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Absolute Control of Helical Handedness in Quinoline Oligoamides

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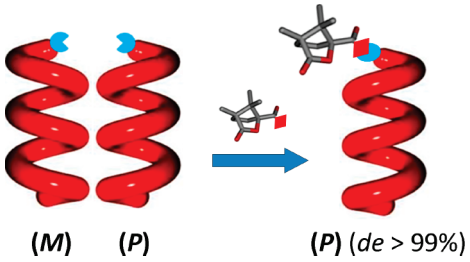

The synthesis of quinoline-derived helically folded aromatic oligoamides functionalized by various chiral functions at their N-terminus is reported. When a (1*S*)-(−)-camphanyl moiety was introduced, it was found that helix handedness was completely shifted to right-handed helicity (de > 99%), in both protic and nonprotic solvents. The absolute helical sense and the de values were unambiguously characterized by using ^{1}H NMR, circular dichroism (CD), and X-ray crystallography. The crystal structure of these compounds allowed us to propose a rationale for the efficiency of helix handedness induction based on a combination of steric factors and intramolecular hydrogen bonding.

Introduction

The induction of helix handedness bias in helical oligomers and polymers has attracted widespread interest for both practical uses (e.g., application in optical devices) and from a fundamental perspective because of its relevance to chiral amplification.[1] Oligomers of aromatic amides, imides, and ureas constitute a rapidly growing class of foldamers which give access to a vast and varied ensemble of stable and predictable folded structures, many of which are helices.[2] Induction of *P* or *M* handedness bias in these systems has been achieved in a number of ways. Simple chiral residues have been appended at the end[3] or inserted into the middle[4] of secondary aromatic amide sequences. Chiral side chains have been introduced into polyureas,[5] secondary[6] and tertiary amides,[7] ureas,[8] and imides.[9] Helical bias has also been achieved upon binding chiral guests in helix cavities[3f,10] or at

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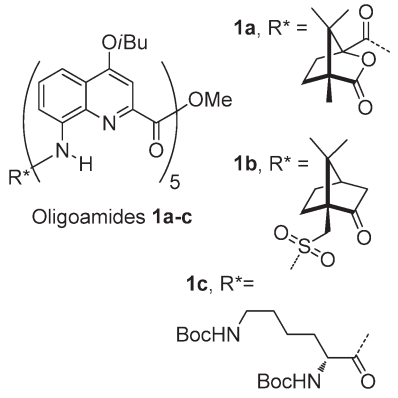
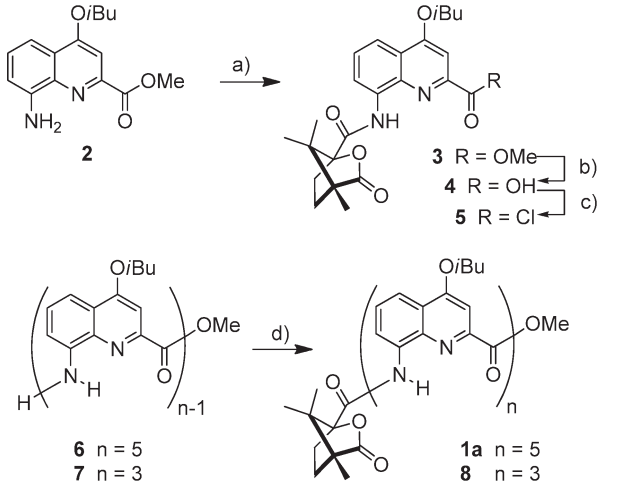
CHART 1. Pentameric Quinolinecarboxamide Oligomers Bearing a Chiral Group at Their N-Terminus



SCHEME 1. Synthesis of Camphanylated Quinolinecarboxamide Oligomers[a]



[a]Reagents and conditions: (a) (1*S*)-(−)-Camphanyl chloride, Et_3N, $CHCl_3$, 25 °C, 86%; (b) NaOH, 1,4-dioxane/water, 25 °C, 92%; (c) $(COCl)_2$, 25 °C, quantitative; (d) **5**, Et_3N, $CHCl_3$, 25 °C, 65% (**1a**), 87% (**8**).

the helix periphery.[3e,11] In addition, relative handedness bias between two helices has been found to occur when they are either attached end-to-end[12] or side-by-side.[13] However, in such systems, evidence for quantitative induction (de > 99%) has been discovered in only a few cases.[10b,12a,12b] We report here that the appendage of a camphanyl moiety at the N-terminus of quinolinecarboxamide oligomers gives rise to complete helix handedness induction.

