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PAPER

Conformational modulation of *Ant–Pro* oligomers using chirality alteration of proline residues†

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Structural modulation of *Ant–Pro* (anthranilic acid–proline) oligomers has been carried out by chirality alteration of the proline residues. The results suggest that the chirality altered oligomers show well-defined helical conformation featuring nine-membered hydrogen bonding interactions – without compromising conformational rigidity.

Introduction

Folding and unfolding of peptides is an important biological phenomenon.[1] Amino acid residues of polypeptides, of both native and synthetic origin, play a crucial role in aiding them to adopt a specific conformation – among the myriad of many possibilities (secondary structures).[2,3] Extensive investigations have revealed that there exist diverse ways to alter backbone conformations. One of the most popular strategies is the substitution of amino acid residues of the native peptide by residues of different dihedral angle preferences leading to conformational diversity.[4] The recent introduction of functionalized homologated amino acids such as α-,β-,γ-,δ- has further fuelled activity in this area, providing considerable insights into the relationship between amino acid substitution and its effect on conformational propensities.[5,6] A strategy which has also been proven effective for backbone conformational modulation is the chirality alteration of backbone amino acid residues.[7] Indeed, there are several examples to suggest that chirality altered peptide sequences, especially those containing ^{D}Pro residues, offer improved conformational stability. For instance, studies with turn inducers featuring ^{D}Pro residues have suggested that heterochiral turn inducers form relatively more stable hairpins/sheets.[8]

Results and discussion

As part of our ongoing program directed towards evaluating the conformational propensity of aromatic–aliphatic hybrid oligomers,[9] we reported Ant–Pro foldamers[9f] that display right handed helical structural architecture. The striking feature of these oligomers is that they display an unusual periodic pseudo-β-turn network of 9-membered hydrogen-bonded rings, involving only two consecutive amino acid residues. In this context, it was thought worthwhile to investigate the effect of chirality alteration on the backbone by changing systematically the chirality of the backbone Pro residues (Fig. 1).

Synthesis

The Ant–Pro oligomers with LL and LD proline chirality were synthesized by conventional solution-phase methods using the segment doubling strategy (Scheme 1).[10] The iodo functionality has been introduced in the oligomers for further functionalization, since aryl halides, in particular iodides, can be extensively subjected to substitutional modulation.[11] Thus, starting from the dimer building blocks Boc-^{L}Pro-Ant(I)-OMe **4a**, and Boc-^{D}Pro-Ant(I)-OMe **6a**, we obtained the higher order homo- and heterochiral oligomers. Coupling of dimer acid **4c** with the corresponding dimer amine **4b**, using HATU as a coupling agent and DIEA as the base, afforded the tetramer **5a**. Octamer **1a** and hexadecamer **3a** were prepared by using HBTU and DCC as the coupling agents, respectively. The heterochiral LD tetramer **7a** was synthesized by coupling the dimer acid **4c** with the dimer amine H-^{D}Pro-Ant(I)-OMe **6b** using HATU as the coupling agent. Iteration of the same coupling protocol furnished octamer **2a**. It is noteworthy that all oligomers having a BOC group at the N-termini caused a rotameric effect due to the slow rotation of the bond connecting the proline nitrogen and the BOC carbonyl. Therefore, a pivaloyl group was introduced at the N-terminus, as

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†Electronic supplementary information (ESI) available: ^{1}H, ^{13}C, DEPT-135 NMR, 2D study spectra, ESI mass spectra and theoretical study of new compounds are included. See DOI: 10.1039/c2ob26132d

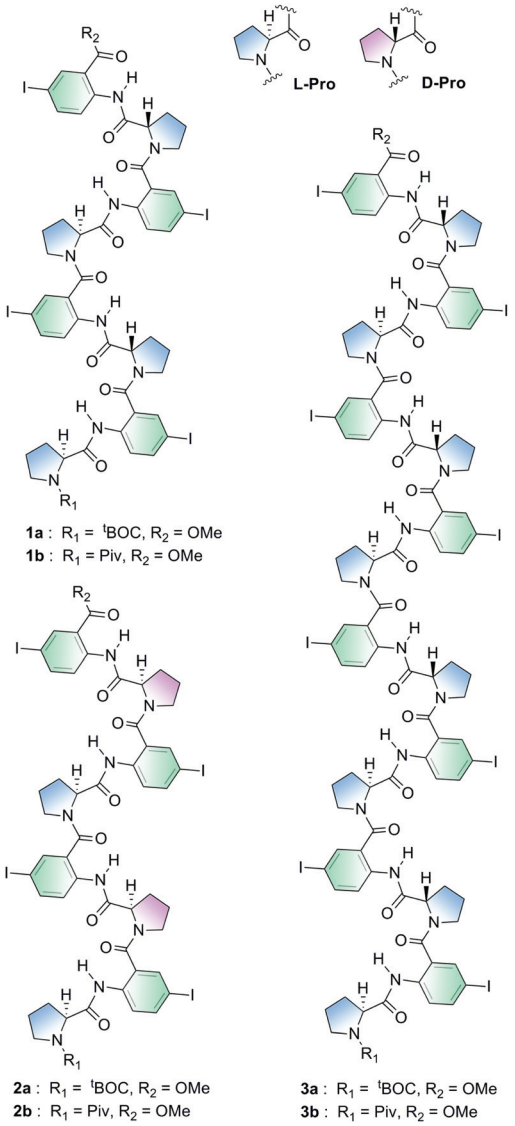
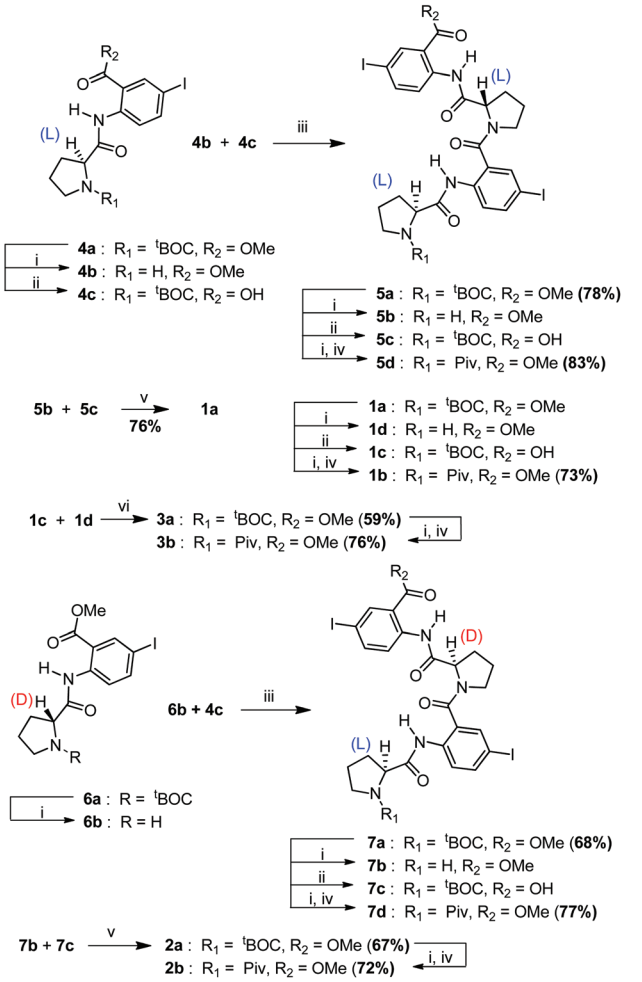


