol) and dimer amine (prepared by the hydrogenolysis of the azide **22** using Raney nickel, 400 mg, 1.41 mmol) using the standard coupling protocol gave the *trans*-FAA tetramer **23** (365 mg, 53%) as colorless amorphous solid. $[\alpha]_D^{25}=-101.3$ ($c=2.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.40$ (d, $J=6.5$ Hz, 1H), 7.22 (d, $J=7.6$ Hz, 1H), 7.06 (d, $J=5.8$ Hz, 1H), 4.60–4.53 (m, 1H), 4.39–4.30 (m, 3H), 4.29–4.25 (m, 1H), 4.24–4.22 (m, 1H), 4.16 (dd, $J=7.1$, 5.0 Hz, 2H), 4.08 (dd, $J=7.9$, 2.0 Hz, 1H), 4.02–3.96 (m, 6H), 3.69 (s, 3H), 2.29–2.20 (m, 3H), 2.08–1.99 (m, 1H), 1.96–1.81 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=31.5$ (t), 32.0 (t), 32.2 (t), 32.2 (t), 52.3 (d), 53.4 (d), 54.5 (d), 54.6 (d), 64.2 (d), 67.9 (t, 2C), 68.0 (t), 68.1 (t), 81.5 (d), 82.1 (d), 82.2 (d), 83.0 (d), 170.3 (s), 170.8 (s), 170.9 (s), 171.4 ppm (s); IR ($CHCl_3$): $\tilde{\nu}=3301$, 2955, 2890, 2106, 1744, 1667, 1524, 1267, 1218, 1086, 759, 729 cm^{-1}; MS (ESI): *m*/*z* (%): 533.0 (100) [M^++Na], 549.0 (33) [M^++K], 511.0 (30) [M^++1], 301 (13) [M^++H_2O−1]; elemental analysis calcd (%) for $C_{21}H_{30}N_6O_9$: C 49.41, H 5.92, N 16.46; found: C 49.39, H 5.99, N 16.51.

Synthesis of *trans*-hexapeptide (24): The same sequence of procedures, as used in the preparation of *cis*-FAA hexamer **20**, was followed. The dimer acid (prepared by alkaline hydrolysis of **22**, 70 mg, 0.245 mmol) and tetramer amine (prepared by the hydrogenolysis of the azide **23** using Raney nickel, 100 mg, 0.195 mmol) gave *trans*-FAA hexamer **24** (53 mg, 35%) as a colorless amorphous solid. $[\alpha]_D^{25}=-79.4$ ($c=0.5$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.53$–7.49 (m, 3H), 7.30 (d, $J=7.5$ Hz, 1H), 7.05 (d, $J=6.6$ Hz, 1H), 4.64 (ddd, $J=11.0$, 7.5, 4.0 Hz, 1H), 4.49–4.40 (m, 4H), 4.39–4.35 (m, 1H), 4.33 (d, $J=3.3$ Hz, 1H), 4.17–4.13 (m, 1H), 4.29 (d, $J=2.8$ Hz, 1H), 4.24–4.18 (m, 4H), 4.10–4.01 (m, 11H), 3.75 (s, 3H), 2.38–2.28 (m, 5H), 2.03–1.88 ppm (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=31.9$ (t), 32.1 (t), 32.2 (t, 2C), 32.3 (t, 2C), 52.4 (d), 53.5 (d), 54.5 (d),

54.6 (d), 54.7 (d, 3C), 64.3 (d), 68.0 (t, 2C), 68.1 (t, 2C), 68.2 (t), 81.6 (d), 82.2 (d), 82.3 (d), 82.4 (d), 83.1 (d, 2C), 170.5 (s), 171.0 (s), 171.2 (s), 171.3 (s, 2C), 171.5 ppm (s); IR ($CHCl_3$): $\tilde{\nu}$ = 3301, 2955, 2106, 1744, 1672, 1667, 1656, 1648, 1528, 1521, 1269, 1085, 729 cm^{-1}; MS (ESI): *m/z* (%): 759.5 (22) [M^++Na], 775.4 (11) [M^++K], 633.5 (77) [M^+−203], 533. (100) [M^+−203]; elemental analysis calcd (%) for $C_{31}H_{44}N_8O_{13}$: C 50.54, H 6.02, N 15.21; found: C 50.63, H 6.09, N 15.18.

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