Results and Discussion

We have previously shown that chiral amines attached to the C-terminus of helical aromatic amide oligomers can result in a helix bias.[3a,b,d,e] For example, helix handedness ratios of up to 9:1 were observed with use of phenylethylamine at the end of helical quinolinecarboxamide oligomers in $CDCl_3$. To complement these findings, we attached several chiral moieties that could potentially bias helix handedness at the N-terminus of pentameric chains via an amide or a sulfonamide group (Chart 1). The decision to initially target pentameric sequences was guided by two factors. First, pentamers are long enough to undergo slow helix handedness inversion on the NMR time scale in $CDCl_3$ solutions at 25 °C.[14] The presence and proportions of two diastereomeric *P* and *M* helices can therefore be assessed by a ^1H NMR spectrum; if helix sens bias takes place, two sets of signals (one for each diastereomer) in different proportions will be revealed. Second, pentamers can be easily accessed from the common amino-tetramer intermediate **6**.[14a] For example, camphanyl chloride is coupled to amino-quinoline monomer **2** (Scheme 1) to give **3**, which is subsequently saponified. Activation of the resulting acid **4** into an acid chloride provides **5**, which is then coupled to the amine of tetramer **6** to yield pentamer **1a**. In a similar manner, coupling to the amine of dimer **7** yields trimer **8**.

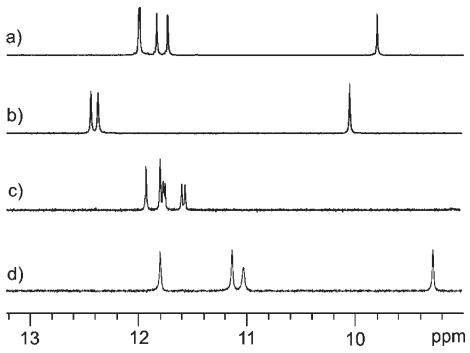


FIGURE 1. Part of the 300 MHz ^1H NMR spectra showing the amide resonances of (a) **1a**, (b) **9**, and (c) **1b** in $CDCl_3$ and of (d) **10** in H_2O/D_2O 9:1 v/v.

The NMR spectra of **1b** and **1c** showed two sets of signals in similar proportions, presumably belonging to the *P* and *M* diastereomers, suggesting poor helix handedness induction in both cases. The spectrum of **1b** is shown in Figure 1c as an example. Two of the four carboxamide resonances between 11 and 12 ppm are clearly split into two signals of equal intensity, while the two others are not. This indicates identical chemical shift values of these resonances in the *P* and *M* helices. In contrast, the NMR spectrum of **1a** (Figure 1a) shows a single set of sharp signals for the expected five carboxamide resonances between 9 and 12 ppm, suggesting a quantitative helical sense bias. The circular dichroism (CD) spectrum of **1a** (possessing a (1*S*)-(−)-camphanyl group) showed intense bands in the absorption region of the quinoline chromophores (Figure 2), confirming that a single handedness prevails. This also demonstrates that the single set of NMR signals does not result from a fortuitous coinciding of all resonances of the *P* and *M* helical diastereomers. By analogy with other quinolinecarboxamide oligomers, the positive sign of the bands at 390 and 410 nm indicates a preferred *P* handedness.[3b]

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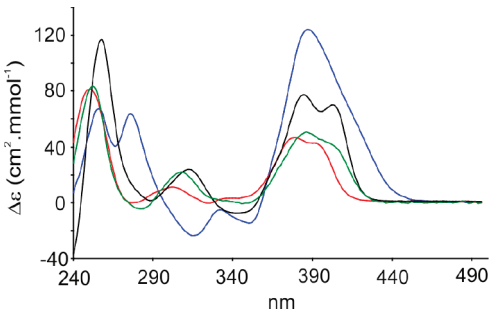
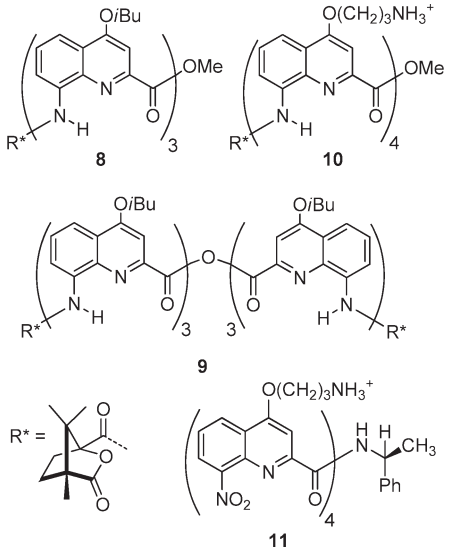


FIGURE 2. CD spectra of **1a** (black), **8** (red), and **9** (blue) in $CHCl_3$, and of **10** (green) in H_2O at 25 °C.