Fig. 1 Designed Ant–Pro oligomers with chirality modulation.

in **1b**, **2b**, **3b**, **5d** and **7d**, in order to arrest the rotameric effect, as described in the literature.[12]

NMR studies

The conformational features of the oligomers in the solution-state have been studied by various NMR studies (*vide infra*). All oligomers were readily soluble in nonpolar organic solvents (≫100 mM in $CDCl_3$) at ambient temperature suggesting that the polar hydrogen-bonding groups are strongly solvent-shielded, preventing the formation of polymeric aggregates.[13] It is noteworthy that conformational ordering is also readily discernible from the high degree of ^{1}H NMR spectral dispersion (see ESI†). The occurrence of intramolecular hydrogen-bonding in the oligomers in solution-state is further supported by DMSO-d_6 titration experiments. The amide NHs of both octamers **1b** and **2b** (LL and LD proline sequences, respectively) show negligible shift in DMSO titration experiments [$\Delta\delta$ (NH) < 0.21 ppm and 0.21 ppm, respectively, ESI, pages S27–S28†]. Nearly complete H/D exchange could be observed for **1a** and **2a** in 440 min (ESI,



Scheme 1 *Reagents and conditions*: (i) TFA : DCM (1 : 1), rt, 2 h; (ii) aq. LiOH, MeOH, rt, 4 h; (iii) HATU, HOBt, DIEA, dry DMF, 12 h; (iv) Piv-Cl, Et_3N, DCM, rt, 4 h; (v) HBTU, HOBt, DIEA, dry DMF, rt, 12 h; (vi) DCC, HOBt, dry DCM, rt, 12 h.

page S29†), further firmly confirming that the amide NHs are strongly involved in intramolecular hydrogen bonding interactions. The oligomers with LL sequences show long-range inter-residual nOes emanating from dipolar couplings between the N- and C-terminal substituents, thereby strongly supporting folded conformation.[9f] Some of the characteristic inter-residual nOes (Fig. 2a) that strongly support the helical conformation of the tetramer **5d** are C2H *vs.* C24H, C3H *vs.* C24H and NH1 *vs.* C24H (see ESI, pages S30–S34†). In the case of tetramer **7d** having LD proline sequences, the characteristic inter-residual nOes that support the folded conformation are C3H *vs.* C24H, C17H *vs.* C9H and NH1 *vs.* C17H (Fig. 2b and ESI, pages S35–S39†). It is noteworthy that the results of the comparison of experimental (nOe) and theoretical (computation) inter-residual distances (ESI, pages S40–S43†) are supportive of the helical architecture of the oligomers **5d** and **7d**.

Circular dichroism studies

Circular dichroism (CD) studies are useful in investigating the secondary structure conformational preferences of peptide