CHART 2. Oligoamides 8−10 with Appended (1*S*)-(−)-Camphanyl Groups and 11 with a C-Terminal Phenylethylamine Group



The NMR spectrum of camphanylated trimer **8** also feature a single set of signals (not shown). However, this alone does not allow us to draw any conclusions since the equilibrium between *P* and *M* helices is expected to be fast on the NMR time scale for such a short oligomer. A single set of average signals is expected regardless of the proportions between *P* and *M* helices. Therefore, the diastereomeric excess of **8** cannot be determined from the NMR spectrum. However, the CD spectrum of **8** shows (slightly blue-shifted) bands having the same sign and intensity ($\Delta\varepsilon$) per monomer as that of **1a**. This indicates that trimer **8** and pentamer **1a** have the same dominant handedness and also a similar diastereomeric excess. The results obtained with hexameric anhydride **9** (Chart 2) also corroborate these findings. Compound **9** was prepared by saponification of **8** followed by condensation of the resulting carboxylic acid into an anhydride. The NMR spectrum of **9** shows three sharp amide resonances (Figure 1b), due to its symmetrical structure; it also confirms the complete prevalence of a single *P* or *M* diastereomer. The CD spectrum of **9** shows an intense band at 390 nm indicative of *P* handedness as for **1a** and **8**. It also features a positive band at 280 nm and a negative band at 315 nm. The sign of these two bands is opposite to those of **1a** and **8**, but this is unlikely to indicate a different handedness for **9**. It is more likely that this results from the fact that **9** is comprised of two trimeric segments oriented head-to-head whereas **1a** and **8** have N- and C- termini. It should be noted that the CD and ^{1}H NMR spectra of **1**, **8**, and **9** in chloroform are not concentration dependent. This indicates that these compounds do not aggregate and remain single helices, as seen with other helical foldamers derived from 8-amino-2-quinolinecarboxylic acid.[12−14] This is unlike the behavior of other aromatic amide foldamers, which show a tendency to assemble in double, triple, or quadruple helices.[3c,15]

The NMR spectrum of **1a** in $CDCl_3$ was unaltered upon heating to 50 °C. Additionally, only one set of signals was also observed in toluene-d_8, DMSO-d_6, and pyridine-d_5, indicating that helix handedness induction also operates in these solvents. To assess whether helix handedness induction also works in protic solvents, water-soluble tetramer **10** (Chart 2) was prepared by direct camphanyl chloride acylation of the tetramer amine precursor possessing Boc protected side chains; these were subsequently deprotected by using TFA. NMR spectra of **10** in CD_3OH and H_2O/D_2O showed a diastereotopic pattern of the side-chain methylene units, indicating that helix handedness is slow on the NMR time scale at 25 °C in protic solvents, despite the helix being shorter in length than **1a** (Figure 1d). Importantly, only one set of signals is observed in these two solvents, again indicating complete handedness induction. CD spectroscopy showed that the same handedness is induced in both protic solvents and chloroform (Figure 2). The efficiency of the camphanyl group at completely inducing handedness in multiple solvents is remarkable and contrasts with the effect of chiral residues introduced at the C-terminus. For example, the helix handedness ratio observed using a C-terminal phenethylamine group (i.e., compound **11**, Chart 2)[3a,b] is 9:1 in $CDCl_3$, decreasing to 7:3 in protic solvents.

To investigate the strong propensity of the camphanyl moiety to induce helix handedness, solid state structural studies were undertaken; however, this proved to be a particularly difficult task. Even though helical aromatic amide foldamers show an excellent propensity to crystallize as racemates,[12−14] in our hands chiral oligomers either yielded crystals unsuitable for analysis by X-ray crystallography, or crystallized as pseudoracemates containing both *P* and *M* helices.[12a,b] Of the numerous structures we have previously described, none have been composed of exclusively one handed helices. Unsurprisingly, this was the case when we attempted to crystallize pentamer **1a**. Fortunately, crystals of the related trimer **8** and of hexameric anhydride **9** could be grown and their structures elucidated both in the $P2_1$ space group (Figure 3). It is intriguing to note that no element of the packing of these compounds in the solid state explains the difficulty we have experienced in growing crystals. Both revealed a right-handed helical structure in agreement with the CD spectra measured in solution (Figure 2). The conformation of the camphanyl moiety is the same in every case and provides a rationale for the strong handedness induction observed. In the structures of **8** and **9**, the bulky *gem*-dimethyl groups of the camphanyl moiety diverge from the helix backbones. The endocyclic lactone oxygen atom is oriented so as to minimize electrostatic repulsions with the neighboring amide carbonyl, forming a

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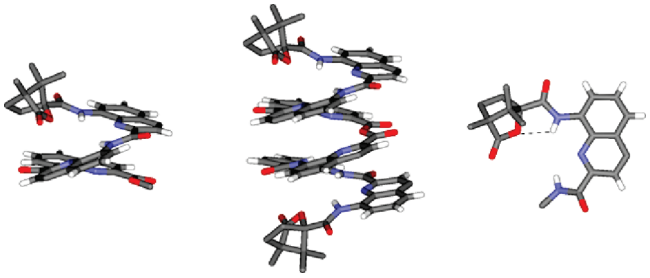

FIGURE 3. Stick representations of the solid-state X-ray crystal structures of right-handed helical trimer **8** (left) and hexameric anhydride **9** (center). A top view of the N-terminal quinoline ring with its attached camphanyl residue is shown on the right. Isobutoxy groups, protons of the camphanyl moiety, and included solvent molecules are not shown for clarity.

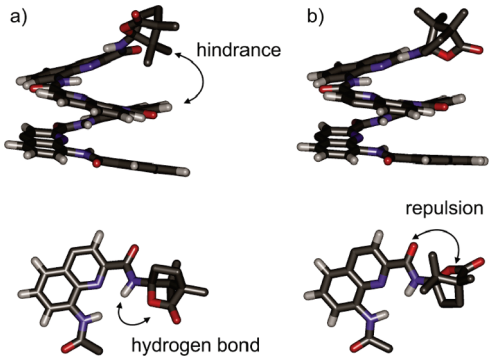

FIGURE 4. Side views (top) and top views (bottom) of two energy minimized (MMFS force field) conformers of the disfavored diastereomer of **1a** having an *M* helix and an (1*S*)-(−)-camphanyl group. In part a, the camphanyl group is oriented so as to establish the same hydrogen bond observed in the solid state structures of **8** and **9**, but steric hindrance caused by the *gem*-dimethyl group perturbs intramolecular $\pi-\pi$ stacking. In part b, hindrance is avoided but no hydrogen bond takes place; instead electrostatic repulsions are expected between oxygen atoms.

bifurcated hydrogen bond with the amide proton (d_{O-N} = 2.17 Å). In contrast, in the unobserved diastereomeric form (i.e., (1*S*)-(−) -camphanyl group on a left-handed helix), local conformational preferences about the lactone−quinoline linkage cannot all be satisfied (Figure 4). To keep the bulky *gem*-dimethyl groups away from the helix backbone, the hydrogen bond has to be broken and electrostatic repulsion introduced. Alternatively, to maintain the hydrogen bond and minimize electrostatic repulsions, the *gem*-dimethyl group is forced to point toward the helix backbone, resulting in a local disturbance of intramolecular $\pi-\pi$ stacking in the helix.

In summary, camphanic acid has been demonstrated to be a versatile, powerful, commercially available, and easily introduced chiral unit, which quantitatively biases the helix sense of folded aromatic oligoamides in a wide range of solvents. On the basis of the knowledge acquired in this study, we are currently looking for an equally efficient and versatile helix handedness inducer that would operate from the C-terminus of these oligomers.

Experimental Section

General Methods. Reactions requiring anhydrous conditions were carried out under an argon atmosphere. The original materials were used directly from commercial suppliers without any purification. Dry THF was distilled from Na/benzophenone, and dry dichloromethane and triethylamine were distilled from CaH_2 prior to use. NMR spectra were recorded on a 300 or 400 MHz spectrometer. Chemical shifts are expressed in parts per million (ppm, δ) using residual solvent protons as internal standards (chloroform: δ 7.26 ppm; DMSO: δ 2.50 ppm). Coupling constants are expressed in hertz. HRMS ESI mass spectra were obtained on an LCT premier spectrometer.