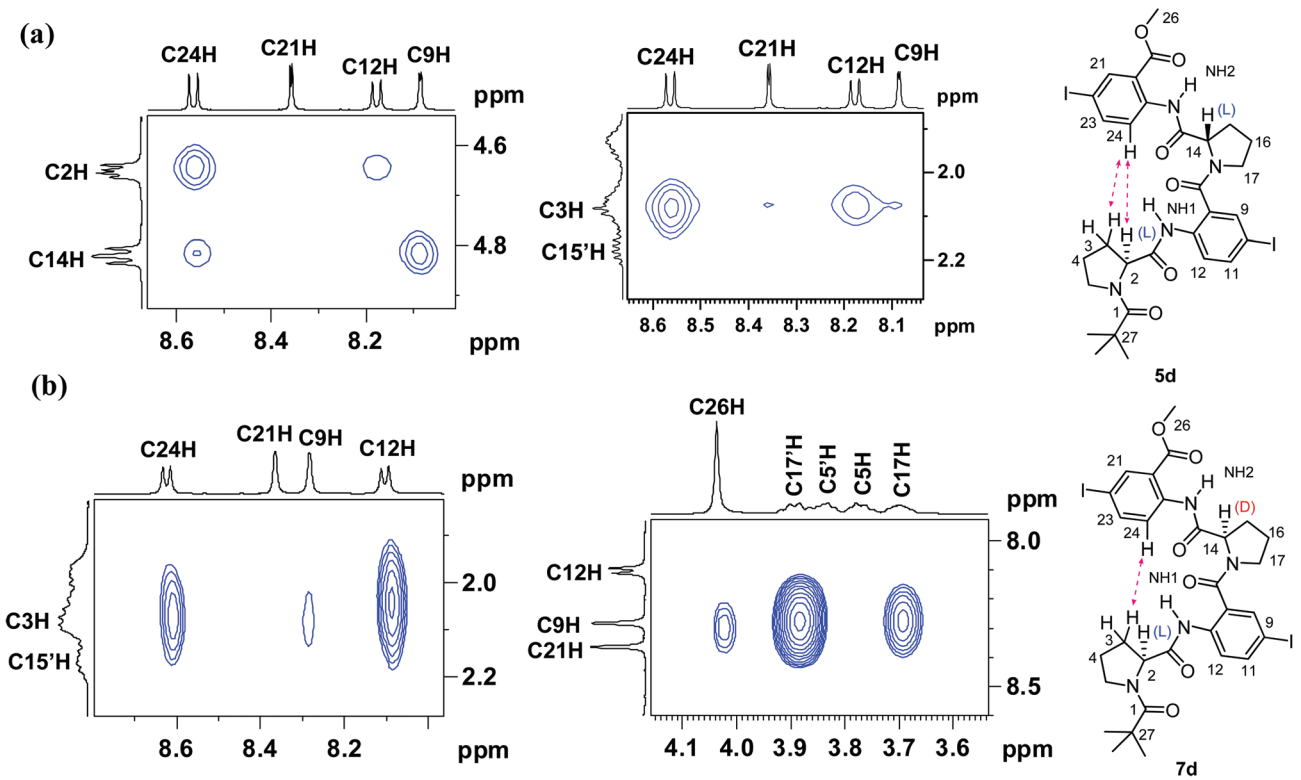


Fig. 2 Selected NOE extracts from the (a) 2D NOESY data of tetramer **5d** ($CDCl_3$, 500 MHz); C2H *vs.* C24H region and C3H *vs.* C24H region; (b) 2D ROESY data of tetramer **7d** ($CDCl_3$, 500 MHz); C3H *vs.* C24H region and C17H *vs.* C9H region.

oligomers. CD spectra of oligomers **5a** and **1a** composed of homochiral proline residues show maxima at about 194 nm, zero-crossing at about 206 nm and strong minima at about 230 nm which support helical conformation of the oligomers as documented in the literature.[9f] The higher oligomer hexadecamer **3a** shows strong maxima at 191 nm, zero-crossing at 223 nm and strong minima at 232 nm, following which a small positive Cotton effect is observed at 218 nm (Fig. 3). The heterochiral derivatives **7a** and **2a** featuring ^{L}Pro-Ant-^{D}Pro-Ant sequences exhibit maxima at about 213 nm, zero crossing at 221 nm and minima at 213 nm. A strong negative absorption band at 269 nm in the case of LL sequences (**5a**, **1a** and **3a**) and a contrasting positive absorption band at 274 nm in the case of LD sequences (**7a** and **2a**) are presumably due to the backbone aromatic groups/aromatic electronic transitions in the oligomers.[14]

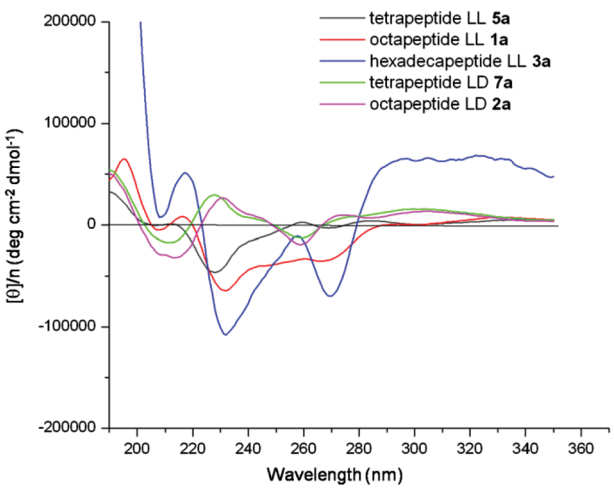


Fig. 3 Representative CD spectra of Pro–Ant oligomers: tetramer **5a**, octamer **1a**, hexadecamer **3a**, tetramer **7a** and octamer **2a**, in trifluoroethanol. All spectra were recorded at 298 K with a concentration of 0.2 mM (for **3a**, 0.02 mM).

Quantum chemical studies

The difficulty in crystallizing the oligomers prompted us to examine their conformation by *ab initio* MO theory. It is noteworthy that computational investigations employing *ab initio* MO theory have considerably contributed to predict and to understand the folding patterns in a wide variety of synthetic oligomers.[15] We have used both Hartree–Fock (HF) and DFT-B3LYP methods to optimize the structures, followed by frequency calculations to confirm the nature of the optimized saddle points. All the calculations were performed in the cep-31g basis set, using Gaussian-09. To map the conformational space of the *Ant–Pro* oligomers, Monte Carlo (MCMM) searches[16a] with the MM2* force field[16b] were performed. All the MCMM were carried out using Hyperchem.[16c] A total of 5000 steps of MCMM were carried out in vacuum for each isomer using the PRCG energy minimization algorithm. The number of conformations found within 5 kcal mol^{-1} of the global energy minimum for **5d**, **1b**, **3b**, **7d** and **2b** was 42, 29, 5, 114 and 17, respectively. Overlapping studies were performed on all conformers to calculate the RMSD value (ESI,

pages S46–S49†). A closer inspection of the results suggests that NH of the Ant(1) ring forms a hydrogen-bond with the carbonyl of Pro(2), which leads to a high degree of conformational rigidity in the Ant–Pro oligomers. Theoretical studies have been performed on the Ant–Pro oligomers, which is suggestive of helical structures for the oligomers involving 9-membered ring hydrogen bonded networks. It is noteworthy that the structural studies accrued from circular dichroism and quantum chemical studies (Fig. 4) suggest a right-handed helical structure for the homochiral sequences and a contrasting left-handed helical structure for the heterochiral sequences.

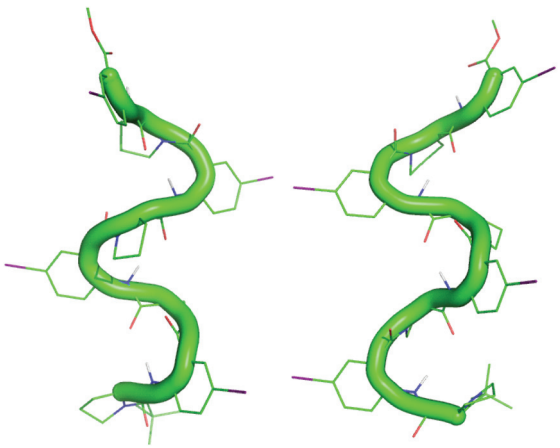


Fig. 4 Representative cartoon representation of oligomers **1b** (left) and **2b** (right) displaying C9 helical turns at the HF/6-31G level of *ab initio* MO theory. Hydrogens, other than at the hydrogen bonding sites, have been omitted for clarity.