8-(1*S*)-(−)-Camphanylamino-4-isobutoxy-2-quinoline Carboxylic Acid, 4. To an ice cold mixture of methyl 8-amino-2-quinolinecarboxylate **2**[14a] (0.12 g, 0.43 mmol) and triethylamine (0.12 mL, 0.87 mmol) in dry $CHCl_3$ (5 mL) was added a solution of (1*S*)-(−)-camphanyl chloride (0.094 g, 0.43 mmol) in dry $CHCl_3$ (2 mL) dropwise under an argon atmosphere. After 10 min, the ice bath was removed and the reaction mixture was stirred at 25 °C for 24 h. Solvents were removed under reduced pressure and the residue was purified by column chromatography (SiO_2) with ethyl acetate/cyclohexane 10:90 v/v to yield intermediate **3** (methyl 8-(1*S*)-(−)-camphanylamino-4-isobutoxy-2-quinolinecarboxylate) as a white solid (0.17 g, 86%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 3H), 1.12−1.15 (d, 6H), 1.18−1.19 (d, 6H), 1.74−1.83 (m, 1H), 1.97−2.17 (m, 2H), 2.23−2.33 (m, 1H), 2.63−2.72 (m, 1H), 4.04−4.06 (d, 2H), 4.08 (s, 3H), 7.55−7.60 (t, 2H), 7.92−7.96 (dd, 1H), 8.71−8.74 (dd, 1H), 10.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.6, 17.5, 20.0, 28.9, 30.0, 31.0, 53.8, 55.1, 56.3, 76.0, 93.5, 101.8, 117.1, 118.0, 122.7, 128.8, 134.8, 139.5, 148.0, 163.7, 166.4, 166.6, 178.3; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{31}N_2O_6$ $[M + H]^+$ 455.2182, found 455.2168. Intermediate **3** (0.17 g, 0.37 mmol) in 1,4-dioxane (25 mL) was then subjected to saponification by addition of NaOH (0.03 g, 0.74 mmol) in water (3 mL) and stirring at 25 °C for 6 h. The reaction was quenched with the addition of 5% aqueous citric acid. The product was extracted with DCM (2 × 100 mL), then washed with water and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated, and dried under vacuum for several hours to afford the title compound **4** as a white solid (0.15 g, 92%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.87 (s, 3H), 0.92 (s, 3H), 1.07−1.09 (d, 12H), 1.18 (s, 3H), 1.47−1.70 (m, 1H), 1.78−1.86 (m, 1H), 2.01−2.10 (m, 1H), 2.16−2.28 (m, 1H), 2.55−2.71 (m, 1H), 4.11−4.15 (m, 2H), 7.60−7.61 (d, 1H), 7.64−7.71 (m, 1H), 7.83−7.94 (dd, 1H), 8.71−8.79 (dd, 1H), 10.54 (s, 1H), 11.04 (s, 1H−COO*H*); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{29}N_2O_6$ $[M + H]^+$ 441.2025, found 441.2044.

General Procedure for the Synthesis of Compounds 1 and 8. Coupling of a camphanylated monomer acid to a quinolinecarboxamide dimer or tetramer having a free amine at the N-terminus.

To an ice-cold solution of **4** (0.13 g, 0.30 mmol) in dry $CHCl_3$ (2 mL) was added oxalyl chloride (0.13 mL, 1.53 mmol). Solvents were removed after the reaction was stirred at 25 °C for 2 h. This freshly prepared acid chloride **5** was then added to a solution of the dimeric quinoline carboxamide **7** having a free amine at the N-terminus[14a] (0.16 g, 0.30 mmol) and triethylamine (0.13 mL, 0.91 mmol) in dry $CHCl_3$ (5 mL) at 0 °C. The ice bath was removed after 10 min and the reaction was allowed to stir at 25 °C for 24 h. Solvents were removed under reduced pressure and the residue was purified by column chromatography (SiO_2) with ethyl acetate/cyclohexane 10:90 v/v to afford compound **8** as a white solid (0.24 g, 87%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.54 (s, 3H), 0.87 (d, 6H), 1.19−1.25 (m, 18H), 1.60−1.68 (m, 1H), 1.77−1.86 (m, 1H), 2.09−2.18 (m, 1H), 2.26−2.46 (m, 4H), 3.54 (s, 3H), 3.85 (d, 2H), 4.09−4.24 (m, 4H), 6.66 (s, 1H), 7.20−7.25 (t, 1H), 7.62−7.68 (m, 2H), 7.71 (s, 1H), 7.77 (s, 1H), 7.87−7.92 (m, 3H), 8.04−8.07 (dd, 1H), 8.91−8.94 (dd, 1H), 8.95−8.98 (dd, 1H), 10.06, (s, 1H), 12.36 (s, 1H), 12.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.8, 16.4, 16.4, 19.3, 19.4,