Conclusions

In conclusion, we have successfully synthesised *Ant–Pro* oligomers having both homo- and heterochiral backbones. Detailed structural investigations have been undertaken, involving solution-state NMR, circular dichroism and theoretical studies, to evaluate their conformational features. The structural studies suggest that homochiral oligomers display right-handed helical architectures. In contrast, the heterochiral oligomers display left-handed helical architectures. However, in both the cases, the robust 9-membered-ring H-bonded networks, formed in the forward direction of the sequence by 1 → 2 amino acid interactions, involving only two consecutive amino acid residues are clearly retained. It is noteworthy that robust helical architectures find extensive utility in biomedical science – particularly for using them as cell penetrating peptides, when conjugated with cationic functionalities on the backbone.[17,18]

Experimental procedures

(*S*)-*tert*-Butyl-2-(4-iodo-2-(methoxycarbonyl)phenylcarbamoyl)-pyrrolidine-1-carboxylate 4a

To a two necked round-bottomed flask containing Boc-L-proline (0.93 g, 4.33 mmol) in dry THF (10 mL) was added TEA (0.6 mL, 4.33 mmol) under a N_2 atmosphere. The resultant solution was cooled to 0 °C. Subsequently, ethyl chloroformate (0.41, 4.33 mmol) was introduced dropwise over a period of 30 min. After the solution was stirred at this temperature for 1 h, methyl 2-amino-5-iodobenzoate (1.0 g, 3.61 mmol) in dry THF (10 mL) was added, under a N_2 atmosphere. The reaction mixture was stirred at 0 °C for 1 h, at room temperature for 2 h, and heated at reflux for 48 h. At the end of the reaction, as judged by TLC analysis, the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated to obtain the crude product, which was further purified by silica-gel column chromatography (eluent: pet ether–ethyl acetate: 70 : 30, R_f: 0.4) to furnish **4a** as a white solid (1.5 g, 88%); mp: 92–95 °C; $[\alpha]_D^{26}$: −78.85° (*c* 6.06, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3260, 3019, 2980, 2361, 1692, 1574, 1508, 1391, 1368, 1306, 1215, 758, 669; ^{1}H NMR (200 MHz, $CDCl_3$) δ: $11.54_{rotamer}$ (0.45H)–$11.45_{rotamer}$ (0.55H), 8.60–8.55 (d, J = 10 Hz, 1H), 8.34 (s, 1H), 7.84–7.80 (m, 1H), $4.44_{rotamer}$ (0.4H), $4.27_{rotamer}$ (0.6H), 3.92 (s, 3H), 3.77–3.41 (m, 2H), 2.39–2.07 (m, 2H), 2.05–1.83 (m, 2H), $1.50_{rotamer}$ (4H), $1.34_{rotamer}$ (5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.9, 171.5, 166.5, 154.5, 153.6, 142.6, 140.3, 140.2, 138.9, 138.7, 121.6, 121.5, 116.6, 84.8, 84.6, 79.7, 62.3, 61.7, 52.4, 52.1, 46.7, 46.4, 31.1, 30.0, 28.0, 27.8, 24.0, 23.5; ESI MS: 497.2713 $(M + Na)^+$, 513.2664 $(M + K)^+$. Anal. Calcd for $C_{18}H_{23}IN_2O_5$: C, 45.58; H, 4.89; N, 5.91. Found: C, 45.10; H, 5.35; N, 5.42.

(*R*)-*tert*-Butyl-2-(4-iodo-2-(methoxycarbonyl)phenylcarbamoyl)-pyrrolidine-1-carboxylate 6a

The product **6a** was obtained as a white solid (86%), following the aforesaid procedure; mp: 91–94 °C; $[\alpha]_D^{26}$: 75.12° (*c* 10, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3021, 2399, 1694, 1574, 1510, 1439, 1390, 1304, 1215, 1161, 1094, 930, 768, 669; ^{1}H NMR (200 MHz, $CDCl_3$) δ: $11.49_{rotamer}$ (0.4H)–$11.40_{rotamer}$ (0.6H), 8.56–8.51 (d, J = 8 Hz, 1H), 8.30 (s, 1H), 7.80–7.76 (d, J = 8 Hz, 1H), $4.40_{rotamer}$ (0.4H), $4.23_{rotamer}$ (0.6H), 3.88 (s, 3H), 3.73–3.37 (m, 2H), 2.39–2.05 (m, 2H), 2.01–1.84 (m, 2H), $1.46_{rotamer}$ (4H), $1.30_{rotamer}$ (5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.4, 171.9, 166.8, 154.9, 154.0, 142.9, 140.6, 140.5, 139.3, 139.1, 122.0, 121.8, 116.9, 85.1, 84.9, 80.1, 62.6, 62.0, 52.6, 52.3, 47.0, 46.7, 31.4, 30.3, 28.1, 24.2, 23.7; ESI MS: 475.3762 $(M + H)^+$, 497.3570 $(M + Na)^+$, 513.3534 $(M + K)^+$. Anal. Calcd for $C_{18}H_{23}IN_2O_5$: C, 45.58; H, 4.89; N, 5.91. Found: C, 45.18; H, 5.30; N, 5.49.

General method for ester hydrolysis (1a, 4a, 5a and 7a)

To the solution of esters **1a**, **4a**, **5a** and **7a** (10 mmol) in methanol (25 mL), $LiOH{\cdot}H_2O$ (40 mmol) was added in water (12 mL) at 0 °C, and the reaction mixture was stirred for 4 h. After the complete consumption of the starting material, the solvent was evaporated under reduced pressure, and the free acid was liberated by treating with sat. $KHSO_4$ solution followed by extraction with DCM (2 × 25 mL) and dried over anhydrous Na_2SO_4. The corresponding acid residue (**1c**, **4c**, **5c** and **7c**) obtained after evaporation of the solvent under reduced pressure

was carried forward for the next reaction, without further purification.

General method for Boc deprotection (1a and 4a–7a)

A solution containing the Boc-oligomer (3 mmol) was subjected to deprotection using DCM : TFA (50%, 10 mL) at 0 °C. After completion of the reaction (2 h), the reaction mixture was stripped of the solvent, neutralized with sat. $NaHCO_3$ solution and the product was repeatedly extracted with DCM (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4. The crude product (**1d** and **4b–7b**), obtained after evaporating the solvent under reduced pressure, was used for the next step without further purification.

Boc-tetramer 5a

A solution containing dimer acid **4c** (2.7 g, 6.07 mmol) and dimer amine **4b** (2.5 g, 6.68 mmol) in dry DMF (30 mL) was cooled to 0 °C. HATU (3.46 g, 9.11 mmol) was added followed by the addition of HOBt (0.40 g, 3.05 mmol) and DIEA (2.07 mL, 12.14 mmol). The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 12 h. Ethyl acetate (100 mL) was added to the reaction mixture and the organic layer was washed sequentially with sat. $KHSO_4$ solution, sat. $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude product which on purification by column chromatography (eluent: pet ether–ethyl acetate: 40 : 60, R_f: 0.4) yielded **5a** (3.5 g, 73%); fluffy solid, mp: 125–128 °C, $[\alpha]_D^{26}$: −63.3° (*c* 3, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3294, 3019, 2399, 1694, 1681, 1573, 1510, 1504, 1404, 1392, 1308, 1215, 928, 772, 669; ^1H NMR (400 MHz, $CDCl_3$) δ: 11.55 (s, 1H), 9.80 (s, 1H), 8.52–8.50 (d, J = 8 Hz, 1H), 8.27 (s, 1H), 8.14–8.04 (m, 2H), 7.75–7.73 (d, J = 8 Hz, 1H), 7.67–7.60 (m, 1H), 4.73–4.78 (m, 1H), $4.43_{rotamer}$ (0.45H), $4.15_{rotamer}$ (0.55H), 3.94 (s, 3H), 3.78–3.72 (m, 1H), 3.59–3.20 (m, 3H), 2.42–2.34 (m, 1H), 2.20–2.07 (m, 2H), 2.06–1.90 (m, 2H), 1.89–1.78 (m, 3H), $1.43_{rotamer}$ (5H), $1.27_{rotamer}$ (4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 171.3, 170.4, 168.3, 167.4, 155.2, 153.6, 143.0, 140.7, 139.4, 139.9, 139.1, 136.5, 136.1, 126.5, 125.1, 123.5, 122.7, 121.9, 116.7, 85.9, 85.6, 85.2, 80.1, 79.7, 62.2, 61.9, 61.2, 53.1, 50.6, 50.5, 47.0, 46.5, 31.1, 29.8, 28.3, 25.2, 24.2, 23.7; MALDI-TOF *m*/*z*: 839.0738 $(M + Na)^+$, 855.0632 $(M + K)^+$. Anal. Calcd for $C_{30}H_{34}I_2N_4O_7$: C, 43.46; H, 3.90; N, 6.99. Found: C, 43.81; H, 4.22; N, 6.55.

Boc-tetramer 7a

Similarly, compound **7a** was synthesized by the above mentioned procedure using dimer acid **4c** and dimer amine **6b**. Yield (71%); mp: 132–135 °C, $[\alpha]_D^{26}$: 6.77° (*c* 5, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3271, 2399, 1690, 1634, 1576, 1508, 1420, 1389, 1292, 1215, 928, 771, 669; ^1H NMR (400 MHz, $CDCl_3$) δ: $11.67–11.63_{rotamer}$ (1H), $9.73_{rotamer}$ (0.5H), $9.49_{rotamer}$ (0.5H), 8.57–8.53 (m, 1H), 8.31 (s, 1H), 8.24–8.18 (m, 1H), 8.02–7.95 (m, 1H), 7.79–7.77 (d, J = 8 Hz, 1H), 7.71–7.63 (m, 1H), 4.75–4.71 (m, 1H), $4.31_{rotamer}$ (0.5H), $4.19_{rotamer}$ (0.5H), 3.97 (s, 3H), 3.85–3.78 (m, 1H), 3.69–3.35 (m, 3H), 2.55–2.36 (m, 2H), 2.20–1.96 (m, 4H), 1.95–1.82 (m, 2H), $1.40_{rotamer}$–$1.32_{rotamer}$ (9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.0, 171.2, 170.6, 169.0, 168.5, 167.6, 155.0, 153.9, 143.2, 140.7, 139.8, 139.2, 136.8, 136.5, 136.1, 126.5, 126.3, 124.0, 123.9, 122.0, 116.7, 86.4, 86.1, 85.4, 85.2, 80.2, 62.7, 62.5, 61.8, 61.1, 53.2, 50.8, 47.0, 46.7, 31.2, 30.0, 29.8, 28.2, 25.5, 24.3, 23.8; MALDI-TOF *m*/*z*: 839.2418 $(M + Na)^+$, 855.2350 $(M + K)^+$. Anal. Calcd for $C_{30}H_{34}I_2N_4O_7$: C, 43.46; H, 3.90; N, 6.99. Found: C, 43.75; H, 4.20; N, 6.68.

Boc-octamer 1a

The tetramer acid **5c** (1.57 g, 1.96 mmol) was coupled with tetramer amine **5b** (1.54 g, 2.15 mmol) using HBTU (0.89 g, 2.35 mmol), HOBt (0.13 g, 0.98 mmol) and DIEA (0.47 mL, 2.7 mmol) in dry DMF and the reaction was allowed to proceed for 12 h, at room temperature. Ethyl acetate (100 mL) was added to the reaction mixture and the organic layer was washed sequentially with sat. $KHSO_4$ solution, sat. $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude product which on purification by column chromatography (eluent: pet ether–ethyl acetate: 25 : 75, R_f: 0.4) afforded **1a** (2.25 g, 76%) as a solid; mp: 189–193 °C; $[\alpha]_D^{26}$: −0.36° (*c* 5.45, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3269, 3019, 2361, 1688, 1632, 1578, 1510, 1439, 1383, 1290, 1251, 928, 762, 669; ^1H NMR (400 MHz, $CDCl_3$) δ: 11.52 (s, 1H), 9.85 (s, 1H), 9.83 (s, 1H), $9.69_{rotamer}$ (0.6H), $9.52_{rotamer}$ (0.4H), 8.49–8.44 (m, 1H), 8.36 (s,1H), 8.30–8.28 (d, J = 8 Hz, 1H), 8.15–8.10 (m, 1H), 8.01–7.95 (m, 1H), 7.88–7.79 (m, 2H), 7.72–7.61 (m, 5H), 4.92–4.73 (m, 3H), $4.44_{rotamer}$ (0.4H), $4.25_{rotamer}$ (0.6H), 3.97 (s, 3H), 3.84–3.71 (m, 2H), 3.66–3.58 (m, 1H), 3.55–3.45 (m, 2H), 3.43–3.22 (m, 2H), 3.20–3.13 (m, 1H), 2.50–2.35 (m, 2H), 2.33–2.25 (m, 1H), 2.21–2.06 (m, 6H), 2.05–1.81 (m, 6H), 1.80–1.70 (m, 1H), $1.42_{rotamer}$ (s, 4H), $1.29_{rotamer}$ (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.1, 171.5, 171.4, 171.1, 170.9, 170.7, 167.6, 167.0, 166.6, 154.7, 153.9, 143.1, 140.5, 139.6, 139.5, 139.3, 139.1, 138.8, 136.3, 135.8, 135.5, 135.4, 135.2, 135.0, 134.7, 128.6, 128.5, 128.1, 126.2, 124.4, 124.0, 123.7, 123.0, 122.6, 122.1, 117.0, 87.6, 87.2, 87.0, 86.6, 85.8, 85.6, 79.8, 79.6, 62.1, 62.0, 61.2, 61.1, 60.9, 60.6, 53.1, 50.2, 49.9, 49.6, 49.1, 47.0, 46.6, 31.8, 31.3, 30.4, 30.2, 29.9, 29.6, 28.4, 28.2, 25.4, 25.3, 25.2, 25.0, 24.3, 23.8; MALDI-TOF: 1523.8236 $(M + Na)^+$, 1539.8209 $(M + K)^+$; Anal. Calcd for $C_{54}H_{56}I_4N_8O_{11}$: C, 43.22; H, 3.76; N, 7.47. Found: C, 42.84; H, 3.99; N, 7.70.