19.4, 27.0, 28.3, 28.3, 28.9, 29.4, 52.5, 53.5, 54.3, 54.9, 75.0, 75.3, 75.6, 92.0, 98.9, 99.1, 100.6, 116.1, 116.3, 116.6, 116.8, 117.4, 121.8, 121.9, 122.4, 126.7, 127.4, 128.0, 132.8, 134.5, 135.0, 137.8, 139.1, 139.1, 145.4, 150.9, 151.4, 162.3, 163.1, 163.6, 163.7, 163.9, 164.1, 164.9, 176.7; HRMS (ESI) m/z calcd for $C_{53}H_{59}N_6O_{10}$ $[M + H]^+$ 939.4292, found 939.4310.

Compounds **1a**, **1b**, and **1c** were prepared from tetramer **6** following the same procedure.

Pentamer 1a: yield 65%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.95 (1H, br), 11.94 (1H, s), 11.78 (1H, s), 11.68 (1H, br), 9.75 (1H, s), 8.65 (1H, d), 8.59 (1H, d), 8.08 (1H, d), 7,99 (1H, t), 7.83 (1H, d), 7.69 (1H, d), 7.43 (1H, s), 7.32 (1H, s), 7.30 (1H, s), 7.23 (1H, s), 7.20 (1H, s), 7.18 (1H, s), 6.83 (1H, s), 6.75 (1H, s), 6.55 (1H, s), 4.44 (3H, m), 4.22 (3H, m), 3.95 (2H, d), 3.88 (2H, t), 3.88 (4H, d), 2.54 (4H, m), 2.36 (4H, m), 2.01 (2H, m), 1.78 (2H, m), 1.29 (24H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 163.5, 162.7, 160.5, 156.8, 139.0, 134.6, 128.7, 120.1, 120.1, 118.4, 112.5, 97.8, 97.8, 80.1, 60.4, 45.6, 28.4, 28.2, 28.3, 25.8, 22.9, 19.5, 18.9; HRMS (ESI) m/z calcd for $C_{81}H_{87}N_{10}O_{14}$ $[M + H]^+$ 1423.6403, found 1423.6419.

Pentamer 1b: yield 85%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.96 (1H, s), 11.83 (1H, s), 11.80 (1H, s), 11.67 (1H, s), 11.59 (1H, s), 8.58 (1H, d), 8.53 (1H, d), 8.16 (1H, d), 8.13 (1H, d), 8.08 (1H, s), 7.99 (1H, t), 7.87 (1H, t), 7.67 (1H, t), 7.52 (1H, t), 7.39 (1H, d), 6.95 (1H, d), 6.83 (1H, d), 6.73 (1H, s), 4.52 (3H, m), 4.25 (3H, m), 3.93 (2H, d), 3.85 (2H, d), 2.47 (4H, t), 2.31 (4H, t), 1.25 (24H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.9, 147.7, 147.1, 138.6, 138.4, 137.8, 137.7, 136.6, 135.9, 134.1, 126.7, 124.8, 124.5, 124.0, 119.1, 116.2, 115.4, 115.3, 100.7, 75.2, 64.6, 58.4, 50.0, 48.6, 46.9, 42.8, 42.5, 39.5, 37.1, 36.5, 35.9, 34.9, 34.52, 34.3, 31.9, 30.2, 29.7, 29.4, 28.1, 26.9, 25.9, 25.2, 22.7, 21.4, 20.5, 19.9, 19.8, 19.2, 16.9, 14.7, 14.1; HRMS (ESI) m/z calcd for $C_{81}H_{89}N_{10}O_{14}S$ $[M + H]^+$ 1457.6274, found 1457.6301.

Pentamer 1c: yield 60%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.29 (1H, br), 11.61 (1H, s), 11.54 (1H, s), 9.07 (1H, br), 8.34 (1H, d), 8.25 (1H, d), 8.08 (1H, d), 8.01 (1H, d), 7.90 (1H, s), 7.82 (1H, t), 7.64 (1H, t), 7.58 (1H, t), 7.43 (1H, t), 6.95 (1H, d), 6.83 (1H, d), 6.73 (1H, s), 4.52 (3H, m), 4.25 (3H, m), 3.93 (2H, d), 3.85 (2H, d), 2.47 (4H, t), 2.31 (4H, t), 1.25 (24H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 163.5, 162.7, 160.5, 156.8, 139.0, 134.6, 128.7, 120.1, 120.1, 118.4, 112.5, 97.8, 97.8, 80.1, 60.4, 45.6, 28.4, 28.2, 28.3, 25.8, 22.9, 19.5, 18.9; HRMS (ESI) m/z calcd for $C_{87}H_{103}N_{12}O_{16}$ $[M + H]^+$ 1571.7609, found 1571.7591.

Hexameric Anhydride 3. To a solution of the trimer methyl ester **2** (0.13 g, 0.13 mmol) in 1,4-dioxane (20 mL) was added a solution of NaOH (0.16 g, 0.415 mmol) in water (2 mL). The reaction mixture was stirred at 25 °C for 36 h and then quenched by adding 5% aqueous citric acid. The product was extracted with DCM (100 mL). The organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated to afford the corresponding crude carboxylic acid. This material (0.09 g) was dissolved in $CHCl_3$ (5 mL) and cooled with an ice bath, then oxalyl chloride was added (0.04 mL, 0.51 mmol). After the solution was stirred at 25 °C for 2 h, all volatiles were removed under reduced pressure. The freshly prepared acid chloride was dissolved in $CHCl_3$ (5 mL) and cooled to 0 °C, then triethylamine (0.04 mL, 0.30 mmol) was added. The ice bath was removed after 10 min and the reaction was allowed to stir at 25 °C for 24 h without any protection from ambient moisture. After evaporation, silica gel column chromatographic purification of the resulting residue eluting with petroleum ether/ethyl acetate (30%) furnished **3** as a light yellow solid (0.087 g, 46%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.27 (s, 6H), 0.67−0.70 (d, 12H), 1.26−1.36 (m, 36 H), 1.40−1.49 (m, 2H), 1.61−1.70 (m, 2H), 1.93−2.02 (m, 2H), 2.10−2.19 (m, 2H), 2.35−2.49 (m, 6H), 3.85−3.89 (m, 2H), 4.00−4.05 (m, 2H), 4.12−4.18 (m, 4H), 4.23−4.34 (m, 4H), 6.54 (s, 2H), 6.98−7.06 (m, 4H), 7.21−7.24 (d, 2H), 7.33−7.39 (m, 4H), 7.42 (s, 2H), 7.52 (s, 2H), 7.53−7.56 (dd, 2H), 7.76−7.79 (dd, 2H), 8.01−8.04 (dd, 2H), 8.26−8.28 (dd, 2H), 9.65 (s, 2H), 11.61 (s, 2H), 11.89 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.4, 16.9, 17.0, 20.3, 20.3, 20.4, 20.4, 20.5, 29.1, 29.2, 29.3, 29.5, 29.7, 54.8, 55.4, 75.6, 75.7, 76.1, 92.5, 99.9, 101.1, 101.5, 116.2, 116.4, 116.9, 117.1, 117.2, 117.9, 121.5, 121.7, 122.3, 126.2, 127.0, 128.0, 133.1, 133.3, 134.7, 138.1, 138.3, 138.6, 144.8, 151.5, 151.6, 158.6, 162.6, 162.9, 163.6, 164.1, 164.4, 165.3, 177.1; HRMS (ESI) m/z calcd for $C_{104}H_{111}N_{12}O_{19}$ $[M + H]^+$ 1831.8088, found 1831.8031.