Boc-octamer 2a

Similarly, compound **2a** was synthesized by the above mentioned procedure using tetramer acid **7c** and tetramer amine **7b**. Yield (67%); mp: 182–186 °C; $[\alpha]_D^{26}$: −4.92° (*c* 3.25, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3021, 2399, 1717, 1684, 1636, 1558, 1541, 1508, 1421, 1215, 930, 766, 669; ^1H NMR (400 MHz, $CDCl_3$) δ: 11.64 (s, 1H), 9.96 (s, 1H), 9.63 (s, 1H), $9.42_{rotamer}$ (0.4H), $9.33_{rotamer}$ (0.6H), 8.55–8.52 (d, J = 12 Hz, 1H), 8.32 (s, 1H), 8.22 (s, 1H), 8.15–7.93 (m, 3H), 7.85 (s, 1H), 7.80–7.78 (d, J = 8 Hz, 1H), 7.59–7.14 (m, 3H), 7.57–7.47 (m, 1H),

4.86–4.70 (m, 3H), 4.37–4.25 (m, 1H), 3.98 (s, 3H), 3.87–3.81 (m, 1H), 3.74–3.55 (m, 3H), 3.53–3.35 (m, 4H), 2.52–2.42 (m, 1H), 2.34–2.25 (m, 2H), 2.23–2.07 (m, 4H), 2.06–1.80 (m, 9H), $1.41_{rotamer}$ (s, 3H), $1.31_{rotamer}$ (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.3, 171.4, 170.4, 170.1, 169.9, 168.8, 167.7, 167.5, 166.9, 154.7, 154.0, 143.2, 140.8, 139.9, 139.6, 139.5, 139.3, 136.9, 136.5, 136.0, 135.7, 135.5, 135.4, 135.2, 127.4, 126.6, 126.4, 125.8, 123.9, 123.6, 123.2, 122.0, 116.7, 86.6, 86.3, 85.3, 80.0, 79.9, 62.8, 62.8, 61.5, 61.4, 61.1, 60.9, 53.2, 51.1, 50.3, 49.8, 47.0, 46.8, 31.4, 30.1, 29.8, 29.5, 28.3, 25.5, 25.2, 24.4, 23.9; MALDI-TOF: 1523.6332 $(M + Na)^+$, 1539.6084 $(M + K)^+$; Anal. Calcd for $C_{54}H_{56}I_4N_8O_{11}$: C, 43.22; H, 3.76; N, 7.47. Found: C, 7.70; H, 4.15; N, 7.23.

Boc-hexadecamer 3a

A solution containing octamer acid **1c** (0.135 g, 0.09 mmol) and octamer amine **1d** (0.14 g, 0.1 mmol) in dry DCM (10 mL) was cooled to 0 °C. DCC (0.028 g, 0.14 mmol) was added followed by HOBt (0.006 g, 0.04 mmol). The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 12 h. The reaction mixture was diluted with DCM (10 mL) and filtered through celite, washed sequentially with sat. $KHSO_4$ solution, sat. $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4, and the crude product obtained on the removal of solvent under reduced pressure was subjected to column purification (eluent: pet ether–ethyl acetate: 5 : 95, R_f: 0.5) to yield **3a** (0.154 g, 59%) as a solid; mp: 208–211 °C; $[\alpha]_D^{25}$: 25.75° (*c* 5.36, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3260, 3019, 2359, 1682, 1634, 1578, 1531, 1435, 1381, 1290, 1254, 1215, 929, 770, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.51 (s, 1H), 9.92–9.85 (m, 4H), 9.84–9.80 (m, 2H), 9.78–9.71 (m, 1H), 8.46–8.43 (d, J = 12 Hz, 1H), 8.36 (s, 1H), 8.32–8.29 (d, J = 12 Hz, 1H), 8.25–8.12 (m, 4H), 8.08–8.05 (d, J = 12 Hz, 1H), 8.01–7.99 (d, J = 8 Hz, 1H), 7.90 (s, 1H), 7.83–7.81 (d, J = 8 Hz, 1H), 7.73 (s, 1H), 7.73–7.60 (m, 12H), 5.11–4.96 (m, 4H), 4.95–4.90 (m, 2H), 4.79–4.75 (m, 1H), $4.53_{rotamer}$ (0.3H), $4.28_{rotamer}$ (0.7H), 3.98 (s, 3H), 3.84–3.80 (m, 1H), 3.75–3.70 (m, 1H), 3.69–3.57 (m, 6H), 3.53–3.40 (m, 2H), 3.36–3.28 (m, 5H), 3.22–3.16 (m, 1H), 2.51–2.30 (m, 8H), 2.24–2.03 (m, 16H), 2.00–1.83 (m, 8H), $1.41_{rotamer}$ (3H), $1.30_{rotamer}$ (6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.3, 172.1, 172.0, 171.3, 171.2, 170.8, 167.5, 166.9, 166.5, 166.4, 166.3, 165.9, 165.8, 154.5, 153.9, 143.1, 140.4, 139.5, 139.4, 139.3, 138.8, 138.7, 138.6, 136.2, 135.6, 135.3, 135.1, 134.8, 134.7, 134.3, 134.1, 134.0, 129.5, 129.1, 129.0, 128.9, 128.5, 128.2, 126.2, 124.0, 123.8, 123.2, 123.0, 122.9, 122.5, 122.2, 122.0, 117.0, 88.0, 87.7, 87.6, 87.5, 87.4, 87.1, 86.8, 86.3, 85.8, 85.5, 79.7, 79.4, 62.0, 61.9, 61.2, 60.9, 60.8, 53.1, 50.1, 49.7, 49.2, 49.1, 48.9, 46.9, 46.6, 31.3, 30.2, 30.1, 29.9, 29.6, 28.4, 28.2, 25.5, 25.3, 25.2, 25.1, 25.0, 24.3, 23.8; MALDI-TOF: 2890.9689 $(M + Na)^+$, 2906.9387 $(M + K)^+$; Anal. Calcd for $C_{102}H_{100}I_8N_{16}O_{19}$: C, 42.70; H, 3.51; N, 7.81. Found: C, 43.12; H, 3.09; N, 8.05.

Piv-tetramer 5d

A solution containing the tetramer **5a** (0.8 g, 0.98 mmol) in dichloromethane (10 mL) was subjected to Boc deprotection using DCM : TFA (50%, 6 mL). After completion of the reaction (2 h), the reaction mixture was stripped of the solvent, neutralized with sat. $NaHCO_3$ solution, diluted with dichloromethane (10 mL) and the product extracted into the organic layer (2 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4, evaporated and dried. The residue thus obtained was taken in dry dichloromethane (10 mL) and cooled to 0 °C. Pivaloyl chloride (0.22 mL, 1.76 mmol) was added to the above reaction mixture followed by the addition of Et_3N (0.49 mL, 3.5 mmol). After stirring at room temperature for 4 h, the reaction mixture was diluted with dichloromethane (10 mL), washed sequentially with potassium hydrogen sulfate solution, sat. sodium bicarbonate solution and water. The organic layer was dried over anhydrous Na_2SO_4, and the crude product obtained on removal of solvent under reduced pressure was subjected to column purification (eluent: pet ether–ethyl acetate: 40 : 60, R_f: 0.3) to yield **5d** as a white solid (0.647 g, 83%); mp: 104–108 °C; $[\alpha]_D^{25}$: −56.8° (*c* 5, $CHCl_3$); IR (ν) $CHCl_3$ (cm^{-1}): 3302, 3019, 2361, 1701, 1686, 1622, 1578, 1508, 1410, 1383, 1292, 1096, 929, 760, 669; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.56 (s, 1H), 9.59 (s, 1H), 8.54–8.52 (d, J = 8 Hz, 1H), 8.32 (s, 1H), 8.15–8.13 (d, J = 8 Hz, 1H), 8.05 (s, 1H), 7.79–7.77 (d, J = 8 Hz, 1H), 7.65–7.63 (d, J = 8 Hz, 1H), 4.80–4.77 (m, 1H), 4.63–4.60 (m, 1H), 3.97 (s, 3H), 3.81–3.75 (m, 3H), 3.58–3.53 (m, 1H), 2.46–2.39 (m, 1H), 2.17–2.10 (m, 1H), 2.09–1.99 (m, 4H), 1.95–1.87(m, 2H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.7, 171.3, 170.7, 168.3, 167.5, 143.1, 140.8, 139.6, 139.3, 136.4, 136.3, 126.2, 123.5, 122.1, 85.7, 85.3, 63.4, 62.3, 53.5, 48.4, 39.0, 30.0, 28.3, 27.4, 25.7, 25.4; MALDI-TOF: 823.1776 $(M + Na)^+$, 839.0825 $(M + K)^+$; Anal. Calcd for $C_{30}H_{34}I_2N_4O_6$: C, 45.02; H, 4.28; N, 7.00. Found: C, 45.37; H, 4.51; N, 6.62.

The oligomers **1b–3b** and **7d** were synthesized by following the above mentioned procedure.

Piv-octamer 1b

The oligomer **1b** was obtained as a white solid (73%); mp: 210–213 °C; $[\alpha]_D^{25}$: −14.4° (*c* 5, $CHCl_3$); IR (ν) $CHCl_3$ (cm^{-1}): 3283, 3019, 2399, 1682, 1630, 1578, 1518, 1504, 1431, 1381, 1290, 1217, 929, 771, 669; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.51 (s, 1H), 9.79 (s, 1H), 9.78 (s, 1H), 9.46 (s, 1H), 8.48–8.46 (d, J = 8 Hz, 1H), 8.34 (s, 1H), 8.12–8.10 (d, J = 8 Hz, 1H), 7.98–7.94 (m, 2H), 7.89–7.87 (d, J = 8 Hz, 1H), 7.81–7.78 (dd, J = 8 Hz, 4 Hz, 1H), 7.70–7.65 (m, 2H), 7.65–7.62 (dd, J = 8 Hz, 4 Hz, 1H), 7.62–7.58 (dd, J = 8 Hz, 4 Hz, 1H), 7.57–7.54 (m, 1H) 4.91–4.87 (m, 1H), 4.83–4.79 (m, 1H), 4.75–4.71 (m, 1H), 4.64–4.61 (m, 1H), 3.97 (s, 3H), 3.75–3.60 (m, 5H), 3.52–3.47 (m, 1H), 3.38–3.33 (m, 1H), 3.30–3.25 (m, 1H), 2.47–2.36 (m, 2H), 2.33–2.25 (m, 1H), 2.22–1.96 (m, 8H), 1.94–1.86 (m, 3H), 1.82–1.74 (m, 2H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.7, 171.9, 171.6, 171.1, 170.7, 167.5, 167.3, 16.9, 166.5, 143.1, 140.5, 139.4, 139.3, 138.9, 135.7, 135.2, 135.1, 134.7, 134.4, 130.1, 128.6, 128.1, 124.8, 123.8, 123.9, 122.1, 116.9, 87.9, 87.2, 86.5, 85.6, 62.7, 62.2, 61.2, 61.0, 53.1, 49.9, 49.3, 49.2, 48.5, 38.6, 30.1, 29.8, 29.7, 28.2, 27.30, 25.8, 25.2, 25.1; MALDI-TOF: 1506.9416 $(M + Na)^+$, 1522.9232 $(M + K)^+$; Anal. Calcd for $C_{54}H_{56}I_4N_8O_{10}$: C, 43.68; H, 3.80; N, 7.55. Found: C, 43.27; H, 4.25; N, 7.40.

Piv-hexadecamer 3b

The oligomer **3b** was obtained as a white solid (76%); mp: 259–262 °C; $[\alpha]_D^{25}$: 15.77° (*c* 5.2, $CHCl_3$); IR (*ν*) $CHCl_3$ (cm^{-1}): 3258, 3019, 2399, 1678, 1634, 1578, 1532, 1439, 1381, 1288, 1216, 930, 762, 669; ^1H NMR (400 MHz, $CDCl_3$) δ: 11.51 (s, 1H), 9.90–9.85 (m, 4H), 9.82 (s, 1H), 9.78 (s, 1H), 9.49 (s, 1H), 8.45–8.43 (d, *J* = 8 Hz, 1H), 8.35 (s, 1H), 8.24–8.22 (d, *J* = 8 Hz, 1H), 8.17–8.12 (m, 4H), 8.07–8.05 (d, *J* = 8 Hz, 1H), 7.99–8.01 (d, *J* = 8 Hz, 1H), 7.90 (s, 1H), 7.83–7.81 (d, *J* = 8 Hz, 1H), 7.73–7.59 (m, 12H), 7.57 (s, 1H), 5.10–4.90 (m, 6H), 4.78–4.73 (m, 2H), 3.97 (s, 3H), 3.78–3.59 (m, 9H), 3.51–3.47 (m, 1H), 3.40–3.27 (m, 6H), 2.50–2.26 (m, 8H), 2.20–2.01 (m, 16H), 1.98–1.84 (m, 8H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.6, 172.1, 172.0, 171.9, 171.7, 171.3, 170.8, 167.5, 167.0, 166.5, 166.2, 165.9, 165.8, 143.1, 140.4, 139.5, 139.3, 138.9, 138.7, 135.7, 135.6, 135.2, 134.7, 134.5, 134.2, 134.0, 129.5, 129.0, 128.2, 124.0, 123.8, 123.1, 122.0, 117.0, 88.0, 87.6, 87.6, 87.5, 87.2, 86.1, 85.8, 62.8, 62.0, 61.2, 60.7, 53.0, 49.7, 48.9, 48.5, 38.6, 30.2, 30.0, 29.9, 27.3, 25.2; MALDI-TOF: 2874.3485 $(M + Na)^+$, 2890.2898 $(M + K)^+$; Anal. Calcd for $C_{102}H_{100}I_8N_{16}O_{18}$: C, 42.94; H, 3.53; N, 7.85. Found: C, 43.31; H, 3.20; N, 8.29.

Piv-tetramer 7d

The oligomer **7d** was obtained as a white solid (77%); mp: 127–131 °C; $[\alpha]_D^{25}$: 21.96° (*c* 5.1, $CHCl_3$); IR (*ν*) $CHCl_3$ (cm^{-1}): 3260, 3019, 2399, 1703, 1693, 1574, 1504, 1408, 1385, 1308, 1292, 1215, 1095, 770, 667; ^1H NMR (500 MHz, $CDCl_3$) *δ*: 11. 65 (s, 1H), 9.67 (s, 1H), 8.57–8.55 (d, *J* = 8 Hz, 1H), 8.30 (s, 1H), 8.22 (s, 1H), 7.98–7.96 (d, *J* = 8 Hz, 1H), 7.79–7.76 (d, *J* = 12 Hz, 1H), 7.66–7.64 (d, *J* = 8 Hz, 1H), 4.80–4.77 (m, 1H), 4.59–4.54 (m, 1H), 3.98 (s, 3H), 3.89–3.79 (m, 2H), 3.79–3.89 (m, 2H), 2.55–2.47 (m, 1H), 2.18–1.92 (m, 7H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 177.3, 171.2, 170.7, 169.2, 167.6, 143.2, 140.8, 139.7, 139.2, 136.7, 136.6, 126.3, 124.1, 122.0, 116.7, 85.9, 85.2, 63.2, 63.2, 62.8, 53.2, 51.1, 48.4, 38.8, 30.0, 28.1, 27.3, 25.8, 25.5; MALDI-TOF: 823.5230 $(M + Na)^+$, 839.4984 $(M + K)^+$; Anal. Calcd for $C_{30}H_{34}I_2N_4O_6$: C, 45.02; H, 4.28; N, 7.00. Found: C, 45.09; H, 3.80; N, 7.38.

Piv-octamer 2b

The oligomer **2b** was obtained as a white solid (71%); mp: 231–235 °C; $[\alpha]_D^{26}$: −1.95° (*c* 4.1, $CHCl_3$); IR (*ν*) $CHCl_3$ (cm^{-1}): 3021, 2399, 1701, 1634, 1539, 1520, 1506, 1436, 1418, 1219, 930, 771, 667; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 11.63 (s, 1H), 10.01 (s, 1H), 9.62 (s, 1H), 9.41 (s, 1H), 8.54–8.52 (d, *J* = 8 Hz, 1H), 8.31 (s, 1H), 8.20 (s, 1H), 8.10–8.08 (d, *J* = 8 Hz, 1H), 8.02–7.94 (m, 2H), 7.85 (s, 1H), 7.79–7.77 (d, *J* = 8 Hz, 2H), 7.68–7.766 (d, *J* = 8 Hz, 1H), 7.63–7.50 (m, 2H), 4.86–4.73 (m, 3H), 4.54–4.47 (m, 1H), 3.97 (s, 3H), 3.87–3.67 (m, 4H), 3.65–3.54 (m, 2H), 3.52–3.42 (m, 2H), 2.52–2.37 (m, 1H), 2.33–2.25 (m, 2H), 2.17–1.83 (m, 13H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 176.9, 171.3, 170.4, 170.1, 170.0, 168.8, 167.6, 143.2, 140.8, 139.9, 139.5, 139.3, 136.8, 136.5, 136.0, 135.6, 126.8, 126.0, 123.8, 123.4, 122.0, 86.5, 86.3, 86.0, 85.3, 63.0, 62.7, 61.4, 61.3, 53.2, 51.1, 50.3, 50.2, 48.4, 38.8, 30.1, 29.5, 29.3, 27.3, 25.4, 25.3, 25.2; MALDI-TOF: 1506.8801 $(M + Na)^+$, 1522.8418 $(M + K)^+$; Anal. Calcd for $C_{54}H_{56}I_4N_8O_{10}$: C, 43.68; H, 3.80; N, 7.55. Found: C, 43.35; H, 4.12; N, 7.27.

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18 The superimposed 3D structures of the Ant–Pro hexadecamer **3b** with the maganin-II helix (ESI, S54†) suggest that the iodines on Ant rings are pointing outside the helical backbone – a structural feature which might offer opportunity to further modify them to useful biomimetics.