Compound 10. A solution of (1*S*)-(−)-camphanyl chloride (12 mg, 0.055 mmol) in DCM (1 mL) was added to a mixture of the relevant quinolinecarboxamide tetramer (having a free amine N-terminus and Boc-protected aminopropyloxy side chains)[16] (70 mg, 0.05 mmol) and triethylamine (0.10 mmol) in DCM (2 mL) at 25 °C and the solution was then stirred overnight. All solvents were evaporated and the residue was purified by chromatography (SiO_2) eluting with dichloromethane/EtOAc 7:3 v/v to afford the camphanylated tetramer with protected side chains as a yellow solid (75 mg, 95%). This compound (30 mg, 0.01 mmol) was dissolved in 1/1 TFA/CH_2Cl_2 (2 mL) and stirred at 25 °C for 4 h. The solvents were evaporated and the product was purified by reverse-phase semipreparative HPLC, using a C18 column (Microsorb C18) and a water/acetonitrile gradient (100% H_2O to 100% CH_3CN) with constant 0.1% TFA, yielding **10** (19 mg, 85%) as a yellow solid. ^{1}H NMR (D_2O/H_2O (1:9 v/v), 300 MHz) δ −0.36 (s, 3H), 0.29 (s, 3H), 0.33 (s, 3H), 1.16 (m, 2H), 2.15 (m, 2H), 2.31 (m, 8H), 3.27 (m, 11H), 3.55−4.58 (m, 8H), 4.86 (m, 1H), 5.47 (m, 1H), 6.06 (m, 1H), 6.65 (s, 1H), 6.99 (t, 1H), 7.09 (t, 1H), 7.24 (m, 3H), 7.37 (s, 1H), 7.53 (m, 2H), 7.66−7.95 (m, 6H), 7.97 (d, 1H), 8.41 (m, 1H), 9.21 (s, 1H), 10.94 (s, 1H), 11.04 (s, 1H), 11.70 (s, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 8.3, 15.1, 15.2, 26.8, 26.9, 36.9, 37.0, 37.2, 51.7, 53.4, 54.1, 54.7, 65.8, 65.9, 66.1, 66.4, 92.3, 97.8, 98.8, 99.4, 100.3, 114.9, 115.6, 116.1, 116.2, 116.4, 116.5, 116.6, 116.7, 116.8, 116.9, 118.7, 118.8, 121.5, 121.7, 121.8, 121.9, 126.8, 127.8, 127.9, 132.2, 132.9, 133.0, 133.6, 134.3, 137.3, 138.0, 138.1, 138.8, 145.4, 148.4, 150.3, 150.4, 151.0, 154.5, 155.3, 161.0, 161.3, 161.8, 162.7, 163.2, 163.3, 163.9, 164.4, 164.8, 177.3; HRMS (ESI) m/z calcd $C_{63}H_{70}N_{12}O_{12}$ $[M + 2H]^{2+}$ 593.2615, found 593.2620.

Compound 11. To a solution of the relevant quinolinecarboxamide tetramer (having a carboxylic acid C-terminus and Boc-protected aminopropyloxy side chains)[16] (50 mg, 0.035 mmol) and HBTU (20 mg, 0.05 mmol) in DMF (2 mL) was added DIPEA (18 mg, 0.14 mmol) under a nitrogen atmosphere. The solution was stirred for 30 min at room temperature and (*S*)-phenethylamine (5 mg, 0.04 mmol) was added. The reaction mixture was stirred at 25 °C for 12 h, then diluted with water (5 mL). The resulting precipitate was isolated by filtration and dried under vacuum. This solid was dissolved in TFA/CH_2Cl_2 (2 mL, 1:1 v/v) and stirred at 25 °C for 4 h. All solvents were evaporated to provide the crude product, which was purified by reverse-phase semipreparative HPLC, using a C18 column (Microsorb C18, Varian) and a water/acetonitrile gradient (100% H_2O to 100% CH_3CN) with constant 0.1% TFA, yielding **11** (33 mg, 85%) as a yellow solid. ^{1}H NMR (CD_3OH, 300 MHz) δ 1.18 (d, 3H), 2.29−2.39 (m, 4H), 2.47−2.60 (m, 4H), 3.27−3.39 (m, 4H), 3.41−3.50 (m, 4H), 4.11−4.35 (m, 2H), 4.50−4.60 (q, 1H), 4.69−4.89 (m, 6H), 6.48 (s, 1H), 6.84 (s, 1H), 6.90−7.10 (m, 5H), 7.31 (t, 1H, J = 6.4 Hz), 7.48 (s, 1H), 7.53−7.69 (m, 3H), 7.79 (t, 1H), 7.86−8.03 (m, 4H), 8.33 (d, 1H), 8.41 (d, 1H), 8.60 (d, 1H), 8.99 (d, 1H), 11.55 (s, 1H), 11.75 (s, 1H), 12.39 (s, 1H); ^{13}C NMR (CD_3OH, 100 MHz) δ 27.8, 28.1, 28.2, 38.3, 38.4, 38.8, 67.0, 67.3, 67.8, 98.6, 99.2, 100.3, 101.0, 116.3, 117.3, 120.1, 122.4, 123.0,

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123.3, 124.5, 126.5, 127.4, 128.1, 128.2, 128.4, 128.9, 129.4, 134.2, 134.3, 136.0, 139.2, 139.3, 139.8, 140.0, 145.5, 146.3, 149.6, 149.9, 151.6, 151.9, 154.3, 162.0, 162.6, 162.7, 163.2, 163.9, 164.0, 164.4, 164.8, 165.0; TOF HRMS (ESI) m/z calcd for $C_{60}H_{62}N_{13}O_{10}$ $[M + H]^+$ 1124.4742, found 1124.4650.

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Supporting Information Available: ^1H, ^{13}C NMR, CD, and crystallographic information files (CIFs). This material is available free of charge via the Internet at http://pubs.acs.